The 46th Annual Meeting of the Japanese Society for Investigative Dermatology

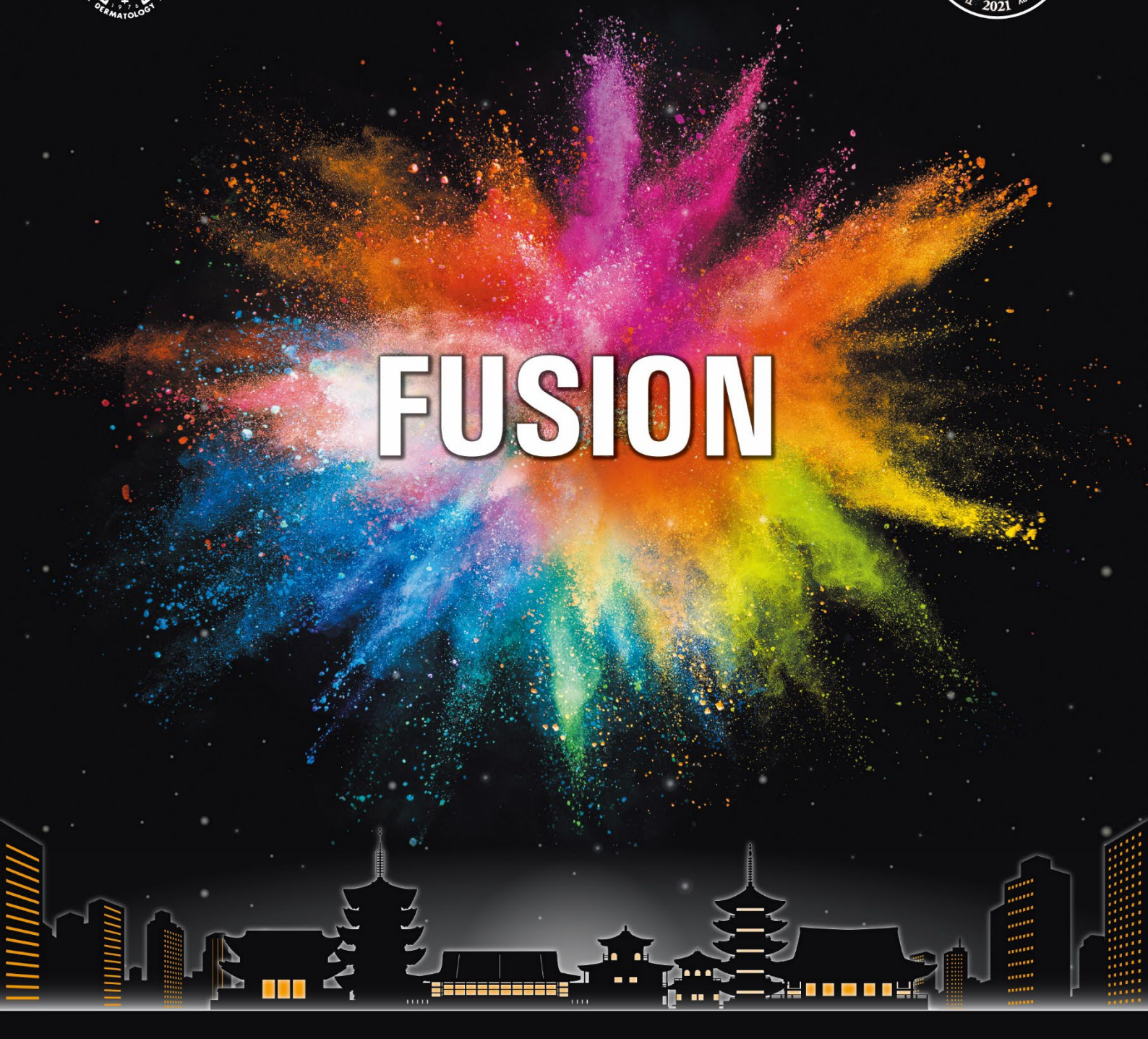
46TH JSID

PROGRAM

Dates December 3(Fri.) - 5(Sun.) 2021

Venue Virtual Meeting

President Masayuki Amagai, M.D., Ph.D.
Department of Dermatology, Keio University School of Medicine



The 46th Annual Meeting of
the Japanese Society for Investigative Dermatology

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Welcome Message

The 46th Annual Meeting of the
Japanese Society for Investigative Dermatology
President, Masayuki Amagai, M.D., Ph.D.
Professor and Chair, Department of Dermatology,
Keio University School of Medicine

Dear Friends and Colleagues,

It is my great honor and pleasure to host the 46th Annual Meeting of the Japanese Society for Investigative Dermatology (JSID) on December 3-5, 2021. Because the COVID-19 pandemic continues to globally disrupt our scientific and daily life, JSID 2021 is planned to be held as a complete virtual meeting. Most of the lectures as well as plenary and concurrent sessions will be available live for our remote participants. The recordings for these sessions will also be shared online for a period following the meeting. The online option has a benefit of easy access to the meeting contents from all over the world.

Because science has advanced so much, enormous efforts are required to master even a single area of expertise. If you continue to deepen the single area, you may sometimes lose your location in a big picture. We do hope that JSID2021 provides a platform for “fusion” of their ideas to create new fields by interacting among investigators from different fields. Academic-industrial collaboration is also encouraged.

JSID has a long tradition to support an international, abstract-driven peer reviewed scientific meeting in English as the official language. The Tanioku Kihei Memorial Lecture, the highest honor in JSID, will be delivered by Prof. Howard Y. Chang, M.D., Ph.D. at Stanford University School of Medicine. World Showcase of Investigative Dermatology, a series of on demand lectures presented by top scientists around the world, will be available during the meeting and for a period following the meeting. In addition, attractive lectures by representative researchers from societies for investigative dermatology in Asia-Oceania region and cutting-edge works by Japanese researchers will be featured in symposiums.

I strongly encourage you to attend this special occasion to present your exciting work, be inspired, reconnect with old friends and make new friends. We look forward to meeting you virtually at JSID2021.

General Information

The 46th Annual Meeting of the Japanese Society for Investigative Dermatology

Outline

The 46th Annual Meeting of the Japanese Society for Investigative Dermatology

Date

December 3 (Fri.) - 5 (Sun.), 2021

Venue

Virtual Meeting
(We hold our meeting online only without on-site.)

Official Language of the Meeting

English

President

Masayuki Amagai (Department of Dermatology, Keio University School of Medicine)

Secretariat

Secretary-General: Hayato Takahashi (Department of Dermatology, Keio University School of Medicine)
Executive Committee Chair: Hiroshi Kawasaki (Institute of Physical and Chemical Research)
Department of Dermatology, Keio University School of Medicine
35 Shinano-machi, Shinjuku, Tokyo, 160-8582, Japan
FAX: +81-3-3351-6880
E-mail: jsid46@dermatol.or.jp
URL: https://jsid46.jp/en/

Program Committee

Tatsuyoshi Kawamura (Univ. of Yamanashi), Hiroyuki Murota (Nagasaki Univ.), Yoshihide Asano (Univ. of Tokyo), Hironobu Fujiwara (RIKEN Center for Biosystems Dynamics Research), Kazumitsu Sugiura (Fujita Health Univ.), Makoto Sugaya (International Univ. of Health and Welfare), Taisuke Ito (Hamamatsu Univ. School of Medicine)

Local Program Committee

Takeshi Ouchi, Akiharu Kubo, Keiji Tanese, Takeru Funakoshi, Jun Yamagami

Referees at Each Category

No	Category	Reviewer
1	Adaptive Immunity	Tatsuyoshi Kawamura, Yoshiko Mizukawa, Saeko Nakajima, Naoko Okiyama, Ryuhei Okuyama, Hidehisa Saeki, Yayoi Tada, Sayuri Yamazaki
7	Innate Immunity, Microbiology, Microbiome	
2	Auto-Immunity	Riichiro Abe, Yumi Aoyama, Tetsuya Honda, Sei-Ichiro Motegi, Kazumitsu Sugiura, Hayato Takahashi, Hideyuki Ujiie, Yukie Yamaguchi
8	Patient Population Research	
11	Photobiology	
5	Epidermal Structure and Barrier Function	Masatoshi Jinnin, Mayumi Komine, Ken Natsuga, Yukinori Okada, Sayaka Shibata, Satoru Shinkuma, John Common, Pui-Yan Kwok
6	Genetic Disease, Gene Regulation and Gene Therapy	
10	Pharmacology and Drug Development	
9	Patient-Targeted Research	Taisuke Ito, Norito Katoh, Hiroyuki Murota, Daisuke Nanba, Manabu Ohyama, Yutaka Shimomura, Ohsang Kwon, Jitlada Meephansan
13	Skin, Appendages, and Stem Cell Biology	
14	Tissue Regeneration and Wound Healing	
3	Carcinogenesis and Cancer	Yoshihide Asano, Hironobu Fujiwara, Takafumi Kadono,Michihiro Kono, Atsushi Otsuka, Makoto Sugaya,Doanh Le Huu, Kiarash Khosrotehrani
4	Cell-Cell Interactions in the Skin	
12	Pigmentation and Melanoma	
15	Translational Studies	

Meeting Information

1. Online Registration

1. Registration fees are as follows:
   (Japanese Dermatological Association members can register by same fee as JSID members.)

   Registration Fees:

Category	on and before Nov. 4	after Nov. 5～Dec. 5 at 14:00
JSID member	JPY 19,000	JPY 20,000
JDA member	JPY 19,000	JPY 20,000
JSID member, Resident/Student*1	JPY 9,000	JPY 10,000
JDA member, Resident/Student*1	JPY 9,000	JPY 10,000
Non-member, Japanese*2	JPY 39,000	JPY 40,000
Non-member, overseas*3	JPY 19,000	JPY 20,000

   *1 Residents and Students are requested to upload their ID or the letter from the head of department when they register via online.
   *2 All JSID or JDA non-members are counted as non-member even if he/she is a resident or student.
   *3 Includes non-Japanese investigator studying in Japanese universities/institutes.

   JSID non-members who joined the JSID by November 2 may participate in the meeting at member fee. If you wish to join the JSID, please check the below.

   If you wish to join the JSID:
   Please click following URL and take the procedure
   How to apply for JSID membership
   http://www.jsid.org/en/admission.html

2. Registration Period and Payment Method
   From Wednesday, September 8 to Sunday December 5, 2021 at 14:00 (Japan standard time)

   You can choose payment method from credit card or bank transfer until November 18, 2021 at 17:00.
   After this date and time, you can choose only credit card payment.

   Registration will be completed when the registration fee is paid.

3. Issue of registration sheet and receipt
   After completing the credit payment, you can issue it on the web by yourself.
   If you participate online during the meeting, you are required the ID/password which will be written in your registration confirmation sheet to log in and view the online lecture. Be sure to print and keep it at hand.

4. Cancellation Policy
   Please note that we cannot accept cancellations after your payment for any reason.

5. Program Book and Abstract
   One Program and Abstract book is sent in advance to JSID Members. Program and Abstract book is also available for 2,000 yen, for non-members. If you need it, please let it know to our secretariat office.
   (E-mail: jsid46@dermatol.or.jp)
   The abstracts will be posted on our website with a password. The download password is fusion2021.

2. 日本皮膚科学会 専門医後実績　＜For JDA Members Only＞

皮膚科専門医の方は、下記の方法で単位取得が可能です。

【学会制度による専門医後実績】
会期中に、いずれか 1 セッションを聴講ください。
聴講は、聴講ログで確認をさせていただきます。
聴講ログの付け方は、聴講開始時（セッション開始 30 分前から開始後 15 分以内までの間）に聴講画面内の「入室」ボタンを、また、聴講が終了しましたら「退出」ボタンを押してください。

会期後、聴講ログが確認できましたら、後実績 10 単位を付与します。
また、聴講ログは、ご自身の視聴サイトページで確認が可能です。

【機構認定専門医制度による後実績単位】
聴講単位が認められているセッションについて、聴講ログを元に、会期後に付与します。
聴講ログの付け方は、聴講開始時（セッション開始 30 分前から開始後 15 分以内までの間）に聴講画面の「入室」ボタンを、また、聴講が終了しましたら「退出」ボタンを押してください。
対象となるセッションは次の通りです。
2 単位…JDS Symposium、State-of-the-Art Symposium of Skin Research、JSID-Asia-Oceania-Forum

3. How to join 46JSID meeting

During the meeting, you can participate in the conference online from your home, lab, etc.
by following the steps below.
The lecture content will be distributed on the same day and at the same time as the timetable, except for some co-sponsored seminars which will be distributed on demand from December 3 to 5, 2021 (Japan standard time).
*World Showcase of Investigative Dermatology will be distributed on demand after the meeting. The distribution period is from December 3 at 8:30 to December 13 at 10:00, 2021.

1. Click “Click here for Live streaming” on the website of the 46JSID (https://jsid46.jp/).
2. Enter your ID and password.
   And click the session you want from the displayed session which is on line.
   *As soon as we are ready, we will post information about the viewing test on this website.
   Be sure to try the viewing test before the session.
   If you have any problems such as not being able to connect or not knowing your password, please contact the secretariat office below. We may not be able to answer inquiries during the meeting.

4. Secretariat Office

Secretariat Office: The Japanese Dermatological Association
1-4, Hongo 4-chome, Bunkyo-ku, Tokyo, 113-0033, Japan
E-mail: jsid46@dermatol.or.jp

5. 2022 Meeting

The 47th Annual Meeting of the Japanese Society for Investigative Dermatology
Date: December 2 (Fri.) - 4 (Sun.), 2022
Venue: DEJIMA MESSE NAGASAKI (Nagasaki, Japan)
President: Shinichi Sato (University of Tokyo)
Secretary-General: Ayumi Yoshizaki
Secretariat: Department of Dermatology, Faculty of Medicine, University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
E-mail: jsid47@dermatol.or.jp

6. Request to the Japanese Presenters

Only the members of the Japanese Society for Investigative Dermatology are able to present their work at the annual meeting. It is requested that non-members join the Japanese Society for Investigative Dermatology by downloading the application form from the JSID website.

● Contact information
Shunkosha Inc.
Shinjuku Lambdax Bldg., 4-12, Okubo 2-chome, Shinjuku-ku, Tokyo 169-0072, Japan
Phone: +81-3-5291-6231, FAX: +81-3-5291-2176
E-mail: jsid-mail@shunkosha.com

7. Chairs' Instructions

1. Please log in 30 minutes prior to the session you will be chairing.
   (The log in URL will be informed 1 week before the meeting.)
2. There will be announcements made at the beginning of the sessions. Please start when the announcements made.
3. The time schedule is very tight. Please finish the session on time.
   ◆ **Plenary sessions & Concurrent oral sessions**
   Plenary sessions: 12 minutes for presentation and 3 minutes for discussion
   Concurrent oral sessions: 9 minutes for presentation and 3 minutes for discussion

◆ 3 minutes presentation and discussion
3 minutes for presentation and 2 minutes for discussion.

8. Concerning Conflict of Interest

All speakers and poster presenters must disclose any COI (Conflict of Interest) on your slide of the presentation or poster.
Please download the form for the disclosure slide from the meeting website (https://jsid46.jp/en/).

9. Oral Presentations (Plenary sessions, Concurrent oral sessions and 3 minutes presentation and discussion)

All presentations should be performed in English.
Plenary and concurrent session presenters can select online or pre-recorded presentation.

1. Online presentation (Only for presenters of Plenary sessions, Concurrent oral sessions)
(1) Please log in our Zoom meeting system (we will let you know the URL later) and present your slide with using "Share screens" function.
(2) After you finish your presentation, chairs will start Q&A session for your lecture. Please answer the question from chairs or participants.

2. Prerecorded data presentation and live discussion
(1) Please prepare your lecture data movie (MP4 file or PPT file with narration).
(Deadline for oral presentation data: Wednesday, November 17, noon (JST))
(2) Secretariat office will deliver your lecture video as per the timetable.
(3) When you prepare your presentation data, please check the cautions of followings.
- All presenters must disclose COI (Conflict of Interest) on your slide.
- Please keep the allotted time strictly.
Plenary sessions: 12 minutes for presentation and 3 minutes for discussion
Concurrent oral sessions: 9 minutes for presentation and 3 minutes for discussion
- Please include Session name, abstract number, lecture title, name and affiliation.
- Please prepare your presentation data in 2GB or less.
- Please prepare your presentation data by PowerPoint*1 *2 file with narration or MP4 movie file.
*1 Version of MS PowerPoint: Windows: 2019/Mac: 2019
*2 For Macintosh users
If you make your presentation data by Keynote, please check your data(character skew etc.) after changing to MS PowerPoint.
- Out screen ratio is 16:9.
- Please use standard fonts on OS.
(4) After livestreaming your lecture video, chairs will start Q&A session for your lecture via Zoom. We would let you know Zoom URL.

＜3 minutes presentation and discussion＞
(1) Please prepare and submit your presentation data (PPT file with no narration).
(Deadline for oral presentation data: Wednesday, November 17, noon (JST))
(2) Secretariat office will share your slide at start and speakers present it on live. If your data has more than one slides, operator will send it to next slide by your instruction.
(3) After you finish your presentation, chairs will start Q&A session (2 minutes) for your lecture. Please answer the question from chairs or participants.

10. Digital Poster Presentations

All accepted abstracts, including oral presentations, are requested to prepare digital posters. You are required to prepare your digital poster data in advance.
Deadline of Digital Poster: Wednesday, November 17 noon (Japan standard time)
*Registration will not be extended, so please register within the period. After the deadline and on-site, we could not accept modifying. Please be careful when you prepare the data.

Digital Poster Viewing date and time: From December 3 at 8:30 to December 5 at 17:00, 2021

[Preparing your digital poster data]
1. All digital posters must be prepared in English.
2. Please register your digital poster data in advance.
(Deadline for digital poster data: Wednesday, November 17, noon (JST))
3. All of the registered poster data will be freely viewable only for 46JSID participants available from December 3, 8:30 to January 11, 10:00.

4. **For digital poster presenters, the 3 minutes presentation and discussion time will be scheduled.**
5. All Poster Presenters must disclose COI (Conflict of Interest) on your slide.
6. Please prepare title slide including title, author's name, affiliation.
7. Please prepare your presentation data 1 page poster and 100MB or less.
   (The standard size is 84.1cm in width × 118.9cm in height)
8. Please prepare your presentation data MS PowerPoint*1, *2 or PDF
   *1. Version of MS PowerPoint (Recommended version: Windows 2019)
   Windows: 2016/2019/Office365
   Mac: 2016/2019/Office365
   *2, For Macintosh users
   If you make your presentation data by Keynote, please check your data (character skew etc.) after changing to MS PowerPoint.
9. Please use standard fonts on the OS.
10. Even if you use animation, movie, sound, these contents do not play.
11. Please refrain from writing in note area of your slide.
12. Secretariat office will delete your digital poster data responsibly after the meeting.

11. On-demand service (After the congress)

We prepare On-demand service after the congress as follows.

1. World Showcase of Investigative Dermatology and Digital Poster
   Period: from December 3, 8:30 to January 11, 10:00
2. Tanioku Kihei Memorial Lecture, JSID Award Lecture, JSID Kisaragi Award, JDS Symposium, State-of-the-Art Symposium of Skin Research, JSID-Asia-Oceania-Forum, Plenary Session and Concurrent oral Session (Except Sponsored seminar and 3 minutes presentation and discussion)
   Period: from two days after the session to January 11, 10:00

Business Meetings

Board of Directors Meeting

December 2 (Thu) Online meeting 14:30-16:00

Councilor's Meeting/General Assembly of Employees

December 2 (Thu) Online meeting 16:30-17:30

New Board of Directors Meeting

December 4 (Sat) Online meeting 7:15-7:50

Program Summary

Tanioku Kihei Memorial Lecture

December 5 (Sun) Room A 10:30-11:00

RNA origin of sex biased immunity
Howard Y. Chang（Stanford University School of Medicine）

JSID Award Lecture

December 4 (Sat) Room A 10:45-11:15

Autoimmune mechanisms in dermatology
Naoko Okiyama (Department of Dermatology, Faculty of Medicine, University of Tsukuba)

JSID Kisaragi Award

December 4 (Sat) Room A 10:40-10:45

The role of Ninjurin-1 in pericytes during skin wound healing: effects on capillary maturation
Risa Matsuo (Department of Dermatology, Graduate School of Medicine, Asahikawa Medical University, Japan)

Award Ceremony

December 3 (Fri) Room A 12:55-13:30

1) Young JSID Award
2) JSID's Fellowship SHISEIDO Research Grant
3) Diploma of Dermatological Scientist
4) JSID Honorary Membership
5) KSID/JSID Young Fellow Collegiality Awards
6) ASDR/JSID Exchange Program

State-of-the-Art Symposium of Skin Research

December 3 (Fri) Room A 14:45-16:45

JDS Symposium

December 4 (Sat) Room D 13:40-15:40

JSID-Asia-Oceania-Forum

December 5 (Sun) Room D 13:50-16:10

The 22nd Maruho Research Award Presentations by award winners and award ceremony

December 4 (Sat) Room A 12:30-13:30

Sun Pharma RISING SUN AWARD 2021

December 3 (Fri) Room A 13:30-14:10

▼ Plenary Session

December 3 (Fri)	Room A	8:30-10:00
December 4 (Sat)	Room A	9:10-10:40
December 5 (Sun)	Room A	9:00-10:30

▼ Concurrent Oral Session

December 3 (Fri)	Room A, Room B, Room C	10:15-11:45
December 4 (Sat)	Room A, Room B, Room C	13:40-15:10
December 5 (Sun)	Room A, Room B, Room C	11:05-12:35
		13:50-15:30

▼ 3 minutes presentation and discussion

December 3 (Fri)	Room B, Room C, Room D	14:45-15:45
		15:45-16:45
December 4 (Sat)	Room A, Room B, Room C	15:20-16:20
		16:20-17:20

▼ Morning Seminar

December 4 (Sat)	Room A, Room B, Room C	8:00-9:00
December 5 (Sun)	Room B, Room C	7:50-8:50

▼ Luncheon Seminar

December 3 (Fri)	Room A, Room B, Room C	11:50-12:50
December 4 (Sat)	Room A, Room B, Room C	11:25-12:25
December 5 (Sun)	Room A, Room B, Room C	12:45-13:45

▼ Evening Seminar

December 3 (Fri)	Room A, Room B, Room C	16:50-17:50
December 4 (Sat)	Room A, Room B, Room C	17:25-18:25

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Program

The 46th Annual Meeting of the Japanese Society for Investigative Dermatology

Timetable

1st Day, December 3, Friday, 2021

Room A

8:20-8:30 **Opening**

8:30-10:00
Plenary Session I
【I-1～I-6】
(K. Kabashima, A. C. Lee, O. Dreesen)

10:15-11:45
Innate Immunity, Microbiology, Microbiome-I
【C01-01～C01-07】
(R. Okuyama, S. Nakajima)

11:50-12:50 P.160
Luncheon Seminar 1
(S. Sato, Y. Tada)
T. Kadono, M. Jinnin
NOV division, TOKIWA Pharmaceutical Co., Ltd

12:55-13:30
Award Ceremony

13:30-14:10 P.145
Sun Pharma RISING SUN AWARD 2021
(K. Kabashima, T. Kawamura, M. Fujimoto)
Y. Ogawa, Y. Matsuoka-Nakamura, M. Jinnin,
Sun Pharma Japan Ltd.

14:45-16:45 P.109
State-of-the-Art Symposium of Skin Research
(H. Takahashi, K. Natsuga)
T. Hirai, H. Fujiwara,
T. Matsui, K. Nagao,
E. K. Nishimura

16:50-17:50 P.175
Evening Seminar 1
(M. Ohtsuki)
M. Kamata
Medical Affairs, AMGEN K.K.

Room B

10:15-11:45
Patient Population Research/ Pharmacology and Drug Development
【C02-01～C02-07】
(K. Sugiura, Y. Yamaguchi)

11:50-12:50 P.162
Luncheon Seminar 2
(K. Yamanaka)
T. Yamamoto
Eisai Co., Ltd./AbbVie GK

Young JSID Award — Presenter: K. Kabashima
JSID's Fellowship Shiseido Research Grant — Presenter: R. Fujiwara
Diploma of Dermatological Scientist — Presenter: K. Kabashima
JSID Honorary Membership — Presenter: K. Kabashima
KSID/JSID Young Fellow Collegiality Awards — Presenter: K. Kabashima
ASDR/JSID Exchange Program — Presenter: K. Kabashima

3 minutes presentation and discussion 1-6

14:45-15:45 **1**
JSID's Fellowship Shiseido Research Grant/Tissue Regeneration and Wound Healing/Translational Studies
【O01-01～O01-12】
(Y. Ogawa, S. Motegi)

15:45-16:45 **4**
Auto-Immunity/ Pharmacology and Drug Development
【O04-01～O04-12】
(J. Yamagami, T. Nomura)

16:50-17:50 P.176
Evening Seminar 2
(S. Ikeda)
K. Hayama, K. Sugiura
Nippon Boehringer Ingelheim Co., Ltd.

Room C

10:15-11:45
Translational Studies-I/Skin, Appendages, and Stem Cell Biology
【C03-01～C03-07】
(H. Murota, D. Nanba, O. Kwon)

11:50-12:50 P.163
Luncheon Seminar 3
(E. Toichi)
T. Honda
TAIHO PHARMACEUTICAL CO., LTD./Janssen Pharmaceutical K.K.

14:45-15:45 **2**
Genetic Disease, Gene Regulation and Gene Therapy/Cell-Cell Interactions in the Skin
【O02-01～O02-11】
(T. Nomura, T. Takeichi)

15:45-16:45 **5**
Innate Immunity, Microbiology, Microbiome
【O05-01～O05-12】
(Y. Matsuoka-Nakamura, T. Kobayashi)

16:50-17:50 P.178
Evening Seminar 3
(M. Sugaya)
T. Hamada, A. Morita
Minophagen Pharmaceutical Co., Ltd.

Room D

14:45-15:45 **3**
Photobiology/ Pigmentation and Melanoma
【O03-01～O03-10】
(Y. Kiniwa, S. Fukushima)

15:45-16:45 **6**
Patient-Targeted Research
【O06-01～O06-12】
(T. Nakahara, A. Uchiyama)

Digital Poster

Dec. 3 (Fri.) 8:30 - Jan. 11 (Tue.) 10:00 P.189

Digital Poster Presentation
2020 JSID's Fellowship Shiseido Research Grant
【SE-1～SE-2】
Adaptive Immunity
【P01-01～P01-21】
Auto-Immunity
【P02-01～P02-22】
Carcinogenesis and Cancer
【P03-01～P03-21】
Cell-Cell Interactions in the Skin
【P04-01～P04-03】
Epidermal Structure and Barrier Function
【P05-01～P05-24】
Genetic Disease, Gene Regulation and Gene Therapy
【P06-01～P06-15】
Innate Immunity, Microbiology, Microbiome
【P07-01～P07-22】
Patient Population Research
【P08-01～P08-12】
Patient-Targeted Research
【P09-01～P09-22】
Pharmacology and Drug Development
【P10-01～P10-10】
Photobiology
【P11-01～P11-16】
Pigmentation and Melanoma
【P12-01～P12-17】
Skin, Appendages, and Stem Cell Biology
【P13-01～P13-17】
Tissue Regeneration and Wound Healing
【P14-01～P14-11】
Translational Studies
【P15-01～P15-06】
Late abstract submission
【L-01～L-13】

on-demand service

Dec. 3 (Fri.) 8:30 - Jan. 11 (Tue.) 10:00 P.93

World Showcase of Investigative Dermatology
M. D. Rosenblum
D. Kaplan
B. S. Kim
A. Payne
J. E. Harris
R. J. Tanaka
K. Andrew P.
A. Oro
W. Ju
G. Valentina
M. Ito
M. Haniffa
M. Gilliet
K. Khosrotehrani

■取得可能単位数
2単位

■機構認定専門医制度の単位取得について
単位は聴講記録（ログ）にて確認いたします。セッション開始15分以内～終了までの聴講記録が確認できた場合にのみ、会期終了後１ヶ月以内に単位付与（登録）いたします。

2nd Day, December 4, Saturday, 2021

Room A

8:00-9:00 P.151
Morning Seminar 1
(S. Imafuku)
T. Hashimoto, N. Kambe
Mitsubishi Tanabe Pharma Corporation/ Teikoku Seiyaku Co., Ltd.

9:10-10:40
Plenary Session II
【II-1～II-6】
(M. Fujimoto, Q. Lu, K. Khosrotehrani)

10:40-10:45 P.89
JSID Kisaragi Award
(K. Kabashima) R. Matsuo

10:45-11:15 P.88
JSID Award Lecture
(K. Kabashima) N. Okiyama

11:25-12:25 P.164
Luncheon Seminar 4
(K. Takahashi, N. Kato)
A. Yoshizaki, M. Komine
Sun Pharma Japan Ltd.

12:30-13:30 P.139
The 22nd Maruho Research Award Presentations by award winners and award ceremony
(M. Amagai, S. Sato, K. Kabashima)
M. Nakamura, R. Sakamoto, T. Maeda, T. Matsuda
Maruho Co., Ltd.

13:40-15:10
Auto-Immunity
【C04-01～C04-07】
(Y. Aoyama, H. Ujiie)

15:20-16:20
7
Adaptive Immunity
【O07-01～O07-11】
(R. Watanabe, T. Matsushita)

16:20-17:20
10
Carcinogenesis and Cancer
【O10-01～O10-12】
(J. Asai, T. Namiki)

17:25-18:25 P.180
Evening Seminar 4
(T. Matsushita)
T. Watanabe, Y. Hashimoto
AbbVie GK

Room B

8:00-9:00 P.153
Morning Seminar 2
(M. Amagai)
D. Tsuruta
Japan Blood Products Organization

11:25-12:25 P.166
Luncheon Seminar 5
(C. Nishigori)
K. Yamasaki, T. Mammone
ELC JAPAN K.K.

13:40-15:10
Pigmentation and Melanoma
【C05-01～C05-07】
(A. Otsuka, T. Kadono)

15:20-16:20
8
Skin, Appendages, and Stem Cell Biology
【O08-01～O08-10】
(Y. Oji, M. Kinoshita)

16:20-17:20
11
Patient Population Research/Pigmentation and Melanoma
【O11-01～O11-12】
(A. Yoshizaki, T. Fujimura)

17:25-18:25 P.182
Evening Seminar 5
(Y. Asano, H. Fujita)
R. Watanabe, H. Nakajima
UCB Japan Co. Ltd.

Room C

8:00-9:00 P.154
Morning Seminar 3
(A. Otsuka)
T. Fujimura, Y. Kiniwa
ONO PHARMACEUTICAL CO., LTD.

11:25-12:25 P.168
Luncheon Seminar 6
(S. Motegi, M. Jinnin)
Y. Yamaguchi, T. Honda
Kyowa Kirin Co., Ltd

13:40-15:10
Cell-Cell Interactions in the Skin/Epidermal Structure and Barrier Function-I
【C06-01～C06-07】
(Y. Asano, H. Fujiwara, J. Common)

15:20-16:20
9
Photobiology/ Epidermal Structure and Barrier Function
【O09-01～O09-11】
(T. Yanagi, T. Matsui)

16:20-17:20
12
Epidermal Structure and Barrier Function/ Auto-Immunity
【O12-01～O12-12】
(K. Ishii, Y. Sawada)

17:25-18:25 P.184
Evening Seminar 6
(N. Kanazawa)
A. Asahina, Y. Tada
Pfizer Japan Inc.

Room D

13:40-15:40 P.117
JDS Symposium
(R. Abe)
R. Abe, M. Kishibe, C. Hsu, S. Shao, A. V. Usandizaga, T. Nomura, H. Habernickel

3 minutes presentation and discussion 7-12

Digital Poster

Dec. 3 (Fri.) 8:30 - P.189
Jan. 11 (Tue.) 10:00

Digital Poster Presentation
2020 JSID's Fellowship Shiseido Research Grant
【SE-1～SE-2】
Adaptive Immunity
【P01-01～P01-21】
Auto-Immunity
【P02-01～P02-22】
Carcinogenesis and Cancer
【P03-01～P03-21】
Cell-Cell Interactions in the Skin
【P04-01～P04-03】
Epidermal Structure and Barrier Function
【P05-01～P05-24】
Genetic Disease, Gene Regulation and Gene Therapy
【P06-01～P06-15】
Innate Immunity, Microbiology, Microbiome
【P07-01～P07-22】
Patient Population Research
【P08-01～P08-12】
Patient-Targeted Research
【P09-01～P09-22】
Pharmacology and Drug Development
【P10-01～P10-10】
Photobiology
【P11-01～P11-16】
Pigmentation and Melanoma
【P12-01～P12-17】
Skin, Appendages, and Stem Cell Biology
【P13-01～P13-17】
Tissue Regeneration and Wound Healing
【P14-01～P14-11】
Translational Studies
【P15-01～P15-06】
Late abstract submission
【L-01～L-13】

on-demand service

Dec. 3 (Fri.) 8:30 - P.93
Jan. 11 (Tue.) 10:00

World Showcase of Investigative Dermatology
M. D. Rosenblum
D. Kaplan
B. S. Kim
A. Payne
J. E. Harris
R. J. Tanaka
K. Andrew P.
A. Oro
W. Ju
G. Valentina
M. Ito
M. Haniffa
M. Gilliet
K. Khosrotehrani

Chair: ( )

3rd Day, December 5, Sunday, 2021

Room A

7:50-8:50 P.156
Morning Seminar 4
(M. Akiyama, M. Fujimoto)
G. Egawa, M. Hide
Maruho Co., Ltd.

9:00-10:30
Plenary Session III
【III-1～III-6】
(M. Ohyama, S. J. Lin, J. H. Cung)

10:30-11:00 P.84
Tanioku Kihei Memorial Lecture
(M. Amagai) H. Y. Chang

11:05-12:35
Epidermal Structure and Barrier Function-II/Tissue Regeneration and Wound Healing
【C07-01～C07-07】
(N. Katoh, M. Jinnin, E. H. Choi)

12:45-13:45 P.170
Luncheon Seminar 7
(M. Sugaya, H. Ujiie)
K. Kabashima, Y. Ishiuji
Eli Lilly Japan K. K.

13:50-15:30
Adaptive Immunity
【C10-01～C10-08】
(T. Kawamura, S. Yamazaki)

Room B

7:50-8:50 P.158
Morning Seminar 5
(K. Kabashima)
A. Fukunaga, B. S. Kim
Sanofi K.K.

11:05-12:20
Innate Immunity, Microbiology, Microbiome-II/Genetic Disease, Gene Regulation and Gene Therapy
【C08-01～C08-06】
(M. Komine, Y. Okada)

12:45-13:45 P.172
Luncheon Seminar 8
(N. Katoh)
G. Tsuji
Sanofi K.K.

13:50-15:30
Carcinogenesis and Cancer
【C11-01～C11-08】
(M. Sugaya, M. Kono)

Room C

11:05-12:35
Translational Studies-II/ Photobiology
【C09-01～C09-07】
(T. Honda, N. Okiyama)

12:45-13:45 P.173
Luncheon Seminar 9
(K. Igawa, T. Yamamoto)
T. Fujiyama, M. Kamata
Novartis Pharma K.K. Medical Division/Maruho Co., Ltd. Medical Affairs Dept.

13:50-15:30
Patient-Targeted Research
【C12-01～C12-08】
(Y. Shimomura, S. Shinkuma)

Room D

13:50-16:10 P.127
JSID-Asia-Oceania-Forum
(H. Ujiie, R. Watanabe)
S. Raghavan, S. Kumari, C. Chen, C. Li, J. H. Kim

Digital Poster

Dec. 3 (Fri.) 8:30 - Jan. 11 (Tue.) 10:00 P.189

Digital Poster Presentation
2020 JSID's Fellowship Shiseido Research Grant
【SE-1～SE-2】
Adaptive Immunity
【P01-01～P01-21】
Auto-Immunity
【P02-01～P02-22】
Carcinogenesis and Cancer
【P03-01～P03-21】
Cell-Cell Interactions in the Skin
【P04-01～P04-03】
Epidermal Structure and Barrier Function
【P05-01～P05-24】
Genetic Disease, Gene Regulation and Gene Therapy
【P06-01～P06-15】
Innate Immunity, Microbiology, Microbiome
【P07-01～P07-22】
Patient Population Research
【P08-01～P08-12】
Patient-Targeted Research
【P09-01～P09-22】
Pharmacology and Drug Development
【P10-01～P10-10】
Photobiology
【P11-01～P11-16】
Pigmentation and Melanoma
【P12-01～P12-17】
Skin, Appendages, and Stem Cell Biology
【P13-01～P13-17】
Tissue Regeneration and Wound Healing
【P14-01～P14-11】
Translational Studies
【P15-01～P15-06】
Late abstract submission
【L-01～L-13】

on-demand service

Dec. 3 (Fri.) 8:30 - Jan. 11 (Tue.) 10:00 P.93

World Showcase of Investigative Dermatology
M. D. Rosenblum
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A. Oro
W. Ju
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M. Ito
M. Haniffa
M. Gilliet
K. Khosrotehrani

December 3, 2021, Room A

Opening

8:20-8:30

Plenary Session I

8:30-10:00 Chairs: Kenji Kabashima, Abel Chih-Hung Lee, Oliver Dreesen

I-1 [P06-01] **CRISPR/Cas9 targeting an intronic region for retrieving Col17 expression in junctional epidermolysis bullosa model mice**

○ Hong Ha Nguyen[1], Satoru Shinkuma[1,2,3], Ryota Hayashi[1], Shota Takashima[3], Masashi Mori[4], Masahito Ikawa[4], Hiroshi Shimizu[3], Riichiro Abe[1]

[1]Division of Dermatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [2]Department of Dermatology, Nara University, Nara, Japan, [3]Department of Dermatology, Hokkaido University, Sapporo, Japan, [4]Department of Experimental Genome Research, Genome Information Research Center, Osaka University, Osaka, Japan

I-2 [P07-01] **Migration and local adaptation of integrinβ7-positive mast cell progenitors in murine allergic skin**

○ Yuki H Keith[1], Tetsuya Honda[2], Sachiko Ono[1], Bernett Lee[3], Satoshi Nakamizo[1], Sho Hanakawa[3], Yoshihiro Ishida[1], Kenji Kabashima[1,3]

[1]Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan, [2]Department of Dermatology, Hamamatsu University School of Medicine, Hamamatsu, Japan, [3]Singapore Immunology Network (SIgN) and Skin Research Institute of Singapore (SRIS), Agency for Science, Technology and Research (A*STAR), Biopolis, Singapore

I-3 [P01-02] **AIM2 regulates anti-tumor immunity and serves as a therapeutic target for melanoma immunotherapy**

○ Keitaro Fukuda[1,2], Ken Okamura[2], Rebecca L. Riding[2], Xueli Fan[2], Sean M. McCauley[3], Jeremy Luban[3,4], Takeru Funakoshi[1], Tomonori Yaguchi[5], Yutaka Kawakami[5], Anastasia Khvorova[6,7], Katherine A. Fitzgerald[8], John E. Harris[2]

[1]Department of Dermatology, Keio University School of Medicine, Tokyo, Japan, [2]Department of Dermatology, University of Massachusetts Medical School, Worcester, MA, [3]Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, MA, [4]Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, MA, [5]Division of Cellular Signaling, Institute for Advanced Medical Research, Keio University School of Medicine, Tokyo, Japan, [6]RNA Therapeutics Institute, University of Massachusetts Medical School, Worcester, MA, [7]Department of Molecular Medicine, University of Massachusetts Medical School, Worcester, MA, [8]Department of Infectious Diseases and Immunology, University of Massachusetts Medical School, Worcester, MA.

I-4 [P07-02] **Type I IFN derived from inflammatory monocytes controls type 2 inflammation by suppressing basophil proliferation in atopic dermatitis**

○ Fumi Miyagawa, Hideo Asada

Department of Dermatology, Nara Medical University School of Medicine, Kashihara, Japan

I-5 [P02-02] **Abnormally activated B cells with TLR9 up-regulation in Fli1-depleted mice: a possible predisposing condition for systemic sclerosis**

○ Kentaro Awaji[1], Takuya Miyagawa[1], Takashi Yamashita[1], Yuki Fukui[1], Jun Omatsu[1], Satoshi Toyama[1], Tetsuya Ikawa[1], Yuta Norimatsu[1], Yusuke Watanabe[1], Ayumi Yoshizaki[1], Maria Trojanowska[2], Shinichi Sato[1], Yoshihide Asano[1]

[1]The Department of Dermatology, University of Tokyo, Tokyo, Japan, [2]Arthritis Center, Boston University Medical Center, Boston, USA

I-6 [P11-01] **Skin regulatory T cells producing proenkephalin expand upon ultraviolet B exposure without ST2-IL33 axis and promote keratinocyte outgrowth**

○ Sayuri Yamazaki[1], Hiroaki Shime[1], Mizuyu Odanaka[1], Makoto Tsuiji[2], Takuma Matoba[1,3], Masaki Imai[1], Yoshiaki Yasumizu[4], Ryuta Uraki[1], Kiyoshi Minohara[1,3], Maiko Watanabe[1], Anthony Bonito[5], Hidehiro Fukuyama[6], Naganari Ohkura[4,7], Shimon Sakaguchi[4], Akimichi Morita[8]

[1]Department of Immunology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan, [2]Department of Microbiology, Hoshi University School of Pharmacy and Pharmaceutical Sciences, Shinagawa-ku, Japan, [3]Department of Oto-rhino-laryngology and Head-and-neck-surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan, [4]Department of Experimental Immunology, World Premier International Research Center Initiative, Immunology Frontier Research Center, Osaka University, Osaka, Japan, [5]Immunoassay Research & Development, Laboratory Diagnostics, Siemens Healthineers, Tarrytown, NY, USA, [6]Laboratory for Lymphocyte Differentiation, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan, [7]Immunopharmaceutical Development Unit, Center of Medical Innovation Research, Graduate School of Medicine, Osaka University, Osaka, Japan, [8]Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Concurrent Oral Session 1
(Innate Immunity, Microbiology, Microbiome-I)

10:15-11:45 Chairs: Ryuhei Okuyama, Saeko Nakajima

C01-01 [P07-03] **CCL2-CCR2 signaling in the skin drives surfactant-induced irritant contact dermatitis via IL-1β-mediated neutrophil accumulation**

○ Rintaro Shibuya[1], Yoshihiro Ishida[1], Sho Hanakawa[2], Tatsuki R. Kataoka[3], Akihiko Kitoh[2], Kenji Kabashima[1,2]

[1]Department of Dermatology, Kyoto University Graduate School of Medicine, [2]Singapore Immunology Network and Skin Research Institute of Singapore, Agency for Science, Technology and Research (A*STAR), Singapore, [3]Department of Molecular Diagnostic Pathology, Iwate Medical University

C01-02 [P07-04] **IκBζ-deficient epidermis mediates systemic autoimmune inflammation via skin dysbiosis**

○ Hitoshi Terui[1], Moyuka Wada-Irimada[1], Mayuko Onodera-Amagai[1], Naokazu Hatchome[1], Masato Mizuashi[1], Riu Yamashita[2], Setsuya Aiba[1], Kenshi Yamasaki[1]

[1]Department of Dermatology, Tohoku University Graduate School of Medicine, Miyagi, Japan, [2]Division of Translational Informatics, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Chiba, Japan

C01-03 [P07-05] **T-cell receptor signaling pathways that regulate functional reprogramming of γδ T cells in the perinatal epidermis**

○ Atsuko Ibusuki[1], Kazuhiro Kawai[1,2], Takuro Kanekura[1]

[1]Department of Dermatology, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan, [2]Department of Dermatology, Kido Hospital, Niigata, Japan

C01-04 [P07-06] **Proteomics analysis of bacterial and fungal composition in skin and serum extracellular vesicles**

○ Toru Kawai[1], Ryota Hayashi[1], Akito Hasegawa[1], Akari Sakai[1], Osamu Ansai[1], Koichi Tomii[1], Tomoki Nishiguchi[1], Jun Adachi[2,3], Takeshi Tomonaga[2,3], Riichiro Abe[1]

[1]Division of Dermatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [2]Laboratory of Proteome Research, National Institute of Biomedical Innovation, Health and Nutrition, [3]Laboratory of Proteomics for Drug Discovery, Center for Drug Design Research, National Institute of Biomedical Innovation, Health and Nutrition

C01-05 [P07-07] **TREM2/APOE-double positive macrophages as possible pathogenic cells in sarcoidosis**

○ Satoshi Nakamizo, Yoshihiro Ishida, Gyohei Egawa, Kenji Kabashima

Department of Dermatology Kyoto University Graduate School of Medicine, Kyoto, Japan

C01-06 [P07-09] **Purinergic molecules in murine bone marrow-derived mast cells**

○ Riko Asakawa, Youichi Ogawa, Shinji Shimada, Tatsuyoshi Kawamura

The Department of Dermatology, Faculty of Medicine, University of Yamanashi, Yamanashi, Japan

C01-07 [P07-10] **Granzyme K cleaves protease-activated receptor-2 and induces itch**

○ Sho Hiroyasu[1,2,3], Matthew R. Zeglinski[2,3], Hongyan Zhao[2,3], Aoi Hiroyasu[1], Daisuke Tsuruta[1], David J. Granville[2,3]

[1]The Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan, [2]International Collaboration On Repair Discoveries (ICORD) Centre, Vancouver, BC, Canada, [3]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada

Luncheon Seminar 1
"Lessons in Dermatology from Experts"

11:50-12:50 Chairs: Shinichi Sato, Yayoi Tada

LS1-1 **Beta7 integrin and cutaneous disorders**

○ Takafumi Kadono

Department of Dermatology, St. Marianna University School of Medicine

LS1-2 **Extracellular vesicles in skin aging**

○ Masatoshi Jinnin

Department of Dermatology, Wakayama Medical University Graduate School of Medicine, Wakayama, Japan

Co-sponsored by NOV division, TOKIWA Pharmaceutical Co., Ltd

Award Ceremony

12:55-13:30

Young JSID Award

Presenter: Kenji Kabashima

Satoshi Nakamizo, Department of Dermatology, Kyoto University Graduate School of Medicine
Chisa Nakashima, Department of Dermatology, Kindai University Hospital
Takashi Sakai, Department of Dermatology, Faculty of Medicine, Oita University

JSID's Fellowship Shiseido Research Grant

Presenter: Rumiko Fujiwara

Protease functions in itch associated with pemphigoid diseases

○Sho Hiroyasu
Department of Dermatology, Osaka City University Graduate School of Medicine

Understanding the mechanism of age-associated decline of skin regenerative capacity through epidermal stem cells

○Daisuke Nanba
Department of Stem Cell Biology, Medical Research Institute, Tokyo Medical and Dental University

Diploma of Dermatological Scientist

Presenter: Kenji Kabashima

Pawit Phadungsaksawasdi, Hamamatsu University School of Medicine

JSID Honorary Membership

Presenter: Kenji Kabashima

KSID/JSID Young Fellow Collegiality Awards

Joonho Shim, Samsung Medical Center, Sungkyunkwan University
Ji Su Lee, Seoul National University Hospital

ASDR/JSID Exchange Program

Ali Azimi, The University of Sydney
Mitchell S. Stark, The University of Queensland

Sun Pharma RISING SUN AWARD 2021

13:30-14:10

Chairs: Kenji Kabashima, Tatsuyoshi Kawamura, Manabu Fujimoto

SRA1 **Neutrophils initiate and exacerbate Stevens-Johnson syndrome and toxic epidermal necrolysis**

○Youichi Ogawa
Department of Dermatology, University of Yamanashi, Yamanashi, Japan

SRA2 **Role of host-microbe interactions in the pathogenesis of inflammatory skin diseases**

○Yumi Matsuoka-Nakamura
Cutaneous Immunology, Immunology Frontier Research Center, Osaka University, Osaka, Japan

SRA3 **Genetic and epigenetic research of skin diseases**

○Masatoshi Jinnin
Department of Dermatology, Wakayama Medical University Graduate School of Medicine, Wakayama, Japan

Co-sponsored by Sun Pharma Japan Ltd.

State-of-the-Art Symposium of Skin Research

14:45-16:45 Chairs: Hayato Takahashi, Ken Natsuga

SAS1 **Interclonal competition for active TGFb preferentially enrich antigen-specific tissue resident memory T cells in the epidermal niche**

○Toshiro Hirai[1,2]

[1]BIKEN Innovative Vaccine Research Alliance Laboratories, Institute for Open and Transdisciplinary Research Initiatives/Research Institute for Microbial Diseases, Osaka University, [2]Departments of Dermatology, University of Pittsburgh

SAS2 **Tracing the origin of hair follicle stem cells**

○Hironobu Fujiwara

RIKEN Center for Biosystems Dynamics Research, Kobe, Japan

SAS3 **A unique mode of functional keratinocyte death, *corneoptosis* requires intracellular acidification**

○Takeshi Matsui[1,2]

[1]School of Bioscience and Biotechnology, Tokyo University of Technology, Tokyo, Japan, [2]RIKEN Center for Integrative Medical Sciences

SAS4 **Dysbiosis leads to inflammatory destruction of the hair follicles mediated by innate lymphoid cells**

○Keisuke Nagao

Dermatology Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health

SAS5 **Stem cell-centric mechanisms of skin aging**

○Emi K. Nishimura

Institute of Medical Science, University of Tokyo, Tokyo, Japan

Evening Seminar 1

16:50-17:50 Chair: Mamitaro Ohtsuki

ES1 **An update on the evidence of apremilast for psoriasis from research to practice**

○Masahiro Kamata

Department of Dermatology, Teikyo University School of Medicine, Tokyo, Japan

Co-sponsored by Medical Affairs, AMGEN K.K.

December 3, 2021, Room B

Concurrent Oral Session 2
(Patient Population Research/Pharmacology and Drug Development)

10:15-11:45 Chairs: Kazumitsu Sugiura, Yukie Yamaguchi

C02-01 [P08-02] **Plasma metabolome-wide analysis in Japanese identifies potential biomarkers of psoriasis and clinical subtypes**

○ Yukinori Okada[1,2], Toshihiro Kishikawa[1,3], Noriko Arase[4], Shigeyoshi Tsuji[5], Yuichi Maeda[6,7], Takuro Nii[6,7], Jun Hirata[1], Ken Suzuki[1], Kenichi Yamamoto[1,8], Shiro Ohshima[5], Hidenori Inohara[3], Atsushi Kumanogoh[2,5], Manabu Fujimoto[2,4]

[1]Department of Statistical Genetics, Osaka University Graduate School of Medicine, Suita, Japan, [2]Immunology Frontier Research Center (WPI-IFReC), Osaka University, Suita, Japan, [3]Department of Otorhinolaryngology-Head and Neck Surgery, Osaka University Graduate School of Medicine, Suita, Japan, [4]Department of Dermatology, Osaka University Graduate School of Medicine, Suita, Japan, [5]NHO Osaka Minami Medical Center, Kawachinagano, Osaka, Japan, [6]Department of Respiratory Medicine and Clinical Immunology, Osaka University Graduate School of Medicine, Suita, Japan, [7]Department of Immune Regulation, Osaka University Graduate School of Medicine, Suita, Japan, [8]Department of Pediatrics, Osaka University Graduate School of Medicine, Suita, Japan

C02-02 [P08-03] **Prevalence, comorbidities, and treatment patterns of Japanese patients with alopecia areata: a descriptive study using JMDC claims database**

○ Eduardo Kawasaki[1], Tomohiro Hirose[1], Manabu Ohyama[2]

[1]Medical Affairs, Pfizer Japan, [2]Department of Dermatology, Kyorin University Faculty of Medicine

C02-03 [P08-05] **Prevalence of malignancies in Japanese psoriasis patients and selected treatments in the West Japan Psoriasis Registry**

○ Takuya Miyagi[1,3], Kenzo Takahashi[1,3], Noriko Tsuruta[2,3], Shinichi Imafuku[2,3]

[1]Department of Dermatology, University of the Ryukyus, Graduate school of medicine, Okinawa, Japan, [2]Fukuoka University, [3]Western Japan Inflammatory Disease Research Group

C02-04 [P10-02] **Vitamins and their derivatives synergistically promote hair shaft elongation *ex vivo* via PlGF/VEGFR-1 signaling activation**

○ Liuying Hu[1], Shun Kimura[1], Sayo Kashiwagi[1], Kyoko Takagi[1], Takashi Shimizu[1], Tsuyoshi Ishii[1], Manabu Ohyama[2]

[1]Basic Research Development Division, ROHTO Pharmaceutical Co., LTD., Kyoto, Japan, [2]Department of Dermatology, Kyorin University Faculty of Medicine, Tokyo, Japan

C02-05 [P10-03] **Formyl peptide receptor 1 triggers cell death signals in keratinocyte as SJS/TEN model**

○ Tomoki Nishiguchi, Akito Hasegawa, Riichiro Abe

Department of dermatology, Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Japan

C02-06 [P10-04] **Konjac-ceramide (kCer) induces semaphorin 3A production in normal human epidermal keratinocytes**

○ Mirei Fujita[1], Yayoi Kamata[1], Mitsutoshi Tominaga[1], Seigo Usuki[2], Katsuyuki Mukai[3], Nobuaki Takahashi[1], Hideoki Ogawa[1], Yasuyuki Igarashi[2], Kenji Takamori[1,4]

[1]Juntendo Itch Research Center (JIRC), Institute for Environmental and Gender-Specific Medicine, Juntendo University Graduate School of Medicine, Chiba, Japan, [2]Lipid Biofunction Section, Faculty of Advanced Life Science, Hokkaido University, [3]Daicel Corporation, [4]Department of Dermatology, Juntendo University Urayasu Hospital

C02-07 [P10-05] **A calpain inhibitor ALLN attenuates bleomycin-induced skin fibrosis in a mice model**

○ Hiroshi Kasamatsu[1], Takenao Chino[1], Takumi Hasegawa[1], Natsuko Utsunomiya[1], Akira Utsunomiya[1], Noritaka Oyama[1], Masami Yamada[2], Minoru Hasegawa[1]

[1]Department of Dermatology, University of Fukui, Fukui, Japan, [2]Department of Cell Biology and Biochemistry, University of Fukui, Fukui, Japan

Luncheon Seminar 2

11:50-12:50 Chair: Keiichi Yamanaka

LS2 **Recent advances in the pathogenesis and therapy of pyoderma gangrenosum and hidradenitis suppurativa**

○ Toshiyuki Yamamoto

The Department of Dermatology, Fukushima Medical University, Fukushima, Japan

Co-sponsored by Eisai Co., Ltd./AbbVie GK

3 minutes presentation and discussion 1 (JSID's Fellowship Shiseido Research Grant/Tissue Regeneration and Wound Healing/Translational Studies)

14:45-15:45 Chairs: Youichi Ogawa, Sei-Ichiro Motegi

O01-01 [SE-1] **Observation of tight junction formation using cultured keratinocytes**

○ Hiroaki Iwata

Department of Dermatology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

O01-02 [SE-2] **Dynamics of epigenetic environment in skin inflammatory diseases**

○ Sayaka Shibata

Department of Dermatology, University of Tokyo Graduate School of Medicine

O01-03 [P14-06] **Calcitriol, the active form of vitamin D, regulates epidermal tight junction barrier function in diabetes**

○ Juan V. Trujillo[1], Le Thanh Hai Nguyen[1,2], Yoshie Umehara[1], Hainan Yue[1,2], Lisa Ikutama[1,2], Miho Takahashi[1,2], Ge Peng[1,2], Hideoki Ogawa[1], Shigaku Ikeda[2], Ko Okumura[1], Francois Niyonsaba[1,3]

[1]Atopy (Allergy) Research Center, Juntendo University, Tokyo, Japan, [2]Department of dermatology and Allergology, Juntendo University, Tokyo, Japan, [3]Faculty of International Liberal Arts, Juntendo University, Tokyo, Japan

O01-04 [P14-07] **Trehalose-induced senescence-associated secretory phenotype accelerates organotypic skin culture development**

○ Jun Muto[1], Shinji Fukuda[2], Kenji Watanabe[3], Xiuju Dai[1], Teruko Tsuda[1], Hideki Mori[1], Ken Shiraishi[1], Masamoto Murakami[1], Shigeki Higashiyama[4,5], Yoichi Mizukami[3], Koji Sayama[1]

[1]Department of Dermatology, Ehime University Graduate School of Medicine, Toon, Japan, [2]Department of Biochemistry, School of Dentistry, Aichi Gakuin University, Nagoya, Japan, [3]Institute of Gene Research, Yamaguchi University Science Research Center, Yamaguchi, Japan, [4]Division of Cell Growth and Tumor Regulation, Proteo-Science Center, Ehime University, Toon, Japan, [5]Department of Molecular and Cellular Biology, Osaka International Cancer Institute, Osaka, Japan

O01-05 [P14-08] **Antioxidant protein Peroxiredoxin 4 uniquely improved aging-related delayed wound healing in mice**

○ Reimon Yamaguchi[1,2], Xin Guo[2], Jianbo Zheng[2], Jing Zhang[2], Jia Han[2], Akihiro Shioya[2], Hidetaka Uramoto[3], Takashi Mochizuki[1], Akira Shimizu[1], Sohsuke Yamada[2]

[1]The Department of Dermatology, Kanazawa Medical University, Ishikawa, Japan, [2]The Department of Pathology and Laboratory Medicine, Kanazawa Medical University, Ishikawa, Japan, [3]The Department of Thoracic Surgery, Kanazawa Medical University, Ishikawa, Japan

O01-06 [P14-09] **AMP-IBP5, an antimicrobial peptide derived from insulin-like growth factor-binding protein 5, promotes diabetic wound healing**

○ Hainan Yue[1,2], Yoshie Umehara[2], Juan Valentin Trujillo-Paez[2], Ge Peng[1,2], Hai Le Thanh Nguyen[1,2], Miho Takahashi[1,2], Risa Ikutama[1,2], Ko Okumura[2], Hideoki Ogawa[2], Shigaku Ikeda[1,2], Francois Niyonsaba[2,3]

[1]Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine, Tokyo, Japan, [2]Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine, Tokyo, Japan, [3]Faculty of International Liberal Arts, Juntendo University Graduate School of Medicine, Tokyo, Japan

O01-07 [P14-10] **Determination of host defense peptide inducers for their therapeutic use in diabetic foot ulcers**

○ Alan Santos[1], Bruno Rivas[1,2]

[1]Posgrado de Ciencias Quimicas, Universidad Autonoma de San Luis Potosi, San Luis Potosi, Mexico, [2]Unidad de Investigacion Biomedica de Zacatecas, Instituto Mexicano del Seguro Social, Zacatecas, Mexico

O01-08 [P14-11] **Effects of antimicrobial peptide human β-defensins on the expression of angiogenin in human dermal fibroblasts**

○ Yoshie Umehara[1], Miho Takahashi[1,2], Hainan Yue[1], Juan Valentin Trujillo-Paez[1], Ge Peng[1], Le Thanh Hai Nguyen[1], Risa Ikutama[1,2], Ko Okumura[1], Hideoki Ogawa[2], François Niyonsaba[1,3]

[1]Atopy (Allergy) Research Center, Juntendo University School of Medicine, Tokyo, Japan, [2]Department of Dermatology and Allergology, Juntendo University School of Medicine, Tokyo, Japan, [3]Faculty of International Liberal Arts, Juntendo University, Tokyo, Japan

O01-09 [P15-01] **Spinal cholecystokinin 2 receptor is involved in induction of alloknesis**

○ Mitsutoshi Tominaga[1], Kotaro Honda[1], Fumiya Kusube[1], Eriko Komiya[1], Masafumi Yokota[1], Masaru Kurosawa[1], Nobuaki Takahashi[1], Sumika Toyama[1], Yayoi Kamata[1], Mirei Fujita[1], Qiao Feng Zhao[1], Yasushi Suga[2], Hideoki Ogawa[1], Kenji Takamori[1,2]

[1]Juntendo Itch Research Center (JIRC), Institute for Environmental and Gender Specific Medicine, Juntendo University Graduate School of Medicine, Chiba, Japan, [2]Department of Dermatology, Juntendo University Urayasu Hospital, Chiba, Japan

O01-10 [P15-04] **The effectivity of metformin solution as a melanogeneis inhibitor: A chromameter analysis on human**

○ Ivan Kurniadi[1], Asnawi Madjid[1], Farida Tabri[1], Arifin Seweng[2], Husaini Umar[3], Firdaus Hamid[4]

[1]Department of Dermatology and Venereology, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia, [2]Faculty of Public Health, Hasanuddin University, Makassar, South Sulawesi, Indonesia, [3]Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia, [4]Department of Clinical Microbiology, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia

O01-11 [P15-05] **Predicting regional Eczema Area and Severity Index from the images of atopic dermatitis using deep convolutional networks**

○ Yutaka Kawashima[1], Daiki Ito[1], Hiroto Horikawa[2], Ayano Nomura[2], Koichi Ashizaki[2,3], Hiroshi Kawasaki[2,4], Masayuki Amagai[2], Yoshimitsu Aoki[1]

[1]Department of Engineering, Keio University School, [2]Department of Dermatology, Keio University School of Medicine, [3]Advanced Data Science Project, Information R&D and Strategy Headqurters, RIKEN, [4]Laboratory for Developmental Genetics, RIKEN Center for Integrative Medical Sciences

O01-12 [P15-06] **Serum biomarkers correlate with disease response in Moderate to Severe Atopic Dermatitis patients treated with baricitinib**

○ Takeshi Nakahara[1], Jonathan_T. Sims[2], Robert Bissonnette[3], Stephanie Colvin[2], Jonathan Janes[2], Venkatesh Krishnan[2], Jason_R. Chan[2], Ferda Cevikbas[2]

[1]Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, [2]Eli Lilly and Company, [3]Innovaderm

3 minutes presentation and discussion 4 (Auto-Immunity/Pharmacology and Drug Development)

15:45-16:45 Chairs: Jun Yamagami, Takashi Nomura

O04-01 [P02-16] **Optimization of ELISAs for IgA antibodies in autoimmune bullous skin diseases**

○ Norito Ishii[1], Kwesi Teye[1], Hiroshi Koga[1], Takashi Hashimoto[2], Takekuni Nakama[1]

[1]Department of Dermatology, Kurume University School of Medicine, and Kurume University Institute of Cutaneous Cell Biology, Kurume, Japan, [2]Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan

O04-02 [P02-17] **Relationship between treatment responsiveness and immune checkpoints in Halo nevus**

○ Shinji Kano, Motoki Nakamura, Maki Yoshimitsu, Tetsuya Magara, Yuka Nojiri, Akihiro Matsubara, Hiroshi Kato, Akimichi Morita

Department of Geriatric and Environmental Dermatology, Nagoya City University

O04-03 [P02-18] **The presence of multiple epitopes within BP180 molecule in a case of dipeptidyl peptidase-4 inhibitor-related bullous pemphigoid**

○ Rikuma Kitao[1], Takeshi Fukumoto[1], Takashi Hashimoto[2], Kentaro Izumi[3], Haruki Jimbo[1], Chikako Nishigori[1,4]

[1]Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, Hyogo, Japan, [2]Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan, [3]Department of Dermatology, Hokkaido University Graduate School of Medicine, Hokkaido, Japan, [4]Department of iPS cell applications, Kobe University Graduate School of Medicine, Hyogo, Japan

O04-04 [P02-19] **Cautions for the discrepancy between CLEIA and ELISA and the presence of non-pathogenic antibodies are needed in pemphigus management**

○ Ai Yoshioka[1], Takeshi Fukumoto[1], Marie Ohata[2], Yumi Aoyama[3], Koji Kamiya[4], Takashi Hashimoto[5], Chikako Nishigori[1,6]

[1]Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, Hyogo, Japan, [2]Department of Dermatology, Kobe Ekisaikai Hospital, Hyogo, Japan, [3]Department of Dermatology, Kawasaki Medical School, Okayama, Japan, [4]Department of Dermatology, Jichi Medical University, Tochigi, Japan, [5]Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan, [6]Department of iPS Cell Applications, Kobe University Graduate School of Medicine, Hyogo, Japan

O04-05 [P02-20] **Effects of decanoic acid on imiquimod-induced psoriasis-like dermatitis in mice**

○ Kinuko Irie, Shohei Igari, Toshiyuki Yamamoto

Department of Dermatology, Fukushima Medical Univercity School of Medicine

O04-06 [P02-21] **Severe skin inflammation leads to salivary gland atrophy and dysfunction**

○ Yoshiaki Matsushima[1], Kento Mizutani[1], Shohei Iida[1], Masako Ichishi[2], Takehisa Nakanishi[1], Karin Okada[1], Ai Umaoka[1], Makoto Kondo[1], Koji Habe[1], Masatoshi Watanabe[2], Keiichi Yamanaka[1]

[1]Department of Dermatology, Mie University, Graduate School of Medicine, Mie, Japan, [2]Oncologic Pathology, Mie University, Graduate School of Medicine, Tsu, Mie, Japan

O04-07 [P02-22] **A new murine model of human eosinophilic fasciitis: role of IL-5 and IL-17**

○ Takashi Ito, Toshiyuki Yamamoto

Fukushima Medical University School of Medicine Department of Dermatology

O04-08 [P10-06] **Spesolimab improves patient-reported outcomes (PROs) in patients with generalized pustular psoriasis (GPP) in the Effisayil 1 study**

○ Akimichi Morita[1], Alexander A Navarini[2], Manuelle Viguier[3], Tsen-Fang Tsai[4], Kristian Reich[5], Eva Kleine[6], Mogana Sivalingam[6], Christian Thoma[7], Mark G Lebwohl[8]

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O04-09 [P10-07] **Induction of Type XVII collagen decreases cellular senescence in Human hTert/KER-CT keratinocytes**

○ Tuba M. Ansary, Koji Kamiya, Md. Razib Hossain, Mayumi Komine, Mamitaro Ohtsuki

Department of Dermatology, Jichi Medical University, Tochigi, Japan

O04-10 [P10-08] **An antimicrobial peptide derived from insulin-like growth factor-binding protein 5 alleviates imiquimod-induced psoriatic skin inflammation**

○ Saori Yoshiba[1], Ge Peng[1,2], Saya Tsukamoto[1,2], Ko Okumura[1], Hideoki Ogawa[1], Shigaku Ikeda[2], Francois Niyonsaba[1,3]

[1]Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine, Tokyo, Japan, [2]Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine, Tokyo, Japan, [3]Faculty of International Liberal Arts, Juntendo University

O04-11 [P10-09] **Difamilast, a novel PDE4B inhibitor, topically improves chronic idiopathic dermatitis induced by persisting psychological stress in mice**

○ Hidetaka Hiyama, Naoya Arichika, Masafumi Shibamori, Hiroki Urashima

Biology and Translational Research Unit, Department of Medical Innovations, New Drug Research Division, Otsuka Pharmaceutical Co., Ltd. Tokushima, Japan

O04-12 [P10-10] **Investigation of *in-vitro* antibacterial activity of selected plant extracts and its combination with a view of developing a face wash**

○ N. A. Sanjeewani[1], H. M. G. M. Dissanayake[1], U. H. W. De Silva[1], W. D. Ratnasooriya[2], P. B. V. Navaratne[3]

[1]Department of Pharmacy, General Sir John Kotelawala Defence University, Sri Lanka, [2]Department of Basic Sciences, General Sir John Kotelawala Defence University, Sri Lanka, [3]Faculty of Medicine, General Sir John Kotelawala Defence University, Sri Lanka

Evening Seminar 2
"New findings in molecular mechanism and patient burden in Neutrophilic inflammatory skin diseases"

16:50-17:50 Chair: Shigaku Ikeda

ES2-1 **Disease burden of neutrophilic dermatoses: Patients' quality of life in generalized pustular psoriasis and hidradenitis suppurativa**

○ Koremasa Hayama, Hideki Fujita

Department of Dermatolgy, Nihon University School of Medicine

ES2-2 **Dynamics of inflammatory cytokines in generalized pustular psoriasis**

○ Kazumitsu Sugiura

Department of Dermatology, Fujita Health University School of Medicine

Co-sponsored by Nippon Boehringer Ingelheim Co., Ltd.

December 3, 2021, Room C

Concurrent Oral Session 3
(Translational Studies-I/Skin, Appendages, and Stem Cell Biology)

10:15-11:45 Chairs: Hiroyuki Murota, Daisuke Nanba, Ohsang Kwon

C03-01 [P15-02] **Early-onset female pattern hair loss: a case-control study for analyzing clinical features and genetic variants**

○Jungyoon Ohn[1,2], Ho-Young Son[3,4], Kyu Han Kim[1,2], Ohsang Kwon[1,2,4], Jong-Il Kim[3,4]

[1]Department of Dermatology, Seoul National University College of Medicine, Seoul, Republic of Korea, [2]Institute of Human-Environment Interface Biology, Medial Research Center, Seoul National University, Seoul, Republic of Korea, [3]Department of Biochemistry and Molecular Biology, Seoul National University College of Medicine, Seoul, Republic of Korea, [4]Genomic Medicine Institute (GMI), Medical Research Center, Seoul National University, Seoul, Republic of Korea

C03-02 [P13-02] **Antifibrotic effects and mechanisms of miR-196b-5p of mesenchymal stem cell-derived exosomes in a systemic sclerosis mouse model**

Hritu Baral[1], ○Akihiko Uchiyama[1], Yoko Yokoyama[1], Akiko Sekiguchi[1], Sahori Yamazaki[1], Syahla Nisaa Amalia[1], Yuta Inoue[1], Sachiko Ogino[1], Ryoko Torii[1], Mari Hosoi[1], Toshiyuki Matsuzaki[2], Sei-ichiro Motegi[1]

[1]Department of Dermatology, Gunma University Graduate School of Medicine, [2]Department of Anatomy and Cell Biology, Gunma University Graduate School of Medicine

C03-03 [P13-03] **Obesity accelerates hair thinning by stem cell-centric converging mechanisms**

○Hironobu Morinaga[1], Emi K. Nishimura[1], Yasuaki Mohri[1], Kyosuke Asakawa[1], Hiroyuki Matsumura[1], Andrzej_A Dlugosz[2], Atsushi Iwama[3]

[1]Department of Stem Cell Biology, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan, [2]Department of Dermatology, University of Michigan Medical School, Ann Arbor, MI, USA, [3]Division of Stem Cell and Molecular Medicine, Center for Stem Cell Biology and Regenerative Medicine, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

C03-04 [P13-04] **Therapeutic potential of adipose-derived stem cells for the treatment of recessive dystrophic epidermolysis bullosa**

○Akinori Matsuda, Toshio Hasegawa, Akino Wada, Shigaku Ikeda

Department of Dermatology and Allergology Juntendo University Graduate School of Medicine, Tokyo, Japan

C03-05 [P13-05] **Perivascular adipose tissue in dermis induces infiltration of immune cells in the murine imiquimod (IMQ)-induced psoriasis model**

○Riko Takimoto-Ito, Satoshi Nakamizo, Gyohei Egawa, Kenji Kabashima

Department of Dermatology, Kyoto University Graduate school of medicine, Kyoto, Japan

C03-06 [P13-06] **Label-free quality control and identification of human keratinocyte stem cells by deep learning-based automated cell tracking**

Takuya Hirose[1], Jun'ichi Kotoku[1], Fujio Toki[2], Emi K. Nishimura[2,3], ○Daisuke Nanba[2]

[1]Graduate School of Medical Care and Technology, Teikyo University, Tokyo, Japan, [2]Department of Stem Cell Biology, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan, [3]Division of Aging and Regeneration, Institute of Medical Science, The University of Tokyo, Tokyo, Japan

C03-07 [P13-07] **Ahed has crucial roles as a spliceosomal protein for cell proliferation of epidermal keratinocytes**

○Mikiro Takaishi[1], Tatsushi Ishimoto[1], Masahiro Tokunaga[2], Chikara Kokubu[3], Junji Takeda[4], Shigetoshi Sano[1]

[1]Department of Dermatology, Kochi Medical School, Kochi University, [2]Dept. Hematol, Suita Municipal Hosp., [3]Child Healthcare and Genetic Science Lab, Grad. School Med., Osaka Univ., [4]Research Inst. Microb. Diseases, Osaka Univ.

Luncheon Seminar 3

11:50-12:50 Chair: Eiko Toichi

LS3 **Diets and psoriasis**

○Tetsuya Honda

Department of Dermatology, Hamamatsu University School of Medicine, Hamamatsu, Japan

Co-sponsored by TAIHO PHARMACEUTICAL CO., LTD./Janssen Pharmaceutical K.K.

3 minutes presentation and discussion 2 (Genetic Disease, Gene Regulation and Gene Therapy/Cell-Cell Interactions in the Skin)

14:45-15:45 Chairs: Toshifumi Nomura, Takuya Takeichi

O02-01 [P06-07] **Aberrant keratin assembly causes impaired mitochondrial movement and function: Implications for epidermolysis bullosa simplex pathogenesis**

○ Osamu Ansai[1], Ryota Hayashi[1], Satoru Shinkuma[2], Asuka Suto[3], Hiroshi Shimizu[3], Riichiro Abe[1]

[1]Division of Dermatology, Niigata University School of Medical and Dental Science, [2]Department of Dermatology, Nara Medical University School of Medicine, [3]Department of Dermatology, Hokkaido University Graduate School of Medicine

O02-02 [P06-08] **Mutations in SAM syndrome and palmoplantar keratoderma patients suggest genotype/phenotype correlations in *DSG1* mutations**

○ So Takeuchi[1], Takuya Takeichi[1], Yuta Koike[2], Hiroyuki Takama[3], Kana Tanahashi[1], Yusuke Okuno[4], Norito Ishii[5], Yoshinao Muro[1], Tomoo Ogi[6], Yasushi Suga[7], Masashi Akiyama[1]

[1]Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan, [2]Department of Dermatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [3]Department of Dermatology, Aichi Medical University, Nagakute, Japan, [4]Medical Genomics Center, Nagoya University Hospital, Nagoya, Japan, [5]Department of Dermatology, Kurume University School of Medicine, Fukuoka, Japan, [6]Department of Genetics, Research Institute of Environmental Medicine, Nagoya University, Nagoya, Japan, [7]Department of Dermatology, Juntendo University Urayasu Hospital, Urayasu, Japan

O02-03 [P06-09] **Atypical epidermolytic palmoplantar keratoderma caused by *KRT1* mutation is considered as mild type epidermolytic ichthyosis**

○ Ryota Hayashi[1], Osamu Ansai[1], Rei Yokoyama[1], Tatsuya Katsumi[1], Mahoko Oginezawa[1], Tomoki Nishiguchi[1], Satoru Shinkuma[2], Riichiro Abe[1]

[1]Division of Dermatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [2]Department of Dermatology, Nara Medical University School of Medicine, Kashihara, Japan

O02-04 [P06-10] **Delineating the functional relevance of different lamin A domains that accelerate human ageing**

○ Oliver Dreesen, Peh Fern Ong, Mattheus XR Foo

Skin Research Institute of Singapore

O02-05 [P06-11] **Evidence for a dominant-negative effect of a missense mutation in the *SERPING1* gene responsible for hereditary angioedema type I**

○ Shuichiro Yasuno[1], Osamu Ansai[2], Sawako Nakamura[1], Yutaka Shimomura[1]

[1]The Department of Dermatology, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan, [2]The Division of Dermatology, Niigata University Graduate School of Medicine and Dental Sciences, Niigata, Japan

O02-06 [P06-12] **Hereditary mucoepithelial dysplasia/autosomal-dominant IFAP syndrome is a clinical spectrum due to *SREBF1* variants**

○ Chiaki Murase[1], Takuya Takeichi[1], Toshifumi Nomura[2], Tomoo Ogi[3], Masashi Akiyama[1]

[1]The Department of Dermatology, Nagoya University Graduate School of Medicine, Aichi, Japan, [2]Department of Dermatology, Faculty of Medicine, University of Tsukuba, [3]Department of Genetics, Research Institute of Environmental Medicine, Nagoya University

O02-07 [P06-13] **Updated allele frequencies of *SERPINB7* founder mutations in Asian patients with Nagashima-type palmoplantar keratosis/keratoderma**

○ Yasutoshi Ito[1], Takuya Takeichi[1], Kenta Ikeda[2], Kana Tanahashi[1], Takenori Yoshikawa[1], Yuya Murase[1], Yoshinao Muro[1], Yoshio Kawakami[3], Jun Muto[4], Kazumitsu Sugiura[5], Yasushi Suga[6], Mariko Seishima[7], Akira Kawada[8], Tomoo Ogi[9], Masashi Akiyama[1]

[1]Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan, [2]Department of Dermatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan, [3]Department of Dermatology, Kurashiki Medical Center, Okayama, Japan, [4]Department of Dermatology, Ehime University Graduate School of Medicine, Ehime, Japan, [5]Department of Dermatology, Fujita Health University School of Medicine, Toyoake, Japan, [6]Department of Dermatology, Juntendo University Urayasu Hospital, Urayasu, Japan, [7]Department of Dermatology, Gifu University Graduate School of Medicine, Gifu, Japan, [8]Department of Dermatology, Kinki University Faculty of Medicine, Osaka-Sayama, Japan, [9]Department of Genetics, Research Institute of Environmental Medicine, Nagoya University, Nagoya, Japan

O02-08 [P06-14] **Bradykinin pathogenesis in hereditary angioedema based on the discovery of novel genetic mutations in ACE and SERPING7 gene**

○ Takuya Omine, Takuya Miyagi, Daisuke Utumi, Sayaka Yamaguhi, Kenzo Takahashi

University of the Ryukyus

O02-09 [P06-15] **A microchip flow-chamber assay can be a powerful tool for detecting platelet function defects in Hermansky-Pudlak syndrome**

○ Satoru Shinkuma[1], Hidetaka Kinoshita[1], Kenichi Ogiwara[2], Kengo Hamada[1], Kohei Ogawa[1], Fumi Miyagawa[1], Keiji Nogami[2], Hideo Asada[1]

[1]Department of Dermatology, Nara Medical University School of Medicine, Kashihara, Japan, [2]Department of Pediatrics, Nara Medical University School of Medicine

O02-10 [P04-02] **Antifibrogenic effects of sunitinib in a bleomycin-induced scleroderma model**

○ Masato Ishikawa, Toshiyuki Yamamoto

Department of Dermatology, Fukushima Medical University, Fukushima, Japan

O02-11 [P04-03] **Anti-glycation properties of Carnosine in 3D skin equivalent models and its implications in prevention of premature skin aging**

○ Jaimie Jerome[1], Ewa Markiewicz[2], Olusola Idowu[2], Tom Mammone[1]

[1]Estee Lauder Companies, [2]HexisLab Limited

3 minutes presentation and discussion 5 (Innate Immunity, Microbiology, Microbiome)

15:45-16:45 Chairs: Yumi Matsuoka-Nakamura, Tetsuro Kobayashi

O05-01 [P07-08] **Dysbiosis mediates inflammatory destruction of the hair follicles**

○ Keiko Sakamoto[1], Seon-Pil Jin[1], Shubham Goel[1], Jay-Hyun Jo[2], Benjamin Voisin[1], Doyoung Kim[1], Vinod Nadella[1], Hai Liang[2], Tetsuro Kobayashi[1], Xin Huang[3], Clay Deming[3], Keisuke Horiuchi[4], Julia_A Segre[3], Heidi_H Kong[2], Keisuke Nagao[1]

[1]Cutaneous Leukocyte Biology Section, Dermatology Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, USA, [2]Cutaneous Microbiome and Inflammation Section, Dermatology Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, USA, [3]Microbial Genomics Section, Translational and Functional Genomics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, USA, [4]Department of Orthopedic Surgery, National Defense Medical College, Saitama, Japan

O05-02 [P07-12] **An antimicrobial peptide cathelicidin triggers skin inflammation with other DAMPs via multiple receptors**

○ Ryo Amagai, Toshiya Takahashi, Taku Fujimura, Kenshi Yamasaki

Department of dermatology, Tohoku University Graduate School of medicine, Miyagi, Japan

O05-03 [P07-13] **Potential role of neutrophil elastase (NE) in the development of nephrogenic systemic fibrosis (NSF) in an in vivo model of renal failure**

○ Syahla N. Amalia[1], A. Adhipatria. P Kartamihardja[2], Anu Bhattarai[3], Akiko Sekiguchi[1], Ayako Taketomi-Takahashi[2], Sei-ichiro Motegi[1], Hiroshi Koyama[4], Yoshito Tsushima[2,5]

[1]Department of Dermatology, Gunma University, Maebashi, [2]Department of Diagnostic Radiology and Nuclear Medicine, Gunma University, Maebashi, Japan, [3]National Academy of Medical Sciences (NAMS), Bir Hospital, Nepal, [4]Department of Public Health, Gunma University, Maebashi, Japan, [5]Division of Integrated Oncology Research, Gunma Initiative for Advanced Research, Japan

O05-04 [P07-14] **Coordinated expression of retrotransposon and type I interferon with distinct interferon pathways in autoimmune diseases**

○ Yuko Kuriyama[1], Akira Shimizu[1,2], Saki Kanai[1], Daisuke Oikawa[3], Fuminori Tokunaga[3], Osamu Ishikawa[1], Sei-ichiro Motegi[1]

[1]The Department of Dermatology, Gunma University Graduate School of Medicine, Gunma, Japan, [2]Department of Dermatology, Kanazawa Medical University, Ishikawa, Japan, [3]Department of Pathobiochemistry, Graduate School of Medicine, Osaka City University, Osaka, Japan

O05-05 [P07-15] **Macrophages express βKlotho in skin lesions of psoriasis patients and the skin of imiquimod-treated mice**

○ Kozo Nakai[1], Reiji Haba[2], Yoshio Kushida[2], Yasuo Kubota[3], Daisuke Tsuruta[1]

[1]Department of Dermatology, Osaka City University Graduate School of Medicine, [2]Department of Diagnostic Pathology, Kagawa University, [3]Department of Dermatology, Kagawa University

O05-06 [P07-16] **Skin Inflammation and Testicular Function**

○ Ai Umaoka[1], Hiroki Takeuchi[2], Kento Mizutani[1], Naohiro Seo[3], Yoshiaki Matsushima[1], Shohei Lida[1], Makoto Kondo[1], Koji Habe[1], Tomoaki Ikeda[2], Keiichi Yamanaka[1]

[1]Department of Dermatology Mie University, Graduate School of Medicine, Japan, [2]Obstetrics and Gynecology, Mie University Graduate School of Medicine, [3]Immuno-Gene Therapy, Mie University Graduate School of Medicine

O05-07 [P07-17] **Roles of interferon regulatory factor 3 in murine models of allergic and irritant dermatitis**

○ Risa Tamagawa-Mineoka[1], Mayumi Ueta[2], Yukiyasu Arakawa[1], Mari Nakanishi[1], Hiromi Nishigaki[1], Risa Yasuike[1], Norito Katoh[1]

[1]Departments of Dermatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, [2]Departments of Ophthalmology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine

O05-08 [P07-18] **Internalization of live atopic dermatitis-derived Staphylococcus aureus into HaCaT cells and inhibition by Staphylococcus epidermidis**

○Tomofumi Numata, Kazumasa Iwamoto, Ryu Miyake, Michihiro Hide, Akio Tanaka

Department of Dermatology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima

O05-09 [P07-19] **Low heterogeneity among isolates of *Cutibacterium modestum*: Resident of human skin with possible infectious nature**

○Itaru Dekio[1,2], Ken-ichi Okuda[3], Masako Nishida[4], Susumu Hamada-Tsutsumi[5], Hiroto Tamura[5], Kenichiro Ohnuma[4], Yoshiyuki Murakami[2], Yuki Kinjo[3], Akihiko Asahina[1]

[1]Department of Dermatology, The Jikei University, Tokyo, Japan, [2]Seikakai Mildix Skin Clinic, Tokyo, Japan, [3]Department of Bacteriology, The Jikei University, Tokyo, Japan, [4]Kobe University Hospital, Kobe, Japan, [5]Department of Environmental Bioscience, Meijo University, Nagoya, Japan

O05-10 [P07-20] **Cutaneous adverse events caused by EGFR inhibitors may result from reduced expression of human β-defensins induced by staphylococci**

○Rie Ommori, Yuki Nishimura, Fumi Miyagawa, Chinatsu Shobatake, Kohei Ogawa, Satoru Shinkuma, Hideo Asada

The Department of Dermatology, Nara Medical University, Nara, Japan

O05-11 [P07-21] **Alternation of the cutaneous microbiome of herpes zoster lesion in a patient with severe coronavirus disease 2019**

○Makoto Kondo[1,2], Asami Ito[2], Yoshiaki Matsushima[1], Shohei Iida[1], Ai Umaoka[1], Takehisa Nakanishi[1], Hiroshi Imai[2], Keiichi Yamanaka[1]

[1]Department of Dermatology Mie University, Graduate School of Medicine, Japan, [2]Emergency Critical Care Center, University of Mie, Mie, Japan

O05-12 [P07-22] **Postbiotics power in supporting skin**

○Nadine Pernodet[1], Don Collins[3], Yulan Qu[2], Nan Frank Huang[2], Jian Richard Cao[2]

[1]Research & Development, The Estee Lauder Companies, Estee Lauder Research Laboratories, [2]Asia Innovation Center, the Estee Lauder Companies, [3]Research & Development, The Estee Lauder Companies

Evening Seminar 3
"Cutaneous T-Cell Lymphoma"

16:50-17:50 Chair: Makoto Sugaya

ES3-1 **Therapeutic approaches for the treatment of cutaneous T-cell lymphoma: an update 2021**

○Toshihisa Hamada

Department of Dermatology, Takamatsu Red Cross Hospital, Takamatsu, Japan

ES3-2 **Photo(chemo)therapy for cutaneous T-cell lymphoma in combination with bexarotene**

○Akimichi Morita

Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Co-sponsored by Minophagen Pharmaceutical Co., Ltd.

December 3, 2021, Room D

3 minutes presentation and discussion 3 (Photobiology/Pigmentation and Melanoma)

14:45-15:45 Chairs: Yukiko Kiniwa, Satoshi Fukushima

O03-01 [P11-12] **Excimer light downregulates interleukin-17 production and induces regulatory T cells in imiquimod-induced psoriasiform dermatitis**

○ Shota Egawa, Masahiro Kamata, Hideaki Uchida, Teruo Shimizu, Makoto Ito, Ryosuke Takeshima, Itsumi Mizukawa, Ayu Watanabe, Yayoi Tada

Department of Dermatology, Teikyo University School of Medicine, Tokyo, Japan

O03-02 [P11-13] **Characterization of the DNA damage response in human skin cell types**

○ Chin Yee Ho[1], A.L Soon[1], C Tan[2], P.F Ong[1], M Ehrman[3], J Oblong[4], S Bellanger[2], O Dreesen[1]

[1]Skin Research Institute of Singapore, A*STAR, Singapore, [2]Stemness, Differentiation and Aging in Human Epidermis, Skin Research Institute of Singapore, A*STAR, Singapore, [3]Proctor & Gamble International Operations SA, Singapore, [4]Beauty Technology Division, The Procter & Gamble Company, Cincinnati, Ohio, USA

O03-03 [P11-14] **A role of elastogenic factors in the pathogenesis of Solar Elastosis**

○ Teruhiko Makino[1], Ko Kagoyama[1], Chisato Murabe[2], Tomoyuki Nakamura[2], Tadamichi Shimizu[1]

[1]Department of Dermatology, University of Toyama, Toyama, Japan, [2]Department of Pharmacology, Kansai Medical University, Osaka, Japan

O03-04 [P11-15] **Photodynamic therapy using portable devices**

○ Rie Teranishi[1], Toshiyuki Ozawa[1], Tsuyoshi Goya[3], Kenji Kuwada[3], Katsuyuki Morii[3,4], Takahiro Nishimura[2], Kunio Awazu[2], Daisuke Tsuruta[1]

[1]The Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan, [2]Department of Quantum Energy Engineering, Graduate School of Engineering, Osaka University, [3]Innovation and Business Division, Nippon Shokubai Co, [4]Nippon Shokubai Research Alliance Laboratories, Osaka University

O03-05 [P11-16] **Usefulness of UVA lamps for the diagnosis of green nail syndrome with or without onychomycosis**

○ Tomotaka Sato, Kazuhiro Aoyama, Norihito Fukada, Akihiko Kinjo

The Department of Dermatology, Teikyo University Chiba Medical Center

O03-06 [P12-12] **Attenuation of melanocyte reoccupation in long-lasting rhododendrol-induced guinea pig model of vitiligo**

○ Yasutaka Kuroda[1,2], Lingli Yang[1], Fei Yang[1,2], Sylvia Lai[1], Tetsuya Sayo[1,2], Yoshito Takahashi[1,2], Daisuke Tsuruta[3], Ichiro Katayama[1]

[1]Department of Pigmentation Research and Therapeutics, Osaka City University Graduate school of medicine, [2]Biological Science Research Laboratories, Kao Corporation, [3]Department of Dermatology, Osaka City University Graduate school of medicine

O03-07 [P12-13] **Methyl-CpG binding domain protein 3 is a new diagnostic marker and potential therapeutic target of melanoma**

○ Takayuki Ishibashi[1], Ikko Kajihara[1], Satoru Mizuhashi[1], Haruka Kuriyama[1], Toshihiro Kimura[1], Hisashi Kanemaru[1], Katsunari Makino[1], Azusa Miyashita[1], Jun Aoi[1], Takamitsu Makino[1], Satoshi Fukushima[1], Kanako Kita[2], Hironobu Ihn[1]

[1]Department of Dermatology and Plastic Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan, [2]Department of Molecular Pathology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

O03-08 [P12-14] **NUAK2 is an important factor in acral melanomas development and progression**

○ Kohei Nojima[1], Masahiro Hayashi[2], Masakazu Kawaguchi[2], Tamio Suzuki[2], Masashi Ishikawa[3], Yasuhiko Kaneko[4], Atsushi Tanemura[5], Ichiro Katayama[6], Taisuke Mori[7], Naoya Yamazaki[8], Hiroki Mori[9], Hiroo Yokozeki[1], Takeshi Namiki[1]

[1]Department of Dermatology, Tokyo Medical and Dental University, [2]Department of Dermatology, Yamagata University, [3]Department of Dermatology, Saitama Cancer Center, [4]Research Institute for Clinical Oncology, Saitama Cancer Center, [5]Department of Dermatology, Osaka University, [6]Department of Dermatology, Osaka City University, [7]Department of Pathology, National Cancer Center Hospital, [8]Department of Dermatologic Oncology, National Cancer Center Hospital, [9]Department of Plastic Surgery, Tokyo Medical and Dental University

O03-09 [P12-15] **Protective efficacy of Sanqi-derived compound K on melanocytes against oxidative stress: in vitro and in vivo evaluation**

○ Suwei Tang[1,5], Lingli Yang[1], Yasutaka Kuroda[2], Sylvia Lai[1], Shaoqiong Xie[5], Huimin Zhang[4], Daisuke Tsuruta[3], Ichiro Katayama[1]

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O03-10 [P12-16] **Genipin contained in gardenia fruit enhanced melanogenesis**

○ Megumi Mizawa[1], Tsugunobu Andoh[2], Tadamichi Shimizu[1]

[1]Department of Dermatology, Faculty of Medicine, Academic Assembly, University of Toyama, Toyama, Japan, [2]Department of Pharmacology and Pathophysiology, College of Pharmacy, Kinjo Gakuin University, Aichi, Japan

3 minutes presentation and discussion 6 (Patient-Targeted Research)

15:45-16:45 Chairs: Takeshi Nakahara, Akihiko Uchiyama

O06-01 [P09-11] **Investigation of the involvement of TIF1γ expression in tumors in the pathogenesis of cancer-associated dermatomyositis**

○Mai Ishikawa, Akiko Sekiguchi, Yuko Kuriyama, Yukie Endo, Sei-ichiro Motegi
The Department of Dermatology, University of Gunma, Gunma, Japan

O06-02 [P09-12] **Identification of serum biomarkers predicting the therapeutic effect of dupilumab in atopic dermatitis by a targeted metabolomics approach**

○Shoko Miyamoto[1], Shin Nishiumi[2], Masako Matsutani[1], Makoto Nagai[1], Kiyofumi Yamanishi[1], Nobuo Kanazawa[1], Yasutomo Imai[1]
[1]Department of Dermatology, Hyogo College of Medicine, [2]Department of Omics Medicine, Hyogo College of Medicine

O06-03 [P09-13] **Predicting RNA sequences of small patch image for Treatment of Atopic Skin Disease by Deep Convolutional Neural Networks**

○Daiki Ito[1], Yutaka Kawashima[1], Hiroto Horikawa[2], Koichi Ashizaki[3], Hiroshi Kawasaki[2], Yoshimitsu Aoki[1]
[1]Department of Engineering, Keio University School, [2]Department of Dermatology, Keio University School of Medicine, [3]Medical Sciences Innovation Hub Program, RIKEN

O06-04 [P09-14] **Dermoscopic diagnostic performance of non-dermatologists for skin tumor is improved by a computer-aided diagnosis system**

○Akane Minagawa[1], Hiroshi Koga[1], Kazuhisa Matsunaga[2], Yuya Hayashi[2], Akira Hamada[2], Yoshiharu Houjou[2], Ryuhei Okuyama[1]
[1]The Department of Dermatology, Shinshu University School of Medicine, Matsumoto, Japan, [2]Casio Computer Co., Ltd., Tokyo, Japan

O06-05 [P09-15] **A possible role of surgical deroofing procedure to cover the disadvantage of adalimumab treatment for hidradenitis suppurativa**

○Natsuko Sasaki, Yu Sawada, Etsuko Okada, Motonobu Nakamura
The Department of Dermatology, University of Occupational and Environmental health, Kitakyusyu, Japan

O06-06 [P09-16] **Dermcidin is a prognostic factor in patients with extramammary Paget's disease**

○Yu Sawada, Shun Ohmori, Motonobu Nakamura
Department of Dermatology, University of Occupational and Environmental Health

O06-07 [P09-17] **Immediate impact of granulocyte and monocyte adsorption apheresis on generalized pustular psoriasis**

○Masahiro Kamata, Hideaki Uchida, Shota Egawa, Mayumi Nagata, Saki Fukaya, Kotaro Hayashi, Atsuko Fukuyasu, Takamitsu Tanaka, Takeko Ishikawa, Takamitsu Ohnishi, Yayoi Tada
Department of Dermatology, Teikyo University School of Medicine, Tokyo, Japan

O06-08 [P09-18] **Safety and efficacy of bexarotene for Japanese patients with CTCL: Real-world experience from a result of post marketing survey**

○Toshihisa Hamada[1], Akimichi Morita[2], Hiraku Suga[3], Hikari Boki[3], Taku Fujimura[4], Yoji Hirai[5], Takatoshi Shimauchi[6], Chiharu Tateishi[7], Eiji Kiyohara[8], Ikko Muto[9], The Japanese Bexarotene Study Group[10]
[1]Department of Dermatology, Takamatsu Red Cross Hospital, Takamatsu, Japan, [2]Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, [3]Department of Dermatology, The University of Tokyo Graduate School of Medicine, Tokyo, [4]Department of Dermatology, Tohoku University Graduate School of Medicine, Sendai, [5]Department of Dermatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, [6]Department of Dermatology, Hamamatsu University School of Medicine, Shizuoka, [7]Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, [8]Department of Dermatology, Course of Integrated Medicine, Graduate School of Medicine, Osaka University, Suita, [9]Department of Dermatology, Kurume University School of Medicine, Kurume, [10]the Japanese Bexarotene Study Group

O06-09 [P09-19] **MicroRNAs in neutrophils as markers of psoriasis**

○Yuko Higashi[1], Munekazu Yamakuchi[2], Tomoko Fukushige[1], Teruto Hashiguchi[2], Takuro Kanekura[1]
[1]Department of Dermatology, Kagoshima University Graduate School of Medical and Dental Sciences, [2]Department of Laboratory and Vascular Medicine, Kagoshima University Graduate School of Medical and Dental Sciences

O06-10 [P09-20] **Chronic hepatitis B virus infection in dupilumab-treated atopic dermatitis patients**

○Masako Matsutani
Department of Dermatology, Hyogo College of Medicine, Nishinomiya, Japan

O06-11 [P09-21] **Comparison of treatment goals between users of biological and non-biological therapies for treatment of psoriasis in Japan**

○Yukari Okubo[1], Ann_Chuo Tang[2], Sachie Inoue[3], Hitoe_Torisu Itakura[2], Mamitaro Ohtsuki[4]
[1]Department of Dermatology, Tokyo Medical University, Tokyo, Japan, [2]Eli Lilly Japan K.K., Tokyo, Japan, [3]Crecon Medical Assessment INC., Tokyo, Japan, [4]Department of Dermatology, Jichi Medical University, Shimotsuke, Tochigi, Japan

O06-12 [P09-22] **A patient with atopic dermatitis and psoriasis vulgaris presenting an unusual reaction for dupilumab**

○Yudai Tsukamoto, Toshifumi Takahashi, Miho Kabuto, Akihiko Yamaguchi, Noriki Fujimoto
Department of dermatology, Shiga university of medical science, Shiga, Japan

December 4, 2021, Room A

Morning Seminar 1
"Mechanism of Chronic Urticaria and Treatment Tips"

8:00-9:00 Chair: Shinichi Imafuku

MS1-1 **Chronic spontaneous urticaria and itch: a “Cinderella” disease with the Devil’s itch**

○ Takashi Hashimoto

Department of Dermatology, National Defense Medical College, Tokorozawa, Japan

MS1-2 **Tips for the treatment of chronic spontaneous urticaria**

○ Naotomo Kambe

Department of Dermatology, Kyoto University Graduate School of Medicine

Co-sponsored by Mitsubishi Tanabe Pharma Corporation/Teikoku Seiyaku Co., Ltd.

Plenary Session II

9:10-10:40 Chairs: Manabu Fujimoto, Qianjin Lu, Kiarash Khosrotehrani

II-1 [P01-01] **Lymphotoxin β from T cells mediates the formation of high endothelial venule-like vessels in atopic dermatitis-like skin lesions in mice**

○ Shuto Kanameishi[1], Sachiko Ono[1], Yuki Honda-Keith[1], Ryota Asahina[1], Tetsuya Honda[2], Kenji Kabashima[1,3]

[1]Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan, [2]Department of Dermatology, Hamamatsu University School of Medicine, Japan, [3]Singapore Immunology Network (SIgN) and Skin Research Institute of Singapore, Agency for Science, Technology and Research, Biopolis, Singapore

II-2 [P02-01] **Autoantigen-specific B cells targeted single-cell RNA-seq reveals the functional heterogeneity in pemphigus patients**

○ Shohei Egami[1,2], Takashi Watanabe[2], Ayano Nomura-Fukushima[1], Hisashi Nomura[1], Hayato Takahashi[1], Jun Yamagami[1], Osamu Ohara[3], Masayuki Amagai[1,2]

[1]The Department of Dermatology, Keio University of Medicine, Tokyo, Japan, [2]Laboratory for Skin Homeostasis, RIKEN Center for Integrative Medical Sciences, [3]Laboratory for integrative genomics, RIKEN Center for Integrative Medical Sciences

II-3 [P03-01] **Keratinocyte Regnase-1, a down-modulator of skin inflammation, contributes to protection from carcinogenesis through regulating COX2**

○ Hiroyuki Morisaka[1], Mikiro Takaishi[1], Shizuo Akira[2,3], Shigetoshi Sano[1]

[1]Department of Dermatology, Kochi Medical School, Kochi University, Kochi, Japan, [2]Laboratory of Host Defense, World Premier Institute Immunology Frontier Research Center (WPI-IFReC), Osaka University, Osaka, Japan, [3]Department of Host Defense, Research Institute for Microbial Diseases, Osaka University, Osaka, Japan

II-4 [P12-01] **A mechanism of cooling hot tumors: lactate and its induced EGR1 are novel key factors that turn hot tumors into cold tumors**

○ Hisashi Kanemaru, Yukari Mizukami, Akira Kaneko, Hidemi Tagawa, Toshihiro Kimura, Haruka Kuriyama, Soichiro Sawamura, Ikko Kajihara, Katsunari Makino, Jun Aoi, Satoshi Fukushima

Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University

II-5 [P09-01] **Basal sweating as unrecognized machinery to maintain skin hydration in the finger: a long-standing paradox in dry skin resolved**

○ Tetsuko Sato, Chieko Katayama, Yuki Hayashida, Yumiko Asanuma, Yumi Aoyama

Department of dermatology, Kawasaki Medical School, Okayama, Japan

II-6 [P09-02] **Increased serum levels ofCCL2 and IL-8 in patients with toxic epidermal necrolysis accompanied by acute respiratory distress syndrome**

○ Tomoya Watanabe, Yuko Watanabe, Michiko Aihara, Yukie Yamaguchi

Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

JSID Kisaragi Award

10:40-10:45 Chair and Presenter: Kenji Kabashima

JKA **The role of Ninjurin-1 in pericytes during skin wound healing: effects on capillary maturation**

○ Risa Matsuo

Department of Dermatology, Graduate School of Medicine, Asahikawa Medical University, Japan

JSID Award Lecture

10:45-11:15 Chair and Presenter: Kenji Kabashima

JAL **Autoimmune mechanisms in dermatology**

○ Naoko Okiyama
Department of Dermatology, Faculty of Medicine, University of Tsukuba

Luncheon Seminar 4
"The Cutting Edge of Psoriasis Research"

11:25-12:25 Chairs: Kenzo Takahashi, Norito Kato

LS4-1 **A Novel Ultra-Low Level Cytokine Assay as a Potential Tool for Selecting Biologics for Psoriasis**

○ Ayumi Yoshizaki
Department of Dermatology, Graduate School of Medicine, The University of Tokyo

LS4-2 **Pathophysiology of Psoriasis and the effect of IL-23 inhibition**

○ Mayumi Komine
Department of Dermatology, Jichi Medical University

Co-sponsored by Sun Pharma Japan Ltd.

The 22nd Maruho Research Award Presentations by award winners and award ceremony

12:30-13:30 Chairs: Masayuki Amagai, Shinichi Sato, Kenji Kabashima

MRA1 **Glucose-6-Phosphate Dehydrogenase Correlates with Tumor Immune Activity and Programmed Death Ligand-1 Expression in Merkel Cell Carcinoma**

○ Motoki Nakamura[1], Kotaro Nagase[2], Maki Yoshimitsu[1], Tetsuya Magara[1], Yuka Nojiri[1], Hiroshi Kato[1], Tadahiro Kobayashi[3], Yukiko Teramoto[4], Masahito Yasuda[5], Hidefumi Wada[6], Toshiyuki Ozawa[7], Yukie Umemori[8], Dai Ogata[9], Akimichi Morita[1]

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MRA2 **Inhibition of endoglin exerts antitumor effects through the regulation of non-Smad TGF-β signaling in angiosarcoma**

○ Ryoko Sakamoto[1], Ikko Kajihara[1], Hitomi Miyauchi[1], Saki Maeda-Otsuka[1], Saori Yamada-Kanazawa[1], Katsunari Makino[1], Jun Aoi[1], Takamitsu Makino[1], Satoshi Fukushima[1], Mamiko Masuzawa[2], Mikio Masuzawa[3], Yasuyuki Amoh[2], Daichi Hoshina[4], Riichiro Abe[5], Hironobu Ihn[1]

[1]Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan, [2]Department of Dermatology, Kitasato University School of Medicine, Kanagawa, Japan, [3]Department of Molecular Diagnostics, School of Allied Health Sciences, Kitasato University, Kanagawa, Japan, [4]Department of Dermatology, Hokkaido University Graduate School of Medicine, Hokkaido, Japan, [5]Department of Dermatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

MRA3 **Extramammary Paget's disease patient-derived xenografts harboring ERBB2 S310F mutation show sensitivity to HER2-targeted therapies**

○ Takuya Maeda[1], Shinya Kitamura[1], Hiroshi Nishihara[2], Teruki Yanagi[1]

[1]Department of Dermatology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan, [2]Genomics Unit, Keio Cancer Center, Keio University School of Medicine, Tokyo, Japan

MRA4 **Clinical characteristics and treatment of 50 cases of Blau syndrome in Japan confirmed by genetic analysis of the *NOD2* mutation**

○ Tomoko Matsuda[1], Yoko Ueki[1], Nobuo Kanazawa[2], Naotomo Kambe[1,3]

[1]Department of Dermatology, Kansai Medical University, Hirakata, Osaka, Japan, [2]Department of Dermatology, Hyogo Medical University, Nishinomiya, Hyogo, Japan, [3]Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Kyoto, Japan

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Concurrent Oral Session 4
(Auto-Immunity)

13:40-15:10 Chairs: Yumi Aoyama, Hideyuki Ujiie

C04-01 [P02-03] **Blockade of CD122 on skin resident memory T cells suppresses the development of mucocutaneous graft-versus-host disease**

○ Noriko Kubota[1], Ryota Tanaka[1], Yuki Ichimura[1], Risa Konishi[1], J Yun Tso[2], Naoya Tsurushita[2], Toshifumi Nomura[1], Naoko Okiyama[1]

[1]The Department of Dermatology, University of Tsukuba, Ibaraki, Japan, [2]JN Biosciences LLC

C04-02 [P02-06] **Activation of TNF/NF-κB signaling by linear ubiquitination specifically exacerbates a murine imiquimod-induced psoriasis model**

○ Ken I. Kosaka, Satoshi Nakamizo, Gyohei Egawa, Kenji Kabashima

Department of Dermatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

C04-03 [P02-07] **Possible involvement of IL-22-producing CD8$^+$CD103$^+$ T cells in the epidermal hyperplasia of atopic dermatitis**

○ Kazuo Kurihara[1], Toshiharu Fujiyama[1], Pawit Phadungsaksawasdi[1], Yoshiki Tokura[1,2], Tetsuya Honda[1]

[1]The Department of Dermatology, Hamamatsu University School of Medicine, Hamamatsu, Japan, [2]Allergic Disease Research Center and Department of Dermatology, Chutoen General Medical Center, Kakegawa, Japan

C04-04 [P02-08] **The role of FcγRIIB in a murine bleomycin-induced scleroderma model**

○ Kaori Sawada[1], Yasuhito Hamaguchi[1], Kie Mizumaki[1], Kyosuke Oishi[1], Shintaro Maeda[1], Yuka Ikawa[1], Akito Komuro[1,2], Kazuhiko Takehara[1], Takashi Matsushita[1]

[1]Department of Dermatology, Kanazawa University, Kanazawa, Japan, [2]Department of Plastic Surgery, Kanazawa University, Kanazawa, Japan

C04-05 [P02-09] **Serine protease inhibitor A3n, an endogenous granzyme B inhibitor, alleviates graft-versus-host disease reaction in human skin**

○ Yuki Ichimura[1], Risa Konishi[1], Ryota Tanaka[1], Noriko Kubota[1], Shoichiro Ishitsuki[1], Katsuhito Sasaki[1], Yasuyuki Nakamura[1], Yasuhiro Fujisawa[1], Toshifumi Nomura[1], Hideki Watanabe[2], Naoko Okiyama[1]

[1]Department of Dermatology, University of Tsukuba, Tsukuba, Japan, [2]Pharmacology Research Group, Research Department, Maruho Co., Ltd.

C04-06 [P02-10] **Occurrence of immune reconstitution inflammatory syndrome can be predicted by cytokine profiles in DPP-4i-associated bullous pemphigoid**

○ Seiko Sugiyama, Takenobu Yamamoto, Yumi Aoyama

Department of Dermatology, Kawasaki Medical School

C04-07 [P02-11] **Persistent dermatitis resulted in the gastro-intestinal amyloidosis, reduced absorption of nutrients, and hypoalbuminemia**

○ Takehisa Nakanishi, Kento Mizutani, Shohei Iida, Yoshiaki Matsushima, Ai Umaoka, Makoto Kondo, Koji Habe, Keiichi Yamanaka

The Department of Dermatology, Mie University Graduate School of Medicine

3 minutes presentation and discussion 7
(Adaptive Immunity)

15:20-16:20 Chairs: Rei Watanabe, Takashi Matsushita

O07-01 [P01-11] **Chronological classification of alopecia areata based on PD-1 expression revealed by scRNA-seq analysis-assisted immunohistochemistry**

○ Akiyoshi Senda, Toshiaki Kogame, Satoshi Nakamizo, Takashi Nomura, Naotomo Kambe, Kenji Kabashima

Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan

O07-02 [P01-12] **Treating pemphigus vulgaris (PV) and foliaceus (PF) by inhibiting the neonatal Fc receptor: phase 2 open-label trial with efgartigimod**

○ Matthias Goebeler[1], Zsuzsanna Bata-Csorgo[2], Clara De Simone[3], Biagio Didona[4], Eva Remenyik[5], Nataliya Reznichenko[6], Enno Schmidt[7], Johanna Stoevesandt[1], E. Sally Ward[8], Wim Parys[9], Hans de Haard[9], Patrick Dupuy[9], Peter Verheesen[9], Pascal Joly[10]

[1]Department of Dermatology, Venereology and Allergology, University Hospital Wuerzburg, Wuerzburg, Germany, [2]Department of Dermatology and Allergology, University of Szeged, Szeged, Hungary, [3]Catholic University Policlinic A. Gemelli, Rome, Italy, [4]Dermatopathic Institute of the Immaculate, Rome, Italy, [5]University of Debrecen, Debrecen, Hungary, [6]Zaporizhzhya State Medical University, Zaporizhzhya, Ukraine, [7]Department of Dermatology, University of Luebeck, Luebeck, Germany, [8]Centre for Cancer Immunology, University of Southampton, Southampton, UK, [9]argenx, Ghent, Belgium, [10]Department of Dermatology, Rouen University Hospital, Rouen, France

O07-03 [P01-13] **Elucidating the role of CARD14 signaling in Type 2 immune response**

○ Alshimaa Mostafa[1], Teruasa Murata[1], Teruki Dainichi[2], Ken Ishii[3], Kenji Kabashima[1,4]

[1]The Department Of dermatology, Kyoto University, Kyoto, Japan, [2]Department of Dermatology, Graduate school of Medicine, Kagawa university, Japan, [3]Institute of Medical Science, Division of Vaccine Science, Department of Microbiology and Immunology, The University of Tokyo, Japan, [4]The Singapore Immunology Network (SIgN) and Skin Research Institute of Singapore (SRIS), Agency for Science, Technology and Research (A*STAR), Singapore

O07-04 [P01-14] **The effect of topical 5-azacytidine in irritant and allergic contact dermatitis**

○ Youichi Ogawa, Shinji Shimada, Tatsuyoshi Kawamura

Department of Dermatology, University of Yamanashi, Yamanashi, Japan

O07-05 [P01-15] **Molecular mechanisms of mucosal mast cell differentiation**

○ Nobuhiro Nakano[1], Jiro Kitaura[1], Ko Okumura[1], Hideoki Ogawa[1,2], Shigaku Ikeda[1,2]

[1]Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine, Tokyo, Japan, [2]Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine, Tokyo, Japan

O07-06 [P01-16] **iSALT structures in B-cell type pseudolymphoma and their potential for local plasmacytoid differentiation in the skin**

○ Kosei Nanya[1], Toshiaki Kogame[1], Masahiro Hirata[2], Riko Takimoto-Ito[1], Masakazu Fujimoto[2], Takashi Nomura[1], Naotomo Kambe[1], Kenji Kabashima[1]

[1]Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan, [2]Department of Diagnostic Pathology, Kyoto University Hospital, Kyoto, Japan

O07-07 [P01-17] **Hyaluronan regulates murine irritant contact dermatitis model via Langerhans cell activation**

○ Mayuko Amagai, Hitoshi Terui, Naokazu Hatchome, Setsuya Aiba, Kenshi Yamasaki

Department of Dermatology, Tohoku University Graduate School of Medicine, Miyagi, Japan

O07-08 [P01-18] **A possible niche for B-cell development in the skin in primary cutaneous plasmacytosis suggesting the presence of a functional unit as iSALT**

○ Keigo Takase[1], Toshiaki Kogame[2], Riko Takimoto-ito[2], Takayoshi Komatsu-Fujii[1], Rintaro Shibuya[2], Takashi Nomura[2], Naotomo Kambe[2], Kenji Kabashima[2]

[1]Department of Dermatology, Tenri Hospital, Tenri, Nara, [2]Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan

O07-09 [P01-19] **Optimal methods for human skin T-cell analysis**

○ Takuya Sato, Youichi Ogawa, Shinji Shimada, Tatsuyoshi Kawamura

Department of Dermatology, University of Yamanashi, Chuo, Japan

O07-10 [P01-20] **Differentially expressed circulating exosomal microRNAs as biomarkers for disease severity in psoriasis patients**

○ Dong Chan Kim[1], Young Joon Park[1], So Min Kim[1], Ji Young Park[1], Mi Jin Park[1], Jae Youn Cheong[2], Eun-So Lee[1]

[1]Department of Dermatology, Ajou University School of Medicine, Suwon, Korea, [2]Ajou Translational Omics Center, Ajou University Medical Center, Suwon, Korea

O07-11 [P01-21] **Anti-inflammation effects of decanoic acid in a mouse of contact hypersensitivity: on a possible new drug for inflammatory skin disease**

○ Shohei Igari[1], Youichi Akama[2], Toshiyuki Yamamoto[1]

[1]The Department of Dermatology, Fukushima Medical University, Fukushima, Japan, [2]Department of Emergency, Minami Tohoku Hospital, Iwanuma, Miyagi

3 minutes presentation and discussion 10 (Carcinogenesis and Cancer)

16:20-17:20 Chairs: Jun Asai, Takeshi Namiki

O10-01 [P03-09] **Combination treatment of topical imiquimod plus anti-programmed cell death 1 antibody exerts significantly potent antitumor effect**

○ Kazumasa Oya[1], Yoshiyuki Nakamura[1], Yasuhiro Fujisawa[1], Naoko Okiyama[1], Manabu Fujimoto[2], Toshifumi Nomura[1]

[1]The Department of Dermatology, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan, [2]Department of Dermatology, Integrated Medicine, Graduate School of Medicine, Osaka University, Suita, Osaka

O10-02 [P03-10] **Skin liquid biopsy method for assessing the lesional environment of cutaneous T-cell lymphoma**

○ Kan Torii[1], Yukinori Okada[2], Akimichi Morita[1]

[1]Department of Geriatric and Environmental Dermatology, Nagoya City University, Aichi, Japan, [2]Department of Statistical Genetics, Osaka University Graduate School of Medicine, Osaka, Japan

O10-03 [P03-11] **Global tyrosine kinome profiling revealed Src pathway as a novel therapeutic target in combination with HDAC inhibitors for CTCL**

○ Kazuyasu Fujii[1,2], Nozomi Jimura[1,2], Ryuto Tsuchiya[2], Yuki Yoshimatsu[2], Tadashi Kondo[2], Takuro Kanekura[1]

[1]The Department of Dermatology, Kagoshima University, Kagoshima, Japan, [2]Division of Rare Cancer Research, National Cancer Center Research Institute, Tokyo, Japan

O10-04 [P03-12] **Matrin-3 is involved in cell cycle and apoptosis for survival in melanoma**

○ Haruka Kuriyama[1], Toshihiro Kimura[1], Etsuko Okada[1], Takayuki Ishibashi[1], Satoru Mizuhashi[1], Hisashi Kanemaru[1], Ikko Kajihara[1], Katsunari Makino[1], Azusa Miyashita[1], Jun Aoi[1], Kanako Kita[1,2], Hironobu Ihn[1], Satoshi Fukushima[1]

[1]Department of Dermatology and Plastic Surgery, Kumamoto University, Kumamoto, Japan, [2]Department of Molecular Pathology, Graduate School of Medical Sciences, Kumamoto University

O10-05 [P03-13] **Frequent *FGFR3* and ras gene mutations in skin tags/acrochordons**

○ Satomi Aoki[1], Hisato Suzuki[2], Yoshiko Hirata[1], Tomoko Kawai[3], Kazuhiko Nakabayashi[3], Kenichiro Hata[3], Kenjiro Kosaki[2], Masayuki Amagai[1], Akiharu Kubo[1]

[1]Department of Dermatology, Keio University School of Medicine, [2]Center for Medical Genetics, Keio University School of Medicine, [3]Department of Maternal-Fetal Biology, National Center for Child Health and Development

O10-06 [P03-14] **Two opposite effects of desmoglein 3 on the growth of oral squamous cell carcinoma between anchorage-dependent and -independent conditions**

○ Michiyoshi Kouno[1], Junichiro Inada[2], Masaki Minabe[2], Yurie Akiyama[2], Kazunari Higa[3], Tetsuhiko Tachikawa[4], Takeshi Nomura[2], Shinichi Takahashi[1]

[1]The Department of Dermatology, Tokyo Dental College Ichikawa General Hospital, Chiba, Japan, [2]The Department of Oral Oncology, Oral and Maxillofacial Surgery, Tokyo Dental College, [3]Cornea Center Eye bank, Tokyo Dental College Ichikawa General Hospital, [4]Division of Molecular Diagnosis and Cancer Prevention, Saitama Cancer Center

O10-07 [P03-15] **AID expression of B cells in the tertiary lymphoid structures implies an immunoglobulin class switching in tumor immunity**

○ Tomoya Takegami, Toshiaki Kogame, Takashi Nomura, Naotomo Kambe, Takaya Komatsu, Kenji Kabashima

Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan

O10-08 [P03-16] **Serum Cytokeratin 18 as a Potential Prognostic, Diagnostic and Therapeutic Marker for Extramammary Paget's Disease**

○ Mariko Takaoka, Hayakazu Sumida, Takuya Miyagawa, Shinichi Sato

Department of Dermatology, Faculty of Medicine, The University of Tokyo, Tokyo, Japan

O10-09 [P03-17] **The MIF-CD74 interaction regulates the expression of PD-L1 in melanoma cells**

○ Keiji Tanese[1,2], Masako Imaoka[2], Yohei Masugi[2], Mutsumi Hayashi[2], Michiie Sakamoto[2]

[1]The Department of Dermatology, Keio University, Tokyo Japan, [2]The Department of Pathology, Keio University, Tokyo Japan

O10-10 [P03-18] **Functional analysis of Rap2 in tumor microenvironment**

○ Kimiko Takei[1,2], Masato Umikawa[2], Tsuyoshi Asato[2], Ken-ichi Kariya[2]

[1]Department of Dermatology, Faculty of Medicine, University of the Ryukyus, [2]Department of Medical Chemistry, Graduate School of Medicine, University of the Ryukyus

O10-11 [P03-19] **Clinicopathological parameters to predict prognosis in cutaneous angiosarcoma -a retrospective analysis**

○ Satoru Yonekura, Yuichiro Endo, Hiroko Fujii, Gyohei Egawa, Kenji Kabashima

The Department of Dermatology, Kyoto University, Kyoto, Japan

O10-12 [P03-21] **Evaluating the efficacy of cetuximab, avelumab and cetuximab plus avelumab in treating perineural invasion of cutaneous SCC**

○ Priscila Oliveira de Lima[1], Benedict Lum[1], Shannon Joseph[1], Brian Tse[2], Kamil Sokolowski[2], Ian Brown[3], Glen Boyle[4], Benedict Panizza[5], Fiona Simpson[1]

[1]The University of Queensland Diamantina Institute, Woolloongabba, QLD, Australia, [2]Translational Research Institute, Woolloongabba, QLD, Australia, [3]Envoi Pathology, Kelvin Grove QLD, Australia, [4]Cancer Drug Mechanisms Group, QIMR Berghofer Medical Research Institute, Herston, QLD, Australia, [5]Otolaryngology-Head and Neck Surgery Department, Princess Alexandra Hospital, Brisbane, QLD, Australia

Evening Seminar 4
"What's Next in Psoriasis ? "

17:25-18:25 Chair: Takashi Matsushita

ES4-1 **The roles of Interferon Regulatory Factor-8 in psoriasis pathogenesis**

○ Tomoya Watanabe

Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

ES4-2 **Personalized nutrition for disease management in psoriasis patients**

○Yuki Hashimoto
Department of Dermatology, faculty of Medicine, Toho University, Tokyo, Japan

Co-sponsored by AbbVie GK

December 4, 2021, Room B

Morning Seminar 2
"Autoimmune bullous diseases"

8:00-9:00 Chair: Masayuki Amagai

MS2 **Elucidating pathomechanism and finding treatment of bullous pemphigoid, our target for research**

○ Daisuke Tsuruta
Department of Dermatology, Osaka City University Graduate School of Medicine

Co-sponsored by Japan Blood Products Organization

Luncheon Seminar 5
"Managing hyperpigmentation: Exploring multiple biological pathways and modulating melanogenesis"

11:25-12:25 Chair: Chikako Nishigori

LS5-1 **Melanogenesis connection with toll-like receptor signals**

○ Kenshi Yamasaki
Tohoku University Hospital

LS5-2 **A multi-prong understanding of hyperpigmentation**

○ Tom Mammone
Estee Lauder Companies

Co-sponsored by ELC JAPAN K.K.

Concurrent Oral Session 5
(Pigmentation and Melanoma)

13:40-15:10 Chairs: Atsushi Otsuka, Takafumi Kadono

C05-01 [P12-02] **TIGIT/CD155 axis mediates resistance to immunotherapy in cancer patients with the inflamed tumor microenvironment**

○ Shusuke Kawashima[1,2], Takashi Inozume[1,2,3], Masahito Kawazu[4], Toshihide Ueno[4], Etsuko Tanji[1], Tatsuyoshi Kawamura[3], Yasuhiro Nakamura[5], Tomonori Kawasaki[6], Yukiko Kiniwa[7], Hiroyoshi Nishikawa[8,9], Hiroyuki Matsue[2], Yosuke Togashi[1,8,10]

[1]Chiba Cancer Center, Research Institute, Chiba, Japan, [2]Department of Dermatology, Graduate School of Medicine, Chiba University, Chiba, Japan, [3]Department of Dermatology, University of Yamanashi, Yamanashi, Japan, [4]Division of Cellular Signaling, National Cancer Center Research Institute, Tokyo, Japan, [5]Department of Skin Oncology/Dermatology, Saitama Medical University International Medical Center, Saitama, Japan, [6]Department of Pathology, Saitama Medical University International Medical Center, Saitama, Japan, [7]Department of Dermatology, Shinshu University School of Medicine, Nagano, Japan, [8]Division of Cancer Immunology, Research Institute/Exploratory Oncology Research and Clinical Trial Center (EPOC), National Cancer Center, Tokyo/Kashiwa, Japan, [9]Department of Immunology, Nagoya University Graduate School of Medicine, Nagoya, Japan, [10]Department of Tumor Microenvironment, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

C05-02 [P12-03] **IPS cell-derived myeloid cells expressing OX40 ligand amplify tumor-infiltrating T cells in advanced melanoma**

○ Toshihiro Kimura[1], Haruka Kuriyama[1], Hisashi Kanemaru[1], Yosuke Kubo[1], Satoshi Nakahara[1], Azusa Miyashita[1], Jun Aoi[1], Hirotake Tsukamoto[2], Yasuharu Nishimura[3,4], Takashi Inozume[5], Rong Zhang[6], Yasushi Uemura[6], Satoru Senju[3], Hironobu Ihn[1], Satoshi Fukushima[1]

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C05-03 [P12-04] **Impact of a *SLC24A5* novel mutation identified in the first Japanese patient with oculocutaneous albinism 6 on retinal pigment epithelium**

○ Toru Saito[1], Ken Okamura[1], Rika Kosaki[2], Kazumasa Wakamatsu[3], Shosuke Ito[3], Osamu Nakajima[4], Hidetoshi Yamashita[5], Yutaka Hozumi[1], Tamio Suzuki[1]

[1]Department of Dermatology, Yamagata University Faculty of Medicine, Yamagata, Japan, [2]Division of Medical Genetics, National Center for Child Health and Development, Tokyo, Japan, [3]Institute for Melanin Chemistry, Fujita Health University, Toyoake, Japan, [4]Research Center for Molecular genetics, Institute for Promotion of Medical Science Research, Yamagata University Faculty of Medicine, Yamagata, Japan, [5]Department of Ophthalmology, Yamagata University Faculty of Medicine, Yamagata, Japan

C05-04 [P12-05] **Molecular and functional characterization of melanocyte subpopulations in the human hairy skin epidermis based on single-cell RNA sequencing**

○ Fumihito Noguchi, Peinan Zhao, Mark Shackleton

Cancer Development and Treatment Group, Department of Medicine Research Laboratories, Alfred Hospital, Monash University, Melbourne, Victoria, Australia

C05-05 [P12-06] **Melanocyte stem cell dynamics underlie de novo melanomagenesis**

○ Sally Eshiba[1], Takeshi Namiki[2], Yasuaki Mohri[1], Tomomi Aida[3,4], Naotaka Serizawa[1], Takakazu Shibata[5], Hironobu Morinaga[1], Daisuke Nanba[1], Keiko Miura[6], Masaru Tanaka[7], Hisashi Uhara[8], Hiroo Yokozeki[2], Toshiaki Saida[9], Emi K. Nishimura[1,10]

[1]Department of Stem cell biology Tokyo medical and dental university, [2]Department of Dermatology, Tokyo Medical and Dental University Graduate School and Faculty of Medicine, Tokyo, Japan, [3]Department of Molecular Neuroscience, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan, [4]Laboratory of Genome Editing for Biomedical Research, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan, [5]Medical Corporation Shibata Dermatology Clinic, Osaka, Japan, [6]Department of Pathology, Tokyo Medical and Dental University Graduate School and Faculty of Medicine, Tokyo, Japan, [7]Department of Dermatology, Tokyo Women's Medical University Medical Center East, Tokyo, Japan, [8]Department of Dermatology, Sapporo Medical University School of Medicine, Hokkaido, Japan, [9]Shinshu University, Professor Emeritus, Saitama, Japan, [10]Division of Aging and Regeneration, Institute of Medical Science, The University of Tokyo, Tokyo, Japan

C05-06 [P12-07] **Liquid biopsy-based analysis by CAPP-Seq and ddPCR in patients with melanoma**

○ Akira Kaneko, Hisashi Kanemaru, Ikko Kajihara, Haruka Kuriyama, Toshihiro Kimura, Soichiro Sawamura, Katsunari Makino, Azusa Miyashita, Jun Aoi, Takamitsu Makino, Shinichi Masuguchi, Satoshi Fukushima

Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

C05-07 [P12-17] **Genome-scale DNA methylation analysis identifies regulatory region and repeat element alterations that modulate the genomic stability of melanocytic nevi**

Meghan E. Muse[1], Drew T. Bergman[1], Lucas A. Salas[1], Lisa N. Tom[2], Jean-Marie Tan[2], Antonia Laino[2], Duncan Lambie[3,4], Richard A. Sturm[2], Helmut Schaider[2,5], H. Peter Soyer[2,6], Brock C. Christensen[1,7,8], ○ Mitchell S. Stark[2]

[1]Department of Epidemiology, Geisel School of Medicine at Dartmouth, Hanover, NH, USA, [2]The University of Queensland Diamantina Institute, The University of Queensland, Dermatology Research Centre, Brisbane, QLD 4102, Australia., [3]IQ Pathology, Brisbane, Queensland, Australia, [4]Pathology Queensland, Princess Alexandra Hospital, Brisbane, Queensland, Australia, [5]Department of Dermatology, Sunshine Coast Hospital and Health Service, Birtinya, Queensland, Australia, [6]Department of Dermatology, Princess Alexandra Hospital, Brisbane, Queensland, Australia, [7]Department of Molecular & Systems Biology, Dartmouth Geisel School of Medicine, Hanover, NH, USA Department of Molecular & Systems Biology, Dartmouth Geisel School of Medicine, Hanover, NH, USA, [8]Department of Community & Family Medicine, Dartmouth Geisel School of Medicine, Hanover, NH, USA

3 minutes presentation and discussion 8 (Skin, Appendages, and Stem Cell Biology)

15:20-16:20 Chairs: Yukiteru Oji, Misaki Kinoshita

O08-01 [P13-08] **Dynamic stem cell selection safeguards the genomic integrity of the epidermis**

○ Tomoki Kato[1], Nan Liu[1], Kyosuke Asakawa[1], Taichi Muraguchi[1], Yuko Muroyama[1], Hironobu Morinaga[1], Mariko Shimokawa[1], Yuriko Nishimori[1], Li Jing Tan[1], Yasuaki Mohri[1], Emi K. Nishimura[1,2]

[1]Department of Stem Cell Biology, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan, [2]Division of Aging and Regeneration, Institute of Medical Science, The University of Tokyo, Japan

O08-02 [P13-09] **Impaired holocrine cell rupture of sebocytes in comedo: Revisiting the mechanism of comedo formation in the study with excised human skins**

○ Toru Atsugi[1], Takashi Teramura[2], Hiroki Ota[3], Tomoko Aida[3], Mika Yamashita[3], Mathieu Lacroix[4], Anne-Laure Desroches[4], Nico Forraz[4], Colin McGuckin[4], Eiji Naru[1]

[1]Dermatology and Cosmeceutical Research Laboratories, KOSÉ Corporation, [2]KOSÉ R&D France, KOSÉ Corporation, [3]Safety and Analytical Research Laboratories, KOSÉ Corporation, [4]CTI BIOTECH

O08-03 [P13-10] **Immunological Properties of Atopic Dermatitis-Associated Alopecia Areata**

○ Reiko Kageyama[1], Taisuke Ito[1], Shiho Hanai[2], Naomi Morishita[1], Shinsuke Nakazawa[1], Toshiharu Fujiyama[1], Tetsuya Honda[1], Yoshiki Tokura[3]

[1]Department of Dermatology, Hamamatsu University School of Medicine, [2]Seirei Hamamatsu General Hospital, [3]Chutoen General Medical Center

O08-04 [P13-11] **Time course changes in peripheral blood mononuclear cell subsets during intravenous corticosteroid pulse therapy for severe alopecia areata**

○ Ryo Takahashi[1], Yohei Sato[2], Momoko Kimishima[2], Manabu Ohyama[1,2]

[1]Flow Cytometry Core Facility, Kyorin University Graduate School of Medicine, Tokyo, Japan, [2]Department of Dermatology, Kyorin University Faculty of Medicine, Tokyo, Japan

O08-05 [P13-12] **Distinct types of stem cell divisions orchestrate organ regeneration and aging in hair follicles**

○ Hiroyuki Matsumura[1], Nan Liu[1], Daisuke Nanba[1], Shizuko Ichinose[2], Aki Takada[1], Sotaro Kurata[3], Hironobu Morinaga[1], Yasuaki Mohri[1], Adèle De Arcangelis[4], Shigeo Ohno[5], Emi K. Nishimura[1]

[1]The Department of Stem cell medicine, Medical Research Institute, Tokyo Medical and Dental University, Japan, [2]Research Center for Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan, [3]Beppu Garden-Hill Clinic, Kurata Clinic, Beppu City, Japan, [4]Institut de Gènètique et de Biologie Molèculaire et Cellulaire, Department of Development and Stem Cells, Universitè de Strasbourg, Illkirch, France, [5]Department of Molecular Biology, Yokohama City University School of Medicine, Yokohama, Kanagawa, Japan

O08-06 [P13-13] **Mu-opioid ligand endomorphin induces alloknesis at the periphery**

○ Eriko Komiya[1], Mitsutoshi Tominaga[1,2], Ryo Hatano[3], Takumi Itoh[3], Kotaro Honda[1], Sumika Toyama[1], Yayoi Kamata[1,2], Haruna Otsuka[3], Kei Ohnuma[3], Chikao Morimoto[3], Kenji Takamori[1,2,4]

[1]Juntendo Itch Research Center (JIRC), Institute for Environmental and Gender Specific Medicine, Graduate School of Medicine, Juntendo University, Chiba, Japan, [2]Anti-Aging Skin Research Laboratory, Juntendo University Graduate School of Medicine, Chiba, Japan, [3]Department of Therapy Development and Innovation for Immune Disorders and Cancers, Graduate School of Medicine, Juntendo University, Tokyo, Japan, [4]Department of Dermatology, Juntendo University Urayasu Hospital, Chiba, Japan

O08-07 [P13-14] **Monocytic lineage cells distributed along sweat glands modulate sweat function**

○ Tadatsune Iida[1], Daisuke Kobayashi[2], Tomoki Tamura[2], Hiroo Yokozeki[1], Takeshi Namiki[1]

[1]Department of dermatology, Tokyo Medical and Dental University, Tokyo, [2]Department of human pathology, Tokyo Medical and Dental University, Tokyo

O08-08 [P13-15] **The potential of hair-follicle-associated pluripotent (HAP) stem cells to treat Parkinson's disease**

○ Michiko Yamane[1], Nanako Takaoka[1,2], Koya Obara[2], Kyoumi Shirai[2], Yuko Hamada[2], Nobuko Arakawa[2], Ryoichi Aki[2], Robert M. Hoffman[3,4], Yasuyuki Amoh[2]

[1]The Department of Dermatology, Department of Dermatology, Kitasato University Grad Sch Med Sci, Kanagawa, Japan, [2]Department of Dermatology, Kitasato University School of Medicine, [3]AntiCancer, Inc., [4]Department of Surgery, University of California San Diego

O08-09 [P13-16] **The potential of hair-follicle-associated pluripotent (HAP) stem cells for heart regeneration**

○ Nanako Takaoka[1,2], Michiko Yamane[1], Koya Obara[2], Kyoumi Shirai[2], Yuko Hamada[2], Nobuko Arakawa[2], Ryoichi Aki[2], Robert M. Hoffman[3,4], Yasuyuki Amoh[2]

[1]Department of Dermatology, Kitasato University Graduate School of Medical Science, Kanagawa, Japan, [2]Department of Dermatology, Kitasato University School of Medicine, Kanagawa, Japan, [3]AntiCancer, Incorporated, California, USA, [4]Department of Surgery, University of California San Diego, California, USA

O08-10 [P13-17] **Exploring the impact of ovariectomy on hair growth; Is ovariectomized mouse a model for investigating female pattern hair loss in human?**

○ Sayaka Togo, Hisayoshi Imanishi, Koji Sugawara, Daisuke Tsuruta

Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan

3 minutes presentation and discussion 11 (Patient Population Research/Pigmentation and Melanoma)

16:20-17:20 Chairs: Ayumi Yoshizaki, Taku Fujimura

O11-01 [P08-04] **Pork allergies in Japanese urban areas are predominantly classified as pork-cat syndrome**

○ Naoko Inomata, Nobuko Sagawa, Fumi Sawada, Saori Sano, Michiko Aihara

Dept. of Environmental Immuno-Dermatology Yokohama City University Graduate School of Medicine

O11-02 [P08-06] **The Clinical Significance of a Shortened Activated Partial Thromboplastin Time in Patients with Connective Tissue Disease**

○ Koji Habe[1], Hideo Wada[2], Kento Mizutani[1], Yoshiaki Matsushima[1], Makoto Kondo[1], Keiichi Yamanaka[1]

[1]Department of Dermatology, Mie University Graduate School of Medicine, Mie, Tsu, Japan, [2]Department of General and Laboratory Medicine, Mie Prefectural General Medical Center

O11-03 [P08-07] **Prevalence and Characteristics of Prurigo Nodules in Adults With Moderate-to-severe Atopic Dermatitis in Japan: a 2-year Observational Study**

○ Norito Katoh[1], Hidehisa Saeki[2], Yoko Kataoka[3], Takafumi Etoh[4], Satoshi Teramukai[5], Yuki Tajima[6], Parul Shah[7], Kazuhiko Arima[6]

[1]Kyoto Prefectural University of Medicine Graduate School of Medical Science, Kyoto, Japan, [2]Nippon Medical School, Tokyo, Japan, [3]Osaka Habikino Medical Care Center, Osaka, Japan, [4]Tokyo Teishin Postal Services Agency Hospital, Tokyo, Japan, [5]Kyoto Prefectural University of Medicine, Kyoto, Japan, [6]Sanofi, K.K., Tokyo, Japan, [7]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

O11-04 [P08-08] **Withdrawn**

O11-05 [P08-09] **Psoriasis Epidemiology Screening Tool (PEST) is a useful tool for psoriatic arthritis in the Japanese population**

○ Ayako Setoyama, Yu Sawada, Motonobu Nakamura

The Department of Dermatology, University of Occupational and Environmental Health, Fukuoka, Japan

O11-06 [P08-10] **The impact of atopic dermatitis on health-related quality of life in Bangladeshi adults**

○ Abir Majbauddin[1], Taheruzzaman Kazi[1], Zubaida Akter[2], Shigeki Inui[1]

[1]Department of Regenerative Dermatology, Graduate School of Medicine, Osaka University, Osaka, Japan, [2]Department of Dermatology & Venereology, Shaheed Suhrawardy Medical College Hospital, Dhaka, Bangladesh

O11-07 [P08-11] **A clinical investigation for superficial type atypical lipomatous tumor**

○ Emi Mashima, Yu Sawada, Motonobu Nakamura

The Department of Dermatology, University of Occupational and Environmental Health, Fukuoka, Japan

O11-08 [P08-12] **A single-center survey of psoriasis patients on biologics during the COVID-19 pandemic**

○ Koji Kamiya, Soichiro Kado, Megumi Kishimoto, Takeo Maekawa, Aya Kuwahara, Junichi Sugai, Mayumi Komine, Mamitaro Ohtsuki

Department of Dermatology, Jichi Medical University, Shimotsuke, Japan

O11-09 [P12-08] **NUMB inhibits melanoma migration, invasion, and metastasis**

○ Takeshi Fukumoto[1], Denitsa M Hristova[2], Xia Hua[2], Haruki Jimbo[1], Chihiro Takemori[1], Chikako Nishigori[1,3], Zhi Wei[4], Rajasekharan Somasundaram[2], Mizuho Fukunaga-Kalabis[2], Meenhard Herlyn[2]

[1]Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, [2]The Wistar Institute, [3]Department of iPS cell applications, Graduate School of Medicine, Kobe University, [4]Department of Computer Science, New Jersey Institute of Technology

O11-10 [P12-09] **Nucleosome assembly protein 1-like 4, a new therapeutic target for melanoma**

○ Satoru Mizuhashi[1], Takayuki Ishibashi[1], Haruka Kuriyama[1], Toshihiro Kimura[1], Hisashi Kanemaru[1], Ikko Kajihara[1], Katsunari Makino[1], Azusa Miyashita[1], Jun Aoi[1], Kanako Kita[2], Hironobu Ihn[1], Satoshi Fukushima[1]

[1]Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan, [2]Department of Comprehensive Molecular Medicine, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

O11-11 [P12-10] **Investigation the mechanism of novel lncRNAs, LncRNA00094, involved in metformin-inducing inhibition of melanoma cells**

○ Hui-Wen Tseng[1,2], Kuo-Wang Tsai[3]

[1]The Department of Dermatology, Kaohsiung Veterans General Hospital, [2]Institute of Biomedical Sciences, National SunYet-sen University, [3]Department of Research, Taipei Tzu Chi Hospital, NewTaipei, Taiwan

O11-12 [P12-11] **Increased expression of SPARC and TIMP3 in epidermotropic melanoma metastasis**

○ Maureen.T Meling, Yukiko Kiniwa, Eisaku Ogawa, Yuki Sato, Ryuhei Okuyama

Department of Dermatology, Shinshu University School of Medicine, Matsumoto, Japan

Evening Seminar 5
"Immunopathology and Holistic care of Psoriasis"

17:25-18:25 Chairs: Yoshihide Asano, Hideki Fujita

ES5-1 **Psoriasis and the metabolic syndrome**

○ Rei Watanabe

Department of Integrative Medicine for Allergic and Immunological Diseases, Graduate School of Medicine/Faculty of Medicine, Osaka University, Osaka, Japan

ES5-2 **Immunological aspects of psoriasis and significance of TNF-α inhibition**

○ Hideki Nakajima

Department of Dermatology, Kochi Medical School, Kochi University, Kochi, Japan

Co-sponsored by UCB Japan Co. Ltd.

December 4, 2021, Room C

Morning Seminar 3
"Therapeutic biomarker in melanoma"

8:00-9:00 Chair: Atsushi Otsuka

MS3-1 **Significance of tumor-associated macrophages to predict the efficacy and immune-related adverse events by anti-PD1 antibodies**

○Taku Fujimura
Department of Dermatology, Tohoku University Graduate School of Medicine, Sendai, Japan

MS3-2 **Monitoring of genetic biomarkers for *BRAF*-mutated melanoma**

○Yukiko Kiniwa
The Department of Dermatology, Shinshu University, Nagano

Co-sponsored by ONO PHARMACEUTICAL CO., LTD.

Luncheon Seminar 6
"The latest research on psoriasis 2021"

11:25-12:25 Chairs: Sei-Ichiro Motegi, Masatoshi Jinnin

LS6-1 **More than skin deep in psoriasis —IL17 and obesity/atherosclerosis—**

○Yukie Yamaguchi
Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

LS6-2 **Understanding of the pathogenesis of psoriasis from the perspective of female hormones**

○Tetsuya Honda
Department of Dermatology, Hamamatsu University School of Medicine, Hamamatsu, Japan

Co-sponsored by Kyowa Kirin Co., Ltd

Concurrent Oral Session 6
(Cell-Cell Interactions in the Skin/Epidermal Structure and Barrier Function-I)

13:40-15:10 Chairs: Yoshihide Asano, Hironobu Fujiwara, John Common

C06-01 [P04-01] **Antibodies to desmocollin (Dsc) 3, but not Dsc1, in pemphigus sera directly block heterophilic transinteraction between desmoglein and Dsc**

○Ken Ishii[1], Norito Ishii[2], Akira Ishiko[1], Takashi Hashimoto[3]
[1]Department of Dermatology, Toho University School of Medicine, Tokyo, Japan, [2]Department of Dermatology, Kurume University School of Medicine, Kurume, Japan, [3]Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan

C06-02 [P05-03] **A skin-derived antimicrobial peptide human beta defensin-3-induced autophagy activation improves the skin barrier in atopic dermatitis**

○Ge Peng[1], Yoshie Umehara[2], Juan Valentin Trujillo-Paez[2], Hainan Yue[1,2], Le Thanh Hai Nguyen[1,2], Risa Ikutama[1,2], Miho Takahashi[1,2], Masaaki Komatsu[3], Ko Okumura[2], Hideoki Ogawa[2], Shigaku Ikeda[1,2], Francois Niyonsaba[2,4]
[1]Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine, Tokyo, Japan, [2]Atopic Research Center, Juntendo University Graduate School of Medicine, Tokyo, [3]Physiology, Juntendo University Graduate School of Medicine, Tokyo, Japan, [4]Faculty of International Liberal Arts, Juntendo University, Tokyo, Japan

C06-03 [P05-04] **Wnt/β-catenin signaling stabilizes hemidesmosomes in keratinocytes**

○Hideyuki Kosumi[1], Mika Watanabe[1,2], Satoru Shinkuma[3], Yu Fujimura[1], Tadasuke Tsukiyama[4], Giacomo Donati[2], Hiroaki Iwata[1], Hideyuki Ujiie[1], Ken Natsuga[1]
[1]The Department of Dermatology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan, [2]Department of Life Sciences and Systems Biology, Molecular Biotechnology Centre, University of Turin, Turin, Italy, [3]Department of Dermatology, Nara Medical University School of Medicine, Kashihara, Japan, [4]Department of Biochemistry, Hokkaido University Graduate School of Medicine, Sapporo, Japan

C06-04 [P05-06] **New transparent three-dimension and deep imaging for skin epidermal structure using a novel fluorescent solvatochromic pyrene probe**

○ Masamoto Murakami[1], Ryosuke Kawakami[2], Yosuke Niko[3], Kazuki Yatsuzuka[1], Hideki Mori[1], Jun Muto[1], Ken Shiraishi[1], Takeshi Imamura[2], Koji Sayama[1]

[1]Department of Dermatology, Ehime University Graduate School of Medicine, Ehime, Japan, [2]Department of Molecular Medicine for Pathogenesis, Ehime University Graduate School of Medicine, Ehime, Japan, [3]Research and Education Faculty, Multidisciplinary Science Cluster, Interdisciplinary Science Unit, Kochi University, Kochi, Japan

C06-05 [P05-07] **IL-33 is a negative regulator in skin barrier homeostasis**

○ Md. Razib Hossain, Tuba M. Ansary, Mayumi Komine

Department of Dermatology, Jichi Medical University, Tochigi, Japan

C06-06 [P05-08] **Loricrin maintains Langerhans cell homeostasis and protects against cutaneous chemical carcinogenesis**

○ Tatsuya Ogawa[1], Yosuke Ishitsuka[2], Manabu Fujimoto[2], Dennis R Roop[3], Toshifumi Nomura[1]

[1]Department of Dermatology, University of Tsukuba, Tsukuba, Japan, [2]Department of Dermatology, Osaka University, Osaka, Japan, [3]Department of Dermatology and Charles C. Gates Center for Regenerative Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO

C06-07 [P05-09] **Effect of ceramide chirality on the lipid lamellar structure in stratum corneum**

○ Yasuko Obata[1], Rie Arai[1], Takayuki Furuishi[1], Kaori Fukuzawa[1], Etsuo Yonemochi[1], Kenya Ishida[2]

[1]Hoshi University, [2]Takasago International Corporation

3 minutes presentation and discussion 9 (Photobiology/Epidermal Structure and Barrier Function)

15:20-16:20 Chairs: Teruki Yanagi, Takeshi Matsui

O09-01 [P11-05] **Deficiency of epidermal ferroportin enhances UV dermatitis in mice**

○ Naokazu Hatchome, Hitoshi Terui, Mayuko Onodera-Amagai, Masayuki Asano, Kenshi Yamasaki, Setsuya Aiba

The Department of Dermatology, University of Tohoku, Miyagi, Japan

O09-02 [P11-08] **Effect of M1 and M2 Macrophages on Production and Degradation of Extracellular Matrix in Dermal Fibroblasts**

○ Munetaka Kawamoto, Ryota Kami, Satoshi Horiba

MIRAI Technology Institute, Shiseido Co.,Ltd

O09-03 [P11-09] **Downregulation of IL-34 Associated with the Skewing of M1/M2 Balance of Macrophages Induces Senescence in Human dermal fibroblasts**

○ Satoshi Horiba, Ryota Kami, Taiki Tsutsui, Junichi Hosoi

Shiseido Co., Ltd MIRAI Technology Institute

O09-04 [P11-11] **Non-invasive assessment of diameter-dependent cutaneous vascular alterations with age using Optical Coherence Tomography Angiography**

○ Takuma Hoshino[1], Yusuke Hara[1], Masato Ninomiya[1], Toyonobu Yamashita[1], Motoki Oguri[1], Masako Katsuyama[1], Chika Katagiri[1], Yuandong J. Li[2], Yuxuan Cheng[2], Nhan M. Le[2], Ruikang Wang[2]

[1]MIRAI Technology Institute, Shiseido Corporation Limited, [2]Department of Bioengineering, University of Washington, Seattle, United States

O09-05 [P05-18] **Antimicrobial peptide AG30/5C modulates tight junction barrier function in keratinocytes via EGFR, aPKC, GSK-3 and Rac1 pathways**

○ Risa Ikutama[1,2], Ge Peng[1,2], Yoshie Umehara[1], Juan V. Trujillo Paez[1], Hainan Yue[1,2], Hai Le Thanh Nguyen[1,2], Miho Takahashi[1,2], Shun Kageyama[3], Masaaki Komatsu[3], Ko Okumura[1], Hideoki Ogawa[1], Shigaku Ikeda[1,2], François Niyonsaba[1,4]

[1]Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine, Tokyo, Japan, [2]Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine, Tokyo, Japan, [3]Physiology, Juntendo University Graduate School of Medicine, Tokyo, Japan, [4]Faculty of International Liberal Arts, Juntendo University, Tokyo, Japan

O09-06 [P05-19] **Mechanisms underlying the suppression of semaphorin 3A expression in atopic dermatitis**

○ Yayoi Kamata[1,2], Mitsutoshi Tominaga[1,2], Yasushi Suga[2,3], Hideoki Ogawa[1], Kenji Takamori[1,2,3]

[1]Juntendo Itch Research Center (JIRC), Institute for Environmental and Gender-Specific Medicine, Juntendo University Graduate School of Medicine, Chiba, Japan, [2]Anti-Aging Skin Research Laboratory, Juntendo University Graduate School of Medicine, Chiba, Japan, [3]Department of Dermatology, Juntendo University Urayasu Hospital, Chiba, Japan

O09-07 [P05-20] **A skin-derived antimicrobial peptide AMP-IBP5 regulates epidermal barrier function**

○ Hai L.T. Nguyen[1,2], Juan V. Trujillo P.[1], Ge Peng[1,2], Hainan Yue[1,2], Risa Ikutama[1,2], Miho Takahashi[1,2], Yoshie Umehara[1], Hideoki Ogawa[1,2], Ko Okumura[1], Shigaku Ikeda[1,2], Francois Niyonsaba[1,3]

[1]Atopy (Allergy) Research Center, Juntendo University, Tokyo, Japan, [2]Department of Dermatology and Allergology, Juntendo University Graduate School of Medecine, Tokyo, Japan, [3]Faculty of International Liberal Arts, Juntendo University, Tokyo, Japan

O09-08 [P05-21] **Spatial distribution of KLK, SPINK, and SERPIN family proteins contributes to dense stratum corneum of normal sole skin and PPK phenotypes**

○ Aoi Ohira, Takuya Omine, Daisuke Utsumi, Sayaka Yamaguchi, Kenzo Takahashi

Department of Dermatology, University of the Ryukyus, Graduate School of Medicine, Okinawa, Japan

O09-09 [P05-22] **Detergent-induced skin inflammation and itch in a mast cell-independent and antihistamine-resistant manner in C57BL/6 mice**

○ Yurie Masutani[1,2], Toshiro Takai[1], Seiji Kamijo[1], Toru Kimitsu[1,2], Tomoko Yoshimura[1,2], Ko Okumura[1], Hideoki Ogawa[2], Shigaku Ikeda[1,2]

[1]Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine, [2]Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine

O09-10 [P05-23] **Possible roles of advanced glycated end-products in pathogenesis of acquired perforating dermatosis**

○ Yuya Murase[1], Takuya Takeichi[1], Kana Tanahashi[1], Hiroyuki Takama[2], Masashi Akiyama[1]

[1]Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan, [2]Department of Dermatology, Aichi Medical University Graduate School of Medicine

O09-11 [P05-24] **Functional analysis of BCL6 in epidermal cells**

○ Kaori Kanemaru[1], Kento Nagasawa[1], Asahi Tanaka[1], Yohsuke Harada[2], Yoshikazu Nakamura[1]

[1]Department of Applied Biological Science, Faculty of Science and Technology, Tokyo University of Science, Chiba, Japan, [2]Laboratory of Pharmaceutical Immunology, Faculty of Pharmaceutical Sciences, Tokyo University of Science, Chiba, Japan

3 minutes presentation and discussion 12 (Epidermal Structure and Barrier Function/Auto-Immunity)

16:20-17:20 Chairs: Ken Ishii, Yu Sawada

O12-01 [P05-05] **Relationship between regulatory T cell distribution and interleukin -33 in a mouse model of skin barrier disruption**

○ Sumika Toyama[1], Catharina Sagita Moniaga[1], Mitsutoshi Tominaga[1], Hideoki Ogawa[1], Kenji Takamori[1,2]

[1]Juntendo Itch Research Center (JIRC), Institute for Environmental and Gender Specific Medicine, Juntendo University Graduate School of Medicine, Chiba, Japan, [2]Department of Dermatology, Juntendo University Urayasu Hospital, Chiba, Japan

O12-02 [P05-12] **Upregulation of the NMF producing enzyme PAD1 by low humidity and low temperature climate gives the skin adaptability to dry environments**

○ Daichi Murata[1,2], Masashi Miyai[1], Toari Hirakawa[1], Hiroko Manabe[1], Katsuyuki Maeno[1], Akira Motoyama[1], Christopher_T Knight[1], Akihito Ishigami[2], Chika Katagiri[1]

[1]Shiseido Co., Ltd MIRAI Technology Institute, Kanagawa, Japan, [2]Molecular Regulation of Aging, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan

O12-03 [P05-13] **The sweating disturbance aggravates contact hypersensitivity reaction in mice footpads**

○ Hironobu Ishimaru[1], Yasuo Okamoto[1], Yumi Aoyama[2]

[1]Department of Pharmacology, Kawasaki Medical School, Okayama, Japan, [2]Department of Dermatology, Kawasaki Medical School, Okayama, Japan

O12-04 [P05-14] **TSLP impairs epidermal barrier integrity by the formation of nuclear IL-33/phosphorylated STAT3 complex in human keratinocytes**

○ Xiuju Dai, Jun Muto, Ken Shiraishi, Ryo Utsunomiya, Hideki Mori, Masamoto Murakami, Koji Sayama

Department of Dermatology, Ehime University Graduate School of Medicine, Ehime, Japan

O12-05 [P05-16] **The contribution of single nucleotide polymorphisms of AKR1C3 to susceptibility of psoriasis**

○ Yuka Nojiri[1], Motoki Nakamura[1], Kyoko Ikumi[1], Haruna Nishihara[1], Aya Nakada[1], Emi Nishida[1], Thomas Haarmann-Stemmann[2], Akimichi Morita[1]

[1]Departments of Geriatric and Environmental Dermatology, Nagoya City University, Nagoya, Japan, [2]Leibniz Research Institute for Environmental Medicine, Dusseldorf, Germany

O12-06 [P05-17] **Sphingosine 1-phosphate receptor 1 (S1PR1) negatively regulates epidermal barrier function**

○ Satomi Igawa[1], Manae Takahashi[1], Risa Matsuo[1], Mari Kishibe[1], Akemi Ishida-Yamamoto[1], Anna Di Nardo[2]

[1]The Department of Dermatology, Asahikawa Medical University, Asahikawa, Japan, [2]The Department of Dermatology, School of Medicine, University of California, San Diego, La Jolla, USA

O12-07 [P02-04] **IFN-γ signaling has both pro-inflammatory and immunoregulatory roles depending on the cell types in interface dermatitis in mouse**

○ Miho Mukai[1], Hayato Takahashi[1], Masayuki Amagai[1,2]

[1]The Department of Dermatology, Keio University School of Medicine, Tokyo, Japan, [2]Laboratory for Skin Homeostasis, RIKEN IMS, Yokohama

O12-08 [P02-05] **IL-9 promotes skin inflammation via Pyy in imiquimod-induced psoriasis-like dermatitis**

○ Shiori Kamiya[1,2], Ippei Ikegami[2], Ryuta Kamekura[2], Keijyu Kobayashi[1,2], Takafumi Kamiya[1], Shingo Ichimiya[2], Hisashi Uhara[1]

[1]Department of Dermatology, Sapporo Medical University School of Medicine, Sapporo, Japan, [2]Department of Human Immunology, Research Institute for Frontier Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan

O12-09 [P02-12] **Periostin may act on monocytes to be differentiated into macrophages with fibrotic phenotype in patients with systemic sclerosis**

○ Mao Suzuki, Asami Akita-Enoki, Miho Asami, Yasushi Ototake, Noriko Komitsu-Ikeda, Yukie Yamaguchi

Department of Environmental Immuno-Dermatology Yokohama City University Graduate School of Medicine, Yokohama, Japan

O12-10 [P02-13] **Apremilast downregulates IL-17 production and induces splenic regulatory B and T cells in imiquimod-induced psoriasis**

○ Hideaki Uchida, Masahiro Kamata, Teruo Shimizu, Shota Egawa, Makoto Ito, Ryosuke Takeshima, Itsumi Mizukawa, Ayu Watanabe, Yayoi Tada

Department of Dermatology, Teikyo University, School of Medicine

O12-11 [P02-14] **Withdrawn**

O12-12 [P02-15] **Establishment of nail psoriasis mouse model by topical application of imiquimod**

○ Kana Yamada, Hisayoshi Imanishi, Daisuke Tsuruta

The Department of Dermatology, University of Osaka city, Osaka, Japan

Evening Seminar 6
"Proper use of MTX in dermatology"

17:25-18:25 Chair: Nobuo Kanazawa

ES6-1 **The Proper Use of Methotrexate for PsA**

○ Akihiko Asahina

Department of Dermatology, The Jikei University School of Medicine

ES6-2 **Let's think about the appropriate use of methotrexate for psoriasis**

○ Yayoi Tada

Department of Dermatology, Teikyo University School of Medicine

Co-sponsored by Pfizer Japan Inc.

December 4, 2021, Room D

JDS Symposium

13:40-15:40 Chair: Riichiro Abe

JDS1 **Introduction of Journal of Dermatological Science Symposium**

○ Riichiro Abe
Division of Dermatology, Niigata University Graduate School of Medical and Dental Sciences, Japan

JDS2 **What we can do to patch the "leaky pipeline": Issues revealed by the first national survey**

○ Mari Kishibe
Department of Dermatology, Asahikawa Medical University

JDS3 **Dissecting the molecular mechanism of acne keloidalis by single-cell transcriptomics**

○ Chao-Kai Hsu
Department of Dermatology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Chinese Taipei

JDS4 **How to publish our work in a decent journal**

○ Shuai Shao, Gang Wang
Department of Dermatology, Xijing Hospital, Fourth Military Medical University, Xi'an, China

JDS5 **How age and sex shape the skin cancer landscape**

○ Amaya Viros Usandizaga[1,2]
[1]Cancer Research UK Manchester Institute, [2]Salford Royal NHS Foundation Trust

JDS6 **Revertant mosaicism in inherited disorders of keratinization**

○ Toshifumi Nomura
Department of Dermatology, University of Tsukuba, Ibaraki, Japan

JDS7 **An Update on Scholarly Publishing in the Wake of the Pandemic in its Second Year**

○ Helen Habernickel
Executive Publisher, Health & Medical Sciences Elsevier, Berlin, Germany

December 5, 2021, Room A

Morning Seminar 4
"What does “itch” mean ? - in atopic dermatitis and urticaria -"

7:50-8:50 Chairs: Masashi Akiyama, Manabu Fujimoto

MS4-1 **Itching mechanism in Atopic Dermatitis -from basic to clinical**

○ Gyohei Egawa
Department of Dermatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

MS4-2 **Itch of urticaria**

○ Michihiro Hide
Hiroshima City Hiroshima Citizens Hospital, Hiroshima, Japan

Co-sponsored by Maruho Co., Ltd.

Plenary Session III

9:00-10:30 Chairs: Manabu Ohyama, Sung-Jan (Jerry) Lin, Jin Ho Cung

III-1 [P05-01] **An important role of Syntaxin-4 in nuclear degradation in corneoptosis, a unique cell death of keratinocytes**

○ Nanako Maekubo-Kadono[1], Keitaro Fukuda[1,2], Takeshi Matsui[1,2,3], Masayuki Amagai[1,2]
[1]Laboratory for Skin Homeostasis, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan, [2]Department of Dermatology, Keio University School of Medicine, Tokyo, Japan, [3]Laboratory for Evolutionary Cell Biology of the Skin, School of Bioscience and Biotechnology, Tokyo University of Technology, Hachioji, Japan

III-2 [P14-01] **CCL5/CCR5 feedforward loop by FLI1 deficiency in microvascular endothelial cells contributes to SSc vasculopathy**

○ Tetsuya Ikawa, Takuya Miyagawa, Yuki Fukui, Satoshi Toyama, Jun Omatsu, Kentaro Awaji, Yuta Norimatsu, Yusuke Watanabe, Ayumi Yoshizaki, Shinichi Sato, Yoshihide Asano
The Department of Dermatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

III-3 [P13-01] **Development of molecular atlas of the human nail unit and hair follicle with spatially resolved transcriptomics**

Dongyoun Lee, ○ Joonho Shim, Ji-Hye Park, Gulimila Abudureyimu, Jong Hee Lee
Department of Dermatology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

III-4 [P05-02] **Type XVII collagen contributes to epidermal patterning**

○ Yunan Wang[1], Hiroyuki Kitahata[2], Hideyuki Kosumi[1], Mika Watanabe[1,3], Yu Fujimura[1], Shota Takashima[1], Shin-Ichi Osada[4], Tomonori Hirose[5], Wataru Nishie[1], Masaharu Nagayama[6], Hideyuki Ujiie[1], Hiroshi Shimizu[1], Ken Natsuga[1]
[1]Department of Dermatology, Hokkaido University Faculty of Medicine and Graduate School of Medicine, Sapporo, Japan, [2]Department of Physics, Graduate School of Science, Chiba University, Chiba, Japan, [3]Department of Life Sciences and Systems Biology, Molecular Biotechnology Centre, University of Turin, Turin, Italy, [4]Department of Dermatology, Nippon Medical School, Tokyo, Japan, [5]Department of Molecular Biology, Yokohama City University Graduate School of Medical Science, Yokohama, Japan, [6]Research Institute for Electronic Science, Hokkaido University, Sapporo, Japan

III-5 [P08-01] **Estimation of cutaneous squamous cell carcinoma incidence attributable to arsenic in U.S. water supplies**

○ Masaoki Kawasumi
Division of Dermatology, Department of Medicine, University of Washington, Seattle, WA, United States

III-6 [P10-01] **Blockade of CX3CL1-CX3CR1 pathway inhibits mouse sclerodermatous chronic graft-versus-host disease model**

○ Akira Utsunomiya[1], Vu Huy Luong[1], Takenao Chino[1], Noritaka Oyama[1], Takashi Matsushita[2], Naoto Ishii[3], Hideaki Ogasawara[3], Toshio Imai[3], Minoru Hasegawa[1]
[1]Dermatology, University of Fukui, [2]Dermatology, Kanazawa University, [3]KAN Research Institute. Inc.

Tanioku Kihei Memorial Lecture

10:30-11:00 Chair: Masayuki Amagai

TML **RNA origin of sex biased immunity**

○ Howard Y. Chang
Stanford University School of Medicine

Concurrent Oral Session 7
(Epidermal Structure and Barrier Function-II/Tissue Regeneration and Wound Healing)

11:05-12:35 Chairs: Norito Katoh, Masatoshi Jinnin, Eung Ho Choi

C07-01 [P05-10] **Development of a novel skin model combining SNF and collagen**

○Mizuki Iijima[1], Kazutoshi Iijima[2]

[1]Graduate School of Engineering Science, Yokohama National University, Yokohama, Japan, [2]Faculty of Engineering, Yokohama National University, Yokohama, Japan

C07-02 [P05-11] **Nuclear factor erythroid 2-related factor 2 regulates epidermal keratinization under psoriatic skin inflammation**

○Yosuke Ishitsuka[1,2], Tatsuya Ogawa[2], Manabu Fujimoto[1]

[1]Department of Dermatology, Osaka University Graduate School of Medicine, Suita, Japan, [2]University of Tsukuba

C07-03 [P05-15] **The ligand of epidermal growth factor receptor, betacellulin, improves Th2 cytokine-mediated impairment of tight junction barrier**

○Saya Tsukamoto[1], Ge Peng[1,2], Saori Yoshiba[1], Ko Okumura[1], Shigaku Ikeda[1,2], Francois Niyonsaba[1,3]

[1]Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine, Tokyo, Japan, [2]Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine, Tokyo, Japan, [3]Faculty of International Liberal Arts, Juntendo University

C07-04 [P14-02] **Ninjurin-1 contributes to skin wound healing through the formation of functional blood vessels**

○Risa Matsuo, Mari Kishibe, Shin Iinuma, Mizue Fujii, Satomi Igawa, Masaru Homma, Akemi Ishida-Yamamoto

The Department of Dermatology, Asahikawa Medical University, Hokkaido, Japan

C07-05 [P14-03] **Odorant-dependent Merkel cell chemosensation: implications for wound healing**

Ilaria Piccini[1], Jeremy Cheret[1,2], Moe Tsutsumi[3], S Sakaguchi[3], Leslie Ponce[1], Luis Almeida[1], K Funk[4], Max Kueckelhaus[5], Kentaro Kajiya[3], Ralf Paus[1,2,6], ○Marta Bertolini[1]

[1]Monasterium Laboratory, Skin and Hair Research Solutions GmbH, Muenster, Germany, [2]Dr. Phillip Frost Dept. of Dermatology & Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA, [3]MIRAI Technology Institute, Shiseido Co., Ltd. Yokohama, Japan, [4]Clinic for Plastic, Aesthetic and Reconstructive Surgery, Munich, Germany, [5]Fachklinik Hornheide, Muenster, Germany, [6]Centre for Dermatology Research, University of Manchester, MAHSC, and Manchester NIHR Biomedical Research Centre, Manchester, UK

C07-06 [P14-04] **Adipose derived stem cells inhibits fibrotic effect of keloid derived dermal fibroblasts**

○Yuki Nukui, Toshio Hasegawa, Akino Wada, Shigaku Ikeda

Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine

C07-07 [P14-05] **Skin-derived human β-defensin-3 promotes wound healing and angiogenesi**

○Miho Takahashi[1,2], Yoshie Umehara[1], Hainan Yue[1,2], Juan Valentin Trujillo[1], Ge Peng[1,2], Hai Le Thanh Nguyen[1,2], Risa Ikutama[1,2], Ko Okumura[1], Hideoki Ogawa[1], Shigaku Ikeda[1], Francois Niyonsaba[1,3]

[1]Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine, Tokyo, Japan, [2]Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine, Tokyo, Japan, [3]Faculty of International Liberal Arts, Juntendo University, Tokyo, Japan

Luncheon Seminar 7
"Treatment of atopic dermatitis～To the next step～"

12:45-13:45 Chairs: Makoto Sugaya, Hideyuki Ujiie

LS7-1 **Novel pathogenesis and therapeutics on atopic dermatitis**

○Kenji Kabashima

Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan

LS7-2 **Neural mechanisms of itch and the role of JAK in atopic dermatitis**

○Yozo Ishiuji

Department of Dermatology, Jikei University School of Medicine, Tokyo, Japan

Co-sponsored by Eli Lilly Japan K. K.

Concurrent Oral Session 10
(Adaptive Immunity)

13:50-15:30 Chairs: Tatsuyoshi Kawamura, Sayuri Yamazaki

C10-01 [P01-03] **Skin immune memory can be compensated by circulating CD4 T cells when the resident memory CD8 T cells are unfunctional**

○ Shuichi Nakai[1,2], Rei Watanabe[2], Kiyoshi Hirahara[3], Toshinori Nakayama[3], Manabu Fujimoto[2]

[1]Research Department, Maruho Co., Ltd., Kyoto, Japan, [2]Department of Dermatology, Graduate School of Medicine, Osaka University, Osaka, Japan, [3]Department of Immunology, Graduate School of Medicine, Chiba University, Chiba, Japan

C10-02 [P01-04] **Neutrophil extracellular traps are involved in enhanced contact hypersensitivity response in IL-36 receptor antagonist-deficient mice**

○ Yurie Hasegawa[1], Yohei Iwata[1], Hidehiko Fukushima[1], Yoshihito Tanaka[1], Soichiro Watanabe[1], Kenta Saito[1], Hiroyuki Ito[1], Mizuki Sugiura[1], Masashi Akiyama[2], Kazumitsu Sugiura[1]

[1]Department of Dermatology, Fujita Health University School of Medicine, Aichi, Japan, [2]Department of Dermatology, Nagoya University Graduate School of Medicine

C10-03 [P01-05] **Tumor necrosis factor-alpha plays crucial role in both the induction and maintenance of cytotoxic T lymphocyte-induced dermatitis**

○ Toshiya Miyake, Satoshi Nakamizo, Gyohei Egawa, Kenji Kabashima

Department of Dermatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

C10-04 [P01-06] **IL-31, a major pruritogen in a mouse model of atopic dermatitis, is generated through the macrophage/TSLP/periostin axis**

○ Takashi Hashimoto, Takahiro Satoh

Department of Dermatology, National Defense Medical College, Tokorozawa, Japan

C10-05 [P01-07] **Attenuation of DTH by oral tolerance depends on regulatory T cells in the sensitization phase**

○ Arisa Akagi[1], Akihiko Kitoh[2], Sho Hanakawa[2], Kenji Kabashima[1,2]

[1]Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan, [2]Singapore Immunology Network and Skin Research Institute of Singapore, Agency for Science, Technology and Research (A*STAR), Singapore

C10-06 [P01-08] **IL-10 production potency in peripheral blood B cells predicts prognosis of alopecia areata**

○ Yutaka Matsumura[1,2], Rei Watanabe[1], Yuumi Nakamura[1], Manabu Fujimoto[1]

[1]Department of Dermatology, Course of Integrated Medicine, Graduate School of Medicine, Osaka University, Osaka, Japan, [2]Department of Dermatology, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan

C10-07 [P01-09] **New epicutaneous sensitization model to protease antigen: itch-associated skin inflammation, a variety of Th subsets and IgE**

○ Tomoko Yoshimura[1,2], Toshiro Takai[1], Seiji Kamijo[1], Toru Kimitsu[1,2], Yurie Masutani[1,2], Takasuke Ogawa[2], Ko Okumura[1], Hideoki Ogawa[2], Shigaku Ikeda[1,2]

[1]Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine, [2]Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine

C10-08 [P01-10] **Revisiting the dogma of contact dermatitis; even single hapten application can induce allergic contact dermatitis in situ**

○ Gyohei Egawa, Kenji Kabashima

Department of Dermatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

December 5, 2021, Room B

Morning Seminar 5
"The novel mechanism of itch in atopic dermatitis"

7:50-8:50 Chair: Kenji Kabashima

MS5-1 **The role of basophils and IL-4Rα in itch in Atopic Dermatitis**

○ Atsushi Fukunaga

Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, Japan

MS5-2 **New Mechanisms of Itch in Atopic Dermatitis**

○ Brian S. Kim[1,2,3,4]

[1]Department of Medicine, Division of Dermatology, [2]Center for the Study of Itch and Sensory Disorders, [3]Department of Anesthesiology, [4]Department of Pathology and Immunology, Division of Biology and Biomedical Sciences, Washington University School of Medicine, St. Louis, MO, USA

Co-sponsored by Sanofi K.K.

Concurrent Oral Session 8
(Innate Immunity, Microbiology, Microbiome-II/Genetic Disease, Gene Regulation and Gene Therapy)

11:05-12:20 Chairs: Mayumi Komine, Yukinori Okada

C08-01 [P07-11] **Involvement of V δ1+ epithelial type of γδT cells in the systemic form of hydroa vacciniforme-like lymphoproliferative disorders**

○ Yoji Hirai[1], Tomoko Miyake[1], Takahide Takahashi[2], Keiji Iwatsuki[1,3,4], Shin Morizane[1]

[1]Department of Dermatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan, [2]Division of Medical Support, Okayama University Hospital, Okayama, Japan, [3]Division of Dermatology, Fukushima Rosai Hospital, Iwaki, Japan, [4]Division of Dermatology, Okazaki Medical Center, Fujita Health University, Okazaki, Japan

C08-02 [P06-02] **Altered replication stress response due to *CARD14* mutations induces somatic genetic reversion**

○ Toshinari Miyauchi[1], Shotaro Suzuki[1], Masae Takeda[1], Jin Teng Peh[1], Masayuki Aiba[1], Ken Natsuga[1], Yasuyuki Fujita[1], Takuya Takeichi[2], Taiko Sakamoto[3], Masashi Akiyama[2], Hiroshi Shimizu[1], Hideyuki Ujiie[1], Toshifumi Nomura[1,4]

[1]Department of Dermatology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan, [2]Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan, [3]Sakamoto Clinic, Fujieda, Japan, [4]Department of Dermatology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan

C08-03 [P06-03] **A novel keratin 14 mutation in epidermolysis bullosa induces more morphological abnormalities in keratin fiber than a hotspot mutation**

○ Mari Kishibe[1], Risa Matsuo[1], Satomi Igawa[1], Akiharu Kubo[2], Akemi Ishida-Yamamoto[1]

[1]Department of Dermatology, Asahikawa Medical University, Asahikawa, Japan, [2]Department of Dermatology, Keio University School of Medicine, Tokyo, Japan

C08-04 [P06-04] **Diversity of Mechanisms Underlying Dysregulating TGF-β Signaling in Recessive Dystrophic Epidermolysis Bullosa**

○ Eijiro Akasaka[1], Alexander Nyström[2], Leena Bruckner-Tuderman[2], Hajime Nakano[1], Daisuke Sawamura[1]

[1]Department of Dermatology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan, [2]Department of Dermatology, Faculty of Medicine and Medical Center - University of Freiburg, Germany

C08-05 [P06-05] **Psoriasis-like skin lesions in a patient carrying *MEFV* variants**

○ Takenori Yoshikawa[1], Takuya Takeichi[1], Tomoo Ogi[2], Masashi Akiyama[1]

[1]Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan, [2]Department of Genetics, Research Institute of Environmental Medicine, Nagoya University, Nagoya, Japan

C08-06 [P06-06] **Transcriptional and translational interference of laminin-332 subunits in junctional epidermolysis bullosa with *LAMB3* mutations**

○ Ping-Chen Hou[1,2,3], Ken Natsuga[4], Wei-Ting Tu[1,3], Hsin-Yu Huang[1], Brandon Chen[3], Liang-Yu Chen[2,3], Wan-Rung Chen[1], Yi-Kai Hong[1,3], Yen-An Tang[5,6], Julia Yu-Yun Lee[1], Peng-Chieh Chen[7,8], H. Sunny Sun[5,6], John A. McGrath[9], Chao-Kai Hsu[1,3,7,10]

[1]Department of Dermatology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [2]School of Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [3]International Center for Wound Repair and Regeneration (iWRR), National Cheng Kung University, Tainan, Taiwan, [4]Department of Dermatology, Hokkaido University Faculty of Medicine and Graduate School of Medicine, Sapporo, Japan, [5]Institute of Molecular Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [6]Center for Genomic Medicine, Innovation Headquarters, National Cheng Kung University, Tainan, Taiwan, [7]Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [8]Center of Clinical Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [9]St John's Institute of Dermatology, King's College London (Guy's Campus), London, UK, [10]Department of Genomic Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Luncheon Seminar 8

12:45-13:45 Chair: Norito Katoh

LS8 **Mechanism and future prospects of IL-4/13 in the treatment of atopic dermatitis**

○ Gaku Tsuji[1,2]

[1]Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [2]Research and Clinical Center for Yusho and Dioxin, Kyushu University Hospital, Fukuoka, Japan

Co-sponsored by Sanofi K.K.

Concurrent Oral Session 11 (Carcinogenesis and Cancer)

13:50-15:30 Chairs: Makoto Sugaya, Michihiro Kono

C11-01 [P03-02] **Frequent driver mutations of *FOXA1* in extramammary Paget's disease**

○ Takuya Takeichi[1], Yusuke Okuno[2], Takaaki Matsumoto[1], Nobuyuki Tsunoda[3], Kyogo Suzuki[4], Kana Tanahashi[1], Michihiro Kono[1,5], Toyone Kikumori[3], Yoshinao Muro[1], Masashi Akiyama[1]

[1]Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan, [2]Medical Genomics Center, Nagoya University Hospital, Nagoya, Japan, [3]Department of Breast and Endocrine Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan, [4]Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan, [5]Akita University Graduate School of Medicine, Akita, Japan

C11-02 [P03-03] **Clonal expansion of somatically-mutated keratinocytes in KID syndrome**

○ Yoshihiro Ishida, Mitsuasa Murata, Kenji Kabashima

Department of Dermatology, Kyoto University

C11-03 [P03-04] **Next-generation sequencing revealed tumor immunity-related factors interacting with tertiary lymphoid structures in cutaneous angiosarcoma**

○ Tetsuya Magara, Motoki Nakamura, Yuka Nojiri, Maki Yoshimitsu, Shinji Kano, Akihiro Matsubara, Hiroshi Kato, Akimichi Morita

Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Science, Japan

C11-04 [P03-05] **Loss of FAM83H plays a promoting role for cell migration and invasion in cutaneous squamous cell carcinoma via altered keratin distribution**

○ Keiko Tokuchi[1], Shinya Kitamura[1], Takuya Maeda[1], Masashi Watanabe[2], Shigetsugu Hatakeyama[2], Hideyuki Ujiie[1], Teruki Yanagi[1]

[1]The Department of Dermatology, Hokkaido University, Sapporo, Japan, [2]Department of Biochemistry, Hokkaido University, Sapporo, Japan

C11-05 [P03-06] **Blockade of glucose-6-phosphate dehydrogenase induces immunogenic cell death in malignant melanoma and Merkel cell carcinoma**

○ Motoki Nakamura, Tetsuya Magara, Maki Yoshimitsu, Yuka Nojiri, Shinji Kano, Akihiro Matsubara, Hiroshi Kato, Akimichi Morita

Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

C11-06 [P03-07] **DUSP4 positively controls the proliferation and infiltration ability of melanoma cells by activating ERK1/2 via downregulation of DUSP6**

○ Hirofumi Kamada[1,2], Shinji Yasuhira[2], Masahiko Shibazaki[2], Hiroo Amano[1], Chihaya Maesawa[2]

[1]Department of Dermatology, School of Medicine, Iwate Medical University, Iwate, Japan, [2]Department of Tumor Biology, Institute of Biomedical Science, Iwate Medical University, Iwate, Japan

C11-07 [P03-08] **Tumor suppressive effect of anti-PD-1 antibody against angiosarcoma in a mouse model**

○ Akiko Sekiguchi, Mai Ishikawa, Chisako Fujiwara, Yuta Inoue, Sahori Yamazaki, Akihiko Uchiyama, Sei-ichiro Motegi

Department of Dermatology, Gunma University Graduate School of Medicine, Maebashi, Japan

C11-08 [P03-20] **Investigating Proteome Changes Between Primary and Metastatic Cutaneous Squamous Cell Carcinoma Using Mass Spectrometry**

○ Ali Azimi[1,2], Kitty Lo[3], Jennifer Kim[4], Pablo Fernandez-Penas[1,2]

[1]Westmead Clinical School, Faculty of Medicine and Health, The University of Sydney, Westmead, New South Wales, Australia, [2]Department of Dermatology, Westmead Hospital, Westmead, New South Wales, Australia, [3]School of Mathematics and Statistics, The University of Sydney, Camperdown, New South Wales, Australia, [4]Department of Tissue Pathology and Diagnostic Oncology, Westmead Hospital, Westmead, New South Wales, Australia

December 5, 2021, Room C

Concurrent Oral Session 9
(Translational Studies-II/Photobiology)

11:05-12:35 Chairs: Tetsuya Honda, Naoko Okiyama

C09-01 [P15-03] **A deep learning framework enables prompt and objective scoring of Nail Psoriasis Severity Index**

○ Hiroto Horikawa, Keiji Tanese, Ryoko Hosokawa, Julia Miyamoto, Kaori Murakami, Risa Kakuta, Hitomi Matsuzaki, Yuhei Kawashima, Masayuki Amagai, Masataka Saito

Department of Dermatology, Keio University School of Medicine, Tokyo, Japan

C09-02 [P11-02] **Analysis of anti-inflammatory effects and the underlying mechanisms of CO2 on skin**

○ Keimon Sayama[1,2], Katsuyuki Yuki[1], Keiichi Sugata[1], Satoko Fukagawa[1], Tetsuji Yamamoto[1], Natsumi Nagamori[1], Takayoshi Inoue[1], Shigaku Ikeda[2], Takatoshi Murase[1]

[1]Biological Science Research, Kao Corporation, Tochigi, Japan, [2]Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine, Tokyo, Japan

C09-03 [P11-03] **Epigenetic regulation in melanocytes differentiated from induced pruripotent stem cells originated from xeroderma pigmentosum**

○ Chihiro Takemori[1], Takeshi Fukumoto[1], Michiyo Koyanagi-Aoi[2,3], Makoto Kunisada[1], Chieko Hosaka[1], Takashi Aoi[2,3], Chikako Nishigori[1,3]

[1]Division of Dermatology, Department of Internal Related, Graduate School of Medicine, Kobe University, Kobe, Japan, [2]Division of Advanced Medical Science, Graduate School of Science, Technology and Innovation, Kobe University, Kobe, Japan, [3]Department of iPS cell applications, Graduate School of Medicine, Kobe University, Kobe, Japan

C09-04 [P11-04] **Identification and Quantification of Senescent Cells In UV-induced Skin Pathologies**

○ Audrey Wang[1], Satoshi Nakamizo[2], Yoshihiro Ishida[2], Genevieve Klassen[3], Priscilla Chong[3], John Lim[4], Graham Wright[4], Oliver Dreesen[1], Kenji Kabashima[1,2]

[1]Skin Research Institute Singapore, [2]Kyoto University Graduate School of Medicine, Japan, [3]School of Biological Sciences, Nanyang Technology University, [4]A*STAR Microscopy Platform

C09-05 [P11-06] **Rapid pustule fixation of palmoplantar pustulosis by UVA1-LED phototherapy**

○ Kyoko Ikumi[1], Tomohiko Kio[2], Kan Torii[1], Hideyuki Masuda[2], Akimichi Morita[1]

[1]Department of Geriatric and Environmental Dermatology Nagoya City University Graduate Schol of Medical Sciences, [2]R&D Group, Biomedical Division, USHIO INC, Tokyo, Japan

C09-06 [P11-07] **Switching the light source of phototherapy from a lamp to a deep ultraviolet light-emitting diodes**

○ Hideyuki Masuda[1,2], Akimichi Morita[1]

[1]Department of Geriatric and Environmental Dermatology, Nagoya City University, Graduate School of Medical Sciences, Nagoya, Japan, [2]Ushio Inc. Tokyo, Japan

C09-07 [P11-10] **Bath-PUVA therapy targets keratinocytes to suppress the secretion of pathogenic chemokines**

○ Yoshifumi Kanayama, Kan Torii, Kyoko Ikumi, Akimichi Morita

Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Luncheon Seminar 9
"Trigger to elucidate the pathophysiology in psoriatic disease"

12:45-13:45 Chairs: Ken Igawa, Toshiyuki Yamamoto

LS9-1 **Molecular and cellular dynamics after anti-IL-17 mAb treatment for psoriasis**

○ Toshiharu Fujiyama

Department of Dermatology, Hamamatsu University School of Medicine

LS9-2 **Psoriasis as a systemic inflammation disease and an impact of IL-17A inhibition on it**

○ Masahiro Kamata

Department of Dermatology, Teikyo University School of Medicine

Co-sponsored by Novartis Pharma K.K. Medical Division/Maruho Co., Ltd. Medical Affairs Dept.

Concurrent Oral Session 12
(Patient-Targeted Research)

13:50-15:30 Chairs: Yutaka Shimomura, Satoru Shinkuma

C12-01 [P09-03] **Decomposition of skin RNA-seq data by Non-negative matrix factorization reveals various pathways in pathogenesis of Atopic dermatitis**

○ Ayano Fukushima-Nomura[1], Hiroshi Kawasaki[1,2], Kiyoshi Yashiro[1], Keiji Tanese[1], Eiryo Kawakami[3], Masayuki Amagai[1]

[1]Department of Dermatology, Keio University School of Medicine, Tokyo, Japan, [2]RIKEN Center for Integrative Medical Sciences, [3]RIKEN Advanced Data Science Project

C12-02 [P09-04] **Automated assessment of the severity of psoriasis by AI**

○ Takashi Okamoto[1], Masataka Kawai[2], Shinji Shimada[1], Tatsuyoshi Kawamura[1]

[1]The Department of Dermatology, University of Yamanashi, Yamanashi, Japan, [2]The Department of Human Pathology, University of Yamanashi, Yamanashi, Japan

C12-03 [P09-05] **Stimulator of IFN genes (STING) expression is a prognostic marker in patients with Merkel cell carcinoma**

○ Sayaka Sato, Yu Sawada, Etsuko Okada, Motonobu Nakamura

Department of Dermatology, University of Occupational and Environmental Health, Fukuoka, Japan

C12-04 [P09-06] **Ultra high-frequency ultrasound provides a novel noninvasive diagnostic method for hair diseases complementing conventional modalities**

○ Misaki Kinoshita-Ise[1,2,3], Manabu Ohyama[1], Stuart Foster[4,5], Shachar Sade[6], Neil H. Shear[3]

[1]The Department of Dermatology, Kyorin University Faculty of Medicine, [2]The Division of Dermatology, Department of Medicine, Sunnybrook Health Sciences Centre, [3]The Division of Dermatology, Department of Medicine, University of Toronto, [4]Sunnybrook Research Institute, [5]The Department of Medical Biophysics, University of Toronto, [6]The Division of Pathology, Department of Medicine, Sunnybrook Health Sciences Centre

C12-05 [P09-07] **Persistent HHV-6 infection has an increased risk of autoimmune disorders in patients with DIHS**

○ Yuki Nishimura[1], Chinatsu Shobatake[1], Fumi Miyagawa[1], Satoru Shinkuma[1], Hideaki Watanabe[2], Masahiro Kira[3], Saeko Nakajima[4], Yuko Higashi[5], Hideo Asada[1]

[1]Department of Dermatology, Nara Medical University School of Medicine, Nara, Japan, [2]Department of Dermatology, Showa University School of Medicine, Tokyo, Japan, [3]Department of Dermatology, Ikeda City Hospital, Ikeda, Japan, [4]Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan, [5]Department of Dermatology, Kagoshima University, Kagoshima, Japan

C12-06 [P09-08] **S100A2 is a potent biomarker of severe drug reaction**

○ Manabu Yoshioka, Yu Sawada, Motonobu Nakamura

Department of Dermatology, University of Occupational and Environmental Health, Fukuoka, Japan

C12-07 [P09-09] **Inflammatory type of acquired idiopathic generalized anhidrosis is characterized by dysregulation of sweat gland immune privilege**

○ Yurie Shimoda, Yoshimi Yamazaki, Yoshiko Mizukawa, Manabu Ohyama

Department of Dermatology, Kyorin University Faculty of Medicine, Tokyo, Japan

C12-08 [P09-10] **Lymphocyte count and neutrophil-to-lymphocyte ratio at the onset of herpes zoster are useful biomarker for predicting life prognosis**

○ Takenobu Yamamoto[1,2], Takuya Ohyama[1], Mariko Yamane[1], Yumi Aoyama[1]

[1]Department of Dermatology, Kawasaki Medical School, Kurashiki, Japan, [2]Department of Dermatology, Kawasaki Medical School General Medical Center, Okayama, Japan

December 5, 2021, Room D

JSID-Asia-Oceania-Forum
"Skin inflammation and autoimmunity"

13:50-16:10 Chairs: Hideyuki Ujiie, Rei Watanabe

JAOF1 **Metabolic Control of Epithelial-Immune Interaction in Skin Inflammation**

○ Srikala Raghavan

A*Star Skin Research Lab (ASRL), Agency for Science, Technology and Research (A*STAR)

JAOF2 **IKK/NF-κB signaling in keratinocytes regulates necroptosis-mediated skin inflammation**

○ Snehlata Kumari[1,2], Trieu-My Van[2], Manolis Pasparakis[2]

[1]The University of Queensland Diamantina Institute, Translational Research Institute, Brisbane, Australia, [2]CECAD Research Center, University of Cologne, Cologne, Germany

JAOF3 **Immune mechanism of immune checkpoint inhibitors-induced Stevens-Johnson syndrome and toxic epidermal necrolysis**

○ Chun-Bing Chen

The Department of Dermatology, Chang Gung Memorial Hospital

JAOF4 **Mechanisms of melanocyte death in vitiligo**

○ Chunying Li

Department of Dermatology, Xijing Hospital, Fourth Military Medical University, China

JAOF5 **The Significance of $CD4^+$ T cells in the Pathogenesis of Pemphigus**

○ Jong Hoon Kim

Yonsei University College of Medicine, Gangnam Severance Hospital, Seoul, Korea

December 3, 8:30 - January 11, 10:00, on-demand service

World Showcase of Investigative Dermatology

WS1 **Early Life Imprinting of a Th2-Stromal Cell Niche in Skin**

○ Michael D. Rosenblum

UCSF, Department of Dermatology

WS2 **Neuronal control of cutaneous inflammation**

○ Daniel Kaplan

University of Pittsburgh, Department of Dermatology/Secondary Appointment Department of Immunology/Cutaneous Biology Research Center/Dermatology Medical Student Research

WS3 **Neuroimmune Regulation of Itch**

○ Brian S. Kim

Department of Medicine, Division of Dermatology, Center for the Study of Itch and Sensory Disorders, Department of Anesthesiology, Department of Pathology and Immunology, Division of Biology and Biomedical Sciences, Washington University School of Medicine

WS4 **Cell therapy for pemphigus: entering the precision medicine era**

○ Aimee Payne

Dermatology, University of Pensylvania

WS5 **Translational research in vitiligo: Launching a new era of targeted treatments**

○ John E. Harris[1,2,3]

[1]Department of Dermatology UMass Medical School, Worcester, MA, [2]Vitiligo Clinic and Research Center, [3]Autoimmune Therapeutics Institute

WS6 **Computational systems medicine approach towards personalised treatment design of atopic dermatitis**

○ Reiko J Tanaka

Department of Bioengineering, Imperial College London

WS7 **The ultrastructure of a novel and dynamic endoplasmic reticulum-desmosome complex: Implications for skin disease**

Bharathan NK[1], Giang W[1], Aaron J[2], Khuon S[2], Chew TL[2], ○ Kowalczyk Andrew P.[1]

[1]Departments of Dermatology and Cellular and Molecular Physiology, Pennsylvania State College of Medicine, Hershey, PA, USA, [2]Advanced Imaging Center, Janelia Research Campus, Howard Hughes Medical Institute, Ashburn, Virginia

WS8 **Chromatin Dynamics for Diagnosis and Therapy**

Annie Collier, Angela Liu, Hanson Zhen, Jessica Torkelson, Kelly McCarthy, Tiffany Patel, ○ Anthony Oro

Program in Epithelial Biology Stanford University School of Medicine, Stanford, CA

WS9 **Scaling the Impact of Research-Based Innovation**

○ William Ju

Advancing Innovation in Dermatology, Inc.

WS10 **Principles of regeneration captured by imaging the skin of live mice**

○ Greco Valentina

Department of Genetics, Cell Biology and Dermatology, Yale University

WS11 **Skin regeneration during wound healing**

○ Mayumi Ito

The Ronald O. Perelman Department of Dermatology and Cell Biology, NYU Grossman School of Medicine, New York, USA

WS12 **Developmental cell programs in inflammatory skin disease**

○ Muzlifah Haniffa

Dermatology and Immunology, Newcastle University

WS13 **SARS-CoV2-driven immunopathology: lessons learned from the skin**

○ Michel Gilliet

Lausanne University Hospital CHUV, Switzerland

WS14 **Potency and activity of endovascular progenitors in wound healing and scarring**

○ Kiarash Khosrotehrani

The University of Queensland Diamantina Institute, Brisbane, Australia

December 3, 8:30 - January 11, 10:00, Digital Poster

Poster Presentation
2020 JSID's Fellowship Shiseido Research Grant

SE-1 [O01-01] **Observation of tight junction formation using cultured keratinocytes**

○ Hiroaki Iwata

Department of Dermatology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

SE-2 [O01-02] **Dynamics of epigenetic environment in skin inflammatory diseases**

○ Sayaka Shibata

Department of Dermatology, University of Tokyo Graduate School of Medicine

Category 1 (P01): Adaptive Immunity

P01-01 [II-1] **Lymphotoxin β from T cells mediates the formation of high endothelial venule-like vessels in atopic dermatitis-like skin lesions in mice**

○ Shuto Kanameishi[1], Sachiko Ono[1], Yuki Honda-Keith[1], Ryota Asahina[1], Tetsuya Honda[2], Kenji Kabashima[1,3]

[1]Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan, [2]Department of Dermatology, Hamamatsu University School of Medicine, Japan, [3]Singapore Immunology Network (SIgN) and Skin Research Institute of Singapore, Agency for Science, Technology and Research, Biopolis, Singapore

P01-02 [I-3] **AIM2 regulates anti-tumor immunity and serves as a therapeutic target for melanoma immunotherapy**

○ Keitaro Fukuda[1,2], Ken Okamura[2], Rebecca L. Riding[2], Xueli Fan[2], Sean M. McCauley[3], Jeremy Luban[3,4], Takeru Funakoshi[1], Tomonori Yaguchi[5], Yutaka Kawakami[5], Anastasia Khvorova[6,7], Katherine A. Fitzgerald[8], John E. Harris[2]

[1]Department of Dermatology, Keio University School of Medicine, Tokyo, Japan, [2]Department of Dermatology, University of Massachusetts Medical School, Worcester, MA, [3]Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, MA, [4]Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, MA, [5]Division of Cellular Signaling, Institute for Advanced Medical Research, Keio University School of Medicine, Tokyo, Japan, [6]RNA Therapeutics Institute, University of Massachusetts Medical School, Worcester, MA, [7]Department of Molecular Medicine, University of Massachusetts Medical School, Worcester, MA, [8]Department of Infectious Diseases and Immunology, University of Massachusetts Medical School, Worcester, MA.

P01-03 [C10-01] **Skin immune memory can be compensated by circulating CD4 T cells when the resident memory CD8 T cells are unfunctional**

○ Shuichi Nakai[1,2], Rei Watanabe[2], Kiyoshi Hirahara[3], Toshinori Nakayama[3], Manabu Fujimoto[2]

[1]Research Department, Maruho Co., Ltd., Kyoto, Japan, [2]Department of Dermatology, Graduate School of Medicine, Osaka University, Osaka, Japan, [3]Department of Immunology, Graduate School of Medicine, Chiba University, Chiba, Japan

P01-04 [C10-02] **Neutrophil extracellular traps are involved in enhanced contact hypersensitivity response in IL-36 receptor antagonist-deficient mice**

○ Yurie Hasegawa[1], Yohei Iwata[1], Hidehiko Fukushima[1], Yoshihito Tanaka[1], Soichiro Watanabe[1], Kenta Saito[1], Hiroyuki Ito[1], Mizuki Sugiura[1], Masashi Akiyama[2], Kazumitsu Sugiura[1]

[1]Department of Dermatology, Fujita Health University School of Medicine, Aichi, Japan, [2]Department of Dermatology, Nagoya University Graduate School of Medicine

P01-05 [C10-03] **Tumor necrosis factor-alpha plays crucial role in both the induction and maintenance of cytotoxic T lymphocyte-induced dermatitis**

○ Toshiya Miyake, Satoshi Nakamizo, Gyohei Egawa, Kenji Kabashima

Department of Dermatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

P01-06 [C10-04] **IL-31, a major pruritogen in a mouse model of atopic dermatitis, is generated through the macrophage/TSLP/periostin axis**

○ Takashi Hashimoto, Takahiro Satoh

Department of Dermatology, National Defense Medical College, Tokorozawa, Japan

P01-07 [C10-05] **Attenuation of DTH by oral tolerance depends on regulatory T cells in the sensitization phase**

○ Arisa Akagi[1], Akihiko Kitoh[2], Sho Hanakawa[2], Kenji Kabashima[1,2]

[1]Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan, [2]Singapore Immunology Network and Skin Research Institute of Singapore, Agency for Science, Technology and Research (A*STAR), Singapore

P01-08 [C10-06] **IL-10 production potency in peripheral blood B cells predicts prognosis of alopecia areata**

○ Yutaka Matsumura[1,2], Rei Watanabe[1], Yuumi Nakamura[1], Manabu Fujimoto[1]

[1]Department of Dermatology, Course of Integrated Medicine, Graduate School of Medicine, Osaka University, Osaka, Japan, [2]Department of Dermatology, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan

P01-09 [C10-07] **New epicutaneous sensitization model to protease antigen: itch-associated skin inflammation, a variety of Th subsets and IgE**

○ Tomoko Yoshimura[1,2], Toshiro Takai[1], Seiji Kamijo[1], Toru Kimitsu[1,2], Yurie Masutani[1,2], Takasuke Ogawa[2], Ko Okumura[1], Hideoki Ogawa[2], Shigaku Ikeda[1,2]

[1]Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine, [2]Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine

P01-10 [C10-08] **Revisiting the dogma of contact dermatitis; even single hapten application can induce allergic contact dermatitis in situ**

○ Gyohei Egawa, Kenji Kabashima

Department of Dermatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

P01-11 [O07-01] **Chronological classification of alopecia areata based on PD-1 expression revealed by scRNA-seq analysis-assisted immunohistochemistry**

○ Akiyoshi Senda, Toshiaki Kogame, Satoshi Nakamizo, Takashi Nomura, Naotomo Kambe, Kenji Kabashima

Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan

P01-12 [O07-02] **Treating pemphigus vulgaris (PV) and foliaceus (PF) by inhibiting the neonatal Fc receptor: phase 2 open-label trial with efgartigimod**

○ Matthias Goebeler[1], Zsuzsanna Bata-Csorgo[2], Clara De Simone[3], Biagio Didona[4], Eva Remenyik[5], Nataliya Reznichenko[6], Enno Schmidt[7], Johanna Stoevesandt[1], E. Sally Ward[8], Wim Parys[9], Hans de Haard[9], Patrick Dupuy[9], Peter Verheesen[9], Pascal Joly[10]

[1]Department of Dermatology, Venereology and Allergology, University Hospital Wuerzburg, Wuerzburg, Germany, [2]Department of Dermatology and Allergology, University of Szeged, Szeged, Hungary, [3]Catholic University Policlinic A. Gemelli, Rome, Italy, [4]Dermatopathic Institute of the Immaculate, Rome, Italy, [5]University of Debrecen, Debrecen, Hungary, [6]Zaporizhzhya State Medical University, Zaporizhzhya, Ukraine, [7]Department of Dermatology, University of Luebeck, Luebeck, Germany, [8]Centre for Cancer Immunology, University of Southampton, Southampton, UK, [9]argenx, Ghent, Belgium, [10]Department of Dermatology, Rouen University Hospital, Rouen, France

P01-13 [O07-03] **Elucidating the role of CARD14 signaling in Type 2 immune response**

○ Alshimaa Mostafa[1], Teruasa Murata[1], Teruki Dainichi[2], Ken Ishii[3], Kenji Kabashima[1,4]

[1]The Department Of dermatology, Kyoto University, Kyoto, Japan, [2]Department of Dermatology, Graduate school of Medicine, Kagawa university, Japan, [3]Institute of Medical Science, Division of Vaccine Science, Department of Microbiology and Immunology, The University of Tokyo, Japan, [4]The Singapore Immunology Network (SIgN) and Skin Research Institute of Singapore (SRIS), Agency for Science, Technology and Research (A*STAR), Singapore

P01-14 [O07-04] **The effect of topical 5-azacytidine in irritant and allergic contact dermatitis**

○ Youichi Ogawa, Shinji Shimada, Tatsuyoshi Kawamura

Department of Dermatology, University of Yamanashi, Yamanashi, Japan

P01-15 [O07-05] **Molecular mechanisms of mucosal mast cell differentiation**

○ Nobuhiro Nakano[1], Jiro Kitaura[1], Ko Okumura[1], Hideoki Ogawa[1,2], Shigaku Ikeda[1,2]

[1]Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine, Tokyo, Japan, [2]Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine, Tokyo, Japan

P01-16 [O07-06] **iSALT structures in B-cell type pseudolymphoma and their potential for local plasmacytoid differentiation in the skin**

○ Kosei Nanya[1], Toshiaki Kogame[1], Masahiro Hirata[2], Riko Takimoto-Ito[1], Masakazu Fujimoto[2], Takashi Nomura[1], Naotomo Kambe[1], Kenji Kabashima[1]

[1]Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan, [2]Department of Diagnostic Pathology, Kyoto University Hospital, Kyoto, Japan

P01-17 [O07-07] **Hyaluronan regulates murine irritant contact dermatitis model via Langerhans cell activation**

○ Mayuko Amagai, Hitoshi Terui, Naokazu Hatchome, Setsuya Aiba, Kenshi Yamasaki

Department of Dermatology, Tohoku University Graduate School of Medicine, Miyagi, Japan

P01-18 [O07-08] **A possible niche for B-cell development in the skin in primary cutaneous plasmacytosis suggesting the presence of a functional unit as iSALT**

○ Keigo Takase[1], Toshiaki Kogame[2], Riko Takimoto-ito[2], Takayoshi Komatsu-Fujii[1], Rintaro Shibuya[2], Takashi Nomura[2], Naotomo Kambe[2], Kenji Kabashima[2]

[1]Department of Dermatology, Tenri Hospital, Tenri, Nara, [2]Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan

P01-19 [O07-09] **Optimal methods for human skin T-cell analysis**

○ Takuya Sato, Youichi Ogawa, Shinji Shimada, Tatsuyoshi Kawamura

Department of Dermatology, University of Yamanashi, Chuo, Japan

P01-20 [O07-10] **Differentially expressed circulating exosomal microRNAs as biomarkers for disease severity in psoriasis patients**

○ Dong Chan Kim[1], Young Joon Park[1], So Min Kim[1], Ji Young Park[1], Mi Jin Park[1], Jae Youn Cheong[2], Eun-So Lee[1]

[1]Department of Dermatology, Ajou University School of Medicine, Suwon, Korea, [2]Ajou Translational Omics Center, Ajou University Medical Center, Suwon, Korea

P01-21 [O07-11] **Anti-inflammation effects of decanoic acid in a mouse of contact hypersensitivity: on a possible new drug for inflammatory skin disease**

○ Shohei Igari[1], Youichi Akama[2], Toshiyuki Yamamoto[1]

[1]The Department of Dermatology, Fukushima Medical University, Fukushima, Japan, [2]Department of Emergency, Minami Tohoku Hospital, Iwanuma, Miyagi

Category 2 (P02): Auto-Immunity

P02-01 [II-2] **Autoantigen-specific B cells targeted single-cell RNA-seq reveals the functional heterogeneity in pemphigus patients**

○ Shohei Egami[1,2], Takashi Watanabe[2], Ayano Nomura-Fukushima[1], Hisashi Nomura[1], Hayato Takahashi[1], Jun Yamagami[1], Osamu Ohara[3], Masayuki Amagai[1,2]

[1]The Department of Dermatology, Keio University of Medicine, Tokyo, Japan, [2]Laboratory for Skin Homeostasis, RIKEN Center for Integrative Medical Sciences, [3]Laboratory for integrative genomics, RIKEN Center for Integrative Medical Sciences

P02-02 [I-5] **Abnormally activated B cells with TLR9 up-regulation in Fli1-depleted mice: a possible predisposing condition for systemic sclerosis**

○ Kentaro Awaji[1], Takuya Miyagawa[1], Takashi Yamashita[1], Yuki Fukui[1], Jun Omatsu[1], Satoshi Toyama[1], Tetsuya Ikawa[1], Yuta Norimatsu[1], Yusuke Watanabe[1], Ayumi Yoshizaki[1], Maria Trojanowska[2], Shinichi Sato[1], Yoshihide Asano[1]

[1]The Department of Dermatology, University of Tokyo, Tokyo, Japan, [2]Arthritis Center, Boston University Medical Center, Boston, USA

P02-03 [C04-01] **Blockade of CD122 on skin resident memory T cells suppresses the development of mucocutaneous graft-versus-host disease**

○ Noriko Kubota[1], Ryota Tanaka[1], Yuki Ichimura[1], Risa Konishi[1], J Yun Tso[2], Naoya Tsurushita[2], Toshifumi Nomura[1], Naoko Okiyama[1]

[1]The Department of Dermatology, University of Tsukuba, Ibaraki, Japan, [2]JN Biosciences LLC

P02-04 [O12-07] **IFN-γ signaling has both pro-inflammatory and immunoregulatory roles depending on the cell types in interface dermatitis in mouse**

○ Miho Mukai[1], Hayato Takahashi[1], Masayuki Amagai[1,2]

[1]The Department of Dermatology, Keio University School of Medicine, Tokyo, Japan, [2]Laboratory for Skin Homeostasis, RIKEN IMS, Yokohama

P02-05 [O12-08] **IL-9 promotes skin inflammation via Pyy in imiquimod-induced psoriasis-like dermatitis**

○ Shiori Kamiya[1,2], Ippei Ikegami[2], Ryuta Kamekura[2], Keijyu Kobayashi[1,2], Takafumi Kamiya[1], Shingo Ichimiya[2], Hisashi Uhara[1]

[1]Department of Dermatology, Sapporo Medical University School of Medicine, Sapporo, Japan, [2]Department of Human Immunology, Research Institute for Frontier Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan

P02-06 [C04-02] **Activation of TNF/NF-κB signaling by linear ubiquitination specifically exacerbates a murine imiquimod-induced psoriasis model**

○ Ken I. Kosaka, Satoshi Nakamizo, Gyohei Egawa, Kenji Kabashima

Department of Dermatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

P02-07 [C04-03] **Possible involvement of IL-22-producing $CD8^+CD103^+$ T cells in the epidermal hyperplasia of atopic dermatitis**

○ Kazuo Kurihara[1], Toshiharu Fujiyama[1], Pawit Phadungsaksawasdi[1], Yoshiki Tokura[1,2], Tetsuya Honda[1]

[1]The Department of Dermatology, Hamamatsu University School of Medicine, Hamamatsu, Japan, [2]Allergic Disease Research Center and Department of Dermatology, Chutoen General Medical Center, Kakegawa, Japan

P02-08 [C04-04] **The role of FcγRIIB in a murine bleomycin-induced scleroderma model**

○ Kaori Sawada[1], Yasuhito Hamaguchi[1], Kie Mizumaki[1], Kyosuke Oishi[1], Shintaro Maeda[1], Yuka Ikawa[1], Akito Komuro[1,2], Kazuhiko Takehara[1], Takashi Matsushita[1]

[1]Department of Dermatology, Kanazawa University, Kanazawa, Japan, [2]Department of Plastic Surgery, Kanazawa University, Kanazawa, Japan

P02-09 [C04-05] **Serine protease inhibitor A3n, an endogenous granzyme B inhibitor, alleviates graft-versus-host disease reaction in human skin**

○ Yuki Ichimura[1], Risa Konishi[1], Ryota Tanaka[1], Noriko Kubota[1], Shoichiro Ishitsuki[1], Katsuhito Sasaki[1], Yasuyuki Nakamura[1], Yasuhiro Fujisawa[1], Toshifumi Nomura[1], Hideki Watanabe[2], Naoko Okiyama[1]

[1]Department of Dermatology, University of Tsukuba, Tsukuba, Japan, [2]Pharmacology Research Group, Research Department, Maruho Co., Ltd.

P02-10 [C04-06] **Occurrence of immune reconstitution inflammatory syndrome can be predicted by cytokine profiles in DPP-4i-associated bullous pemphigoid**

○ Seiko Sugiyama, Takenobu Yamamoto, Yumi Aoyama

Department of Dermatology, Kawasaki Medical School

P02-11 [C04-07] **Persistent dermatitis resulted in the gastro-intestinal amyloidosis, reduced absorption of nutrients, and hypoalbuminemia**

○ Takehisa Nakanishi, Kento Mizutani, Shohei Iida, Yoshiaki Matsushima, Ai Umaoka, Makoto Kondo, Koji Habe, Keiichi Yamanaka
The Department of Dermatology, Mie University Graduate School of Medicine

P02-12 [O12-09] **Periostin may act on monocytes to be differentiated into macrophages with fibrotic phenotype in patients with systemic sclerosis**

○ Mao Suzuki, Asami Akita-Enoki, Miho Asami, Yasushi Ototake, Noriko Komitsu-Ikeda, Yukie Yamaguchi
Department of Environmental Immuno-Dermatology Yokohama City University Graduate School of Medicine, Yokohama, Japan

P02-13 [O12-10] **Apremilast downregulates IL-17 production and induces splenic regulatory B and T cells in imiquimod-induced psoriasis**

○ Hideaki Uchida, Masahiro Kamata, Teruo Shimizu, Shota Egawa, Makoto Ito, Ryosuke Takeshima, Itsumi Mizukawa, Ayu Watanabe, Yayoi Tada
Department of Dermatology, Teikyo University, School of Medicine

P02-14 [O12-11] **Withdrawn**

P02-15 [O12-12] **Establishment of nail psoriasis mouse model by topical application of imiquimod**

○ Kana Yamada, Hisayoshi Imanishi, Daisuke Tsuruta
The Department of Dermatology, University of Osaka city, Osaka, Japan

P02-16 [O04-01] **Optimization of ELISAs for IgA antibodies in autoimmune bullous skin diseases**

○ Norito Ishii[1], Kwesi Teye[1], Hiroshi Koga[1], Takashi Hashimoto[2], Takekuni Nakama[1]
[1]Department of Dermatology, Kurume University School of Medicine, and Kurume University Institute of Cutaneous Cell Biology, Kurume, Japan, [2]Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan

P02-17 [O04-02] **Relationship between treatment responsiveness and immune checkpoints in Halo nevus**

○ Shinji Kano, Motoki Nakamura, Maki Yoshimitsu, Tetsuya Magara, Yuka Nojiri, Akihiro Matsubara, Hiroshi Kato, Akimichi Morita
Department of Geriatric and Environmental Dermatology, Nagoya City University

P02-18 [O04-03] **The presence of multiple epitopes within BP180 molecule in a case of dipeptidyl peptidase-4 inhibitor-related bullous pemphigoid**

○ Rikuma Kitao[1], Takeshi Fukumoto[1], Takashi Hashimoto[2], Kentaro Izumi[3], Haruki Jimbo[1], Chikako Nishigori[1,4]
[1]Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, Hyogo, Japan, [2]Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan, [3]Department of Dermatology, Hokkaido University Graduate School of Medicine, Hokkaido, Japan, [4]Department of iPS cell applications, Kobe University Graduate School of Medicine, Hyogo, Japan

P02-19 [O04-04] **Cautions for the discrepancy between CLEIA and ELISA and the presence of non-pathogenic antibodies are needed in pemphigus management**

○ Ai Yoshioka[1], Takeshi Fukumoto[1], Marie Ohata[2], Yumi Aoyama[3], Koji Kamiya[4], Takashi Hashimoto[5], Chikako Nishigori[1,6]
[1]Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, Hyogo, Japan, [2]Department of Dermatology, Kobe Ekisaikai Hospital, Hyogo, Japan, [3]Department of Dermatology, Kawasaki Medical School, Okayama, Japan, [4]Department of Dermatology, Jichi Medical University, Tochigi, Japan, [5]Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan, [6]Department of iPS Cell Applications, Kobe University Graduate School of Medicine, Hyogo, Japan

P02-20 [O04-05] **Effects of decanoic acid on imiquimod-induced psoriasis-like dermatitis in mice**

○ Kinuko Irie, Shohei Igari, Toshiyuki Yamamoto
Department of Dermatology, Fukushima Medical Univercity School of Medicine

P02-21 [O04-06] **Severe skin inflammation leads to salivary gland atrophy and dysfunction**

○ Yoshiaki Matsushima[1], Kento Mizutani[1], Shohei Iida[1], Masako Ichishi[2], Takehisa Nakanishi[1], Karin Okada[1], Ai Umaoka[1], Makoto Kondo[1], Koji Habe[1], Masatoshi Watanabe[2], Keiichi Yamanaka[1]
[1]Department of Dermatology, Mie University, Graduate School of Medicine, Mie, Japan, [2]Oncologic Pathology, Mie University, Graduate School of Medicine, Tsu, Mie, Japan

P02-22 [O04-07] **A new murine model of human eosinophilic fasciitis: role of IL-5 and IL-17**

○ Takashi Ito, Toshiyuki Yamamoto
Fukushima Medical University School of Medicine Department of Dermatology

Category 3 (P03): Carcinogenesis and Cancer

P03-01 [II-3] **Keratinocyte Regnase-1, a down-modulator of skin inflammation, contributes to protection from carcinogenesis through regulating COX2**

○ Hiroyuki Morisaka[1], Mikiro Takaishi[1], Shizuo Akira[2,3], Shigetoshi Sano[1]

[1]Department of Dermatology, Kochi Medical School, Kochi University, Kochi, Japan, [2]Laboratory of Host Defense, World Premier Institute Immunology Frontier Research Center (WPI-IFReC), Osaka University, Osaka, Japan, [3]Department of Host Defense, Research Institute for Microbial Diseases, Osaka University, Osaka, Japan

P03-02 [C11-01] **Frequent driver mutations of *FOXA1* in extramammary Paget's disease**

○ Takuya Takeichi[1], Yusuke Okuno[2], Takaaki Matsumoto[1], Nobuyuki Tsunoda[3], Kyogo Suzuki[4], Kana Tanahashi[1], Michihiro Kono[1,5], Toyone Kikumori[3], Yoshinao Muro[1], Masashi Akiyama[1]

[1]Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan, [2]Medical Genomics Center, Nagoya University Hospital, Nagoya, Japan, [3]Department of Breast and Endocrine Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan, [4]Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan, [5]Akita University Graduate School of Medicine, Akita, Japan

P03-03 [C11-02] **Clonal expansion of somatically-mutated keratinocytes in KID syndrome**

○ Yoshihiro Ishida, Mitsuasa Murata, Kenji Kabashima

Department of Dermatology, Kyoto University

P03-04 [C11-03] **Next-generation sequencing revealed tumor immunity-related factors interacting with tertiary lymphoid structures in cutaneous angiosarcoma**

○ Tetsuya Magara, Motoki Nakamura, Yuka Nojiri, Maki Yoshimitsu, Shinji Kano, Akihiro Matsubara, Hiroshi Kato, Akimichi Morita

Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Science, Japan

P03-05 [C11-04] **Loss of FAM83H plays a promoting role for cell migration and invasion in cutaneous squamous cell carcinoma via altered keratin distribution**

○ Keiko Tokuchi[1], Shinya Kitamura[1], Takuya Maeda[1], Masashi Watanabe[2], Shigetsugu Hatakeyama[2], Hideyuki Ujiie[1], Teruki Yanagi[1]

[1]The Department of Dermatology, Hokkaido University, Sapporo, Japan, [2]Department of Biochemistry, Hokkaido University, Sapporo, Japan

P03-06 [C11-05] **Blockade of glucose-6-phosphate dehydrogenase induces immunogenic cell death in malignant melanoma and Merkel cell carcinoma**

○ Motoki Nakamura, Tetsuya Magara, Maki Yoshimitsu, Yuka Nojiri, Shinji Kano, Akihiro Matsubara, Hiroshi Kato, Akimichi Morita

Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

P03-07 [C11-06] **DUSP4 positively controls the proliferation and infiltration ability of melanoma cells by activating ERK1/2 via downregulation of DUSP6**

○ Hirofumi Kamada[1,2], Shinji Yasuhira[2], Masahiko Shibazaki[2], Hiroo Amano[1], Chihaya Maesawa[2]

[1]Department of Dermatology, School of Medicine, Iwate Medical University, Iwate, Japan, [2]Department of Tumor Biology, Institute of Biomedical Science, Iwate Medical University, Iwate, Japan

P03-08 [C11-07] **Tumor suppressive effect of anti-PD-1 antibody against angiosarcoma in a mouse model**

○ Akiko Sekiguchi, Mai Ishikawa, Chisako Fujiwara, Yuta Inoue, Sahori Yamazaki, Akihiko Uchiyama, Sei-ichiro Motegi

Department of Dermatology, Gunma University Graduate School of Medicine, Maebashi, Japan

P03-09 [O10-01] **Combination treatment of topical imiquimod plus anti-programmed cell death 1 antibody exerts significantly potent antitumor effect**

○ Kazumasa Oya[1], Yoshiyuki Nakamura[1], Yasuhiro Fujisawa[1], Naoko Okiyama[1], Manabu Fujimoto[2], Toshifumi Nomura[1]

[1]The Department of Dermatology, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan, [2]Department of Dermatology, Integrated Medicine, Graduate School of Medicine, Osaka University, Suita, Osaka

P03-10 [O10-02] **Skin liquid biopsy method for assessing the lesional environment of cutaneous T-cell lymphoma**

○ Kan Torii[1], Yukinori Okada[2], Akimichi Morita[1]

[1]Department of Geriatric and Environmental Dermatology, Nagoya City University, Aichi, Japan, [2]Department of Statistical Genetics, Osaka University Graduate School of Medicine, Osaka, Japan

P03-11 [O10-03] **Global tyrosine kinome profiling revealed Src pathway as a novel therapeutic target in combination with HDAC inhibitors for CTCL**

○ Kazuyasu Fujii[1,2], Nozomi Jimura[1,2], Ryuto Tsuchiya[2], Yuki Yoshimatsu[2], Tadashi Kondo[2], Takuro Kanekura[1]

[1]The Department of Dermatology, Kagoshima University, Kagoshima, Japan, [2]Division of Rare Cancer Research, National Cancer Center Research Institute, Tokyo, Japan

P03-12 [O10-04] **Matrin-3 is involved in cell cycle and apoptosis for survival in melanoma**

○ Haruka Kuriyama[1], Toshihiro Kimura[1], Etsuko Okada[1], Takayuki Ishibashi[1], Satoru Mizuhashi[1], Hisashi Kanemaru[1], Ikko Kajihara[1], Katsunari Makino[1], Azusa Miyashita[1], Jun Aoi[1], Kanako Kita[1,2], Hironobu Ihn[1], Satoshi Fukushima[1]

[1]Department of Dermatology and Plastic Surgery, Kumamoto University, Kumamoto, Japan, [2]Department of Molecular Pathology, Graduate School of Medical Sciences, Kumamoto University

P03-13 [O10-05] **Frequent *FGFR3* and ras gene mutations in skin tags/acrochordons**

○ Satomi Aoki[1], Hisato Suzuki[2], Yoshiko Hirata[1], Tomoko Kawai[3], Kazuhiko Nakabayashi[3], Kenichiro Hata[3], Kenjiro Kosaki[2], Masayuki Amagai[1], Akiharu Kubo[1]

[1]Department of Dermatology, Keio University School of Medicine, [2]Center for Medical Genetics, Keio University School of Medicine, [3]Department of Maternal-Fetal Biology, National Center for Child Health and Development

P03-14 [O10-06] **Two opposite effects of desmoglein 3 on the growth of oral squamous cell carcinoma between anchorage-dependent and -independent conditions**

○ Michiyoshi Kouno[1], Junichiro Inada[2], Masaki Minabe[2], Yurie Akiyama[2], Kazunari Higa[3], Tetsuhiko Tachikawa[4], Takeshi Nomura[2], Shinichi Takahashi[1]

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P03-15 [O10-07] **AID expression of B cells in the tertiary lymphoid structures implies an immunoglobulin class switching in tumor immunity**

○ Tomoya Takegami, Toshiaki Kogame, Takashi Nomura, Naotomo Kambe, Takaya Komatsu, Kenji Kabashima

Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan

P03-16 [O10-08] **Serum Cytokeratin 18 as a Potential Prognostic, Diagnostic and Therapeutic Marker for Extramammary Paget's Disease**

○ Mariko Takaoka, Hayakazu Sumida, Takuya Miyagawa, Shinichi Sato

Department of Dermatology, Faculty of Medicine, The University of Tokyo, Tokyo, Japan

P03-17 [O10-09] **The MIF-CD74 interaction regulates the expression of PD-L1 in melanoma cells**

○ Keiji Tanese[1,2], Masako Imaoka[2], Yohei Masugi[2], Mutsumi Hayashi[2], Michiie Sakamoto[2]

[1]The Department of Dermatology, Keio University, Tokyo Japan, [2]The Department of Pathology, Keio University, Tokyo Japan

P03-18 [O10-10] **Functional analysis of Rap2 in tumor microenvironment**

○ Kimiko Takei[1,2], Masato Umikawa[2], Tsuyoshi Asato[2], Ken-ichi Kariya[2]

[1]Department of Dermatology, Faculty of Medicine, University of the Ryukyus, [2]Department of Medical Chemistry, Graduate School of Medicine, University of the Ryukyus

P03-19 [O10-11] **Clinicopathological parameters to predict prognosis in cutaneous angiosarcoma -a retrospective analysis**

○ Satoru Yonekura, Yuichiro Endo, Hiroko Fujii, Gyohei Egawa, Kenji Kabashima

The Department of Dermatology, Kyoto University, Kyoto, Japan

P03-20 [C11-08] **Investigating Proteome Changes Between Primary and Metastatic Cutaneous Squamous Cell Carcinoma Using Mass Spectrometry**

○ Ali Azimi[1,2], Kitty Lo[3], Jennifer Kim[4], Pablo Fernandez-Penas[1,2]

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P03-21 [O10-12] **Evaluating the efficacy of cetuximab, avelumab and cetuximab plus avelumab in treating perineural invasion of cutaneous SCC**

○ Priscila Oliveira de Lima[1], Benedict Lum[1], Shannon Joseph[1], Brian Tse[2], Kamil Sokolowski[2], Ian Brown[3], Glen Boyle[4], Benedict Panizza[5], Fiona Simpson[1]

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Category 4 (P04): Cell-Cell Interactions in the Skin

P04-01 [C06-01] **Antibodies to desmocollin (Dsc) 3, but not Dsc1, in pemphigus sera directly block heterophilic transinteraction between desmoglein and Dsc**

○ Ken Ishii[1], Norito Ishii[2], Akira Ishiko[1], Takashi Hashimoto[3]

[1]Department of Dermatology, Toho University School of Medicine, Tokyo, Japan, [2]Department of Dermatology, Kurume University School of Medicine, Kurume, Japan, [3]Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan

P04-02 [O02-10] **Antifibrogenic effects of sunitinib in a bleomycin-induced scleroderma model**

○ Masato Ishikawa, Toshiyuki Yamamoto

Department of Dermatology, Fukushima Medical University, Fukushima, Japan

P04-03 [O02-11] **Anti-glycation properties of Carnosine in 3D skin equivalent models and its implications in prevention of premature skin aging**

○ Jaimie Jerome[1], Ewa Markiewicz[2], Olusola Idowu[2], Tom Mammone[1]

[1]Estee Lauder Companies, [2]HexisLab Limited

Category 5 (P05): Epidermal Structure and Barrier Function

P05-01 [III-1] **An important role of Syntaxin-4 in nuclear degradation in corneoptosis, a unique cell death of keratinocytes**

○ Nanako Maekubo-Kadono[1], Keitaro Fukuda[1,2], Takeshi Matsui[1,2,3], Masayuki Amagai[1,2]

[1]Laboratory for Skin Homeostasis, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan, [2]Department of Dermatology, Keio University School of Medicine, Tokyo, Japan, [3]Laboratory for Evolutionary Cell Biology of the Skin, School of Bioscience and Biotechnology, Tokyo University of Technology, Hachioji, Japan

P05-02 [III-4] **Type XVII collagen contributes to epidermal patterning**

○ Yunan Wang[1], Hiroyuki Kitahata[2], Hideyuki Kosumi[1], Mika Watanabe[1,3], Yu Fujimura[1], Shota Takashima[1], Shin-Ichi Osada[4], Tomonori Hirose[5], Wataru Nishie[1], Masaharu Nagayama[6], Hideyuki Ujiie[1], Hiroshi Shimizu[1], Ken Natsuga[1]

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P05-03 [C06-02] **A skin-derived antimicrobial peptide human beta defensin-3-induced autophagy activation improves the skin barrier in atopic dermatitis**

○ Ge Peng[1], Yoshie Umehara[2], Juan Valentin Trujillo-Paez[2], Hainan Yue[1,2], Le Thanh Hai Nguyen[1,2], Risa Ikutama[1,2], Miho Takahashi[1,2], Masaaki Komatsu[3], Ko Okumura[2], Hideoki Ogawa[2], Shigaku Ikeda[1,2], Francois Niyonsaba[2,4]

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P05-04 [C06-03] **Wnt/β-catenin signaling stabilizes hemidesmosomes in keratinocytes**

○ Hideyuki Kosumi[1], Mika Watanabe[1,2], Satoru Shinkuma[3], Yu Fujimura[1], Tadasuke Tsukiyama[4], Giacomo Donati[2], Hiroaki Iwata[1], Hideyuki Ujiie[1], Ken Natsuga[1]

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P05-05 [O12-01] **Relationship between regulatory T cell distribution and interleukin -33 in a mouse model of skin barrier disruption**

○ Sumika Toyama[1], Catharina Sagita Moniaga[1], Mitsutoshi Tominaga[1], Hideoki Ogawa[1], Kenji Takamori[1,2]

[1]Juntendo Itch Research Center (JIRC), Institute for Environmental and Gender Specific Medicine, Juntendo University Graduate School of Medicine, Chiba, Japan, [2]Department of Dermatology, Juntendo University Urayasu Hospital, Chiba, Japan

P05-06 [C06-04] **New transparent three-dimension and deep imaging for skin epidermal structure using a novel fluorescent solvatochromic pyrene probe**

○ Masamoto Murakami[1], Ryosuke Kawakami[2], Yosuke Niko[3], Kazuki Yatsuzuka[1], Hideki Mori[1], Jun Muto[1], Ken Shiraishi[1], Takeshi Imamura[2], Koji Sayama[1]

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P05-07 [C06-05] **IL-33 is a negative regulator in skin barrier homeostasis**

○ Md. Razib Hossain, Tuba M. Ansary, Mayumi Komine

Department of Dermatology, Jichi Medical University, Tochigi, Japan

P05-08 [C06-06] **Loricrin maintains Langerhans cell homeostasis and protects against cutaneous chemical carcinogenesis**

○ Tatsuya Ogawa[1], Yosuke Ishitsuka[2], Manabu Fujimoto[2], Dennis R Roop[3], Toshifumi Nomura[1]

[1]Department of Dermatology, University of Tsukuba, Tsukuba, Japan, [2]Department of Dermatology, Osaka University, Osaka, Japan, [3]Department of Dermatology and Charles C. Gates Center for Regenerative Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO

P05-09 [C06-07] **Effect of ceramide chirality on the lipid lamellar structure in stratum corneum**

○ Yasuko Obata[1], Rie Arai[1], Takayuki Furuishi[1], Kaori Fukuzawa[1], Etsuo Yonemochi[1], Kenya Ishida[2]

[1]Hoshi University, [2]Takasago International Corporation

P05-10 [C07-01] **Development of a novel skin model combining SNF and collagen**

○ Mizuki Iijima[1], Kazutoshi Iijima[2]

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P05-11 [C07-02] **Nuclear factor erythroid 2-related factor 2 regulates epidermal keratinization under psoriatic skin inflammation**

○ Yosuke Ishitsuka[1,2], Tatsuya Ogawa[2], Manabu Fujimoto[1]

[1]Department of Dermatology, Osaka University Graduate School of Medicine, Suita, Japan, [2]University of Tsukuba

P05-12 [O12-02] **Upregulation of the NMF producing enzyme PAD1 by low humidity and low temperature climate gives the skin adaptability to dry environments**

○ Daichi Murata[1,2], Masashi Miyai[1], Toari Hirakawa[1], Hiroko Manabe[1], Katsuyuki Maeno[1], Akira Motoyama[1], Christopher_T Knight[1], Akihito Ishigami[2], Chika Katagiri[1]

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P05-13 [O12-03] **The sweating disturbance aggravates contact hypersensitivity reaction in mice footpads**

○ Hironobu Ishimaru[1], Yasuo Okamoto[1], Yumi Aoyama[2]

[1]Department of Pharmacology, Kawasaki Medical School, Okayama, Japan, [2]Department of Dermatology, Kawasaki Medical School, Okayama, Japan

P05-14 [O12-04] **TSLP impairs epidermal barrier integrity by the formation of nuclear IL-33/phosphorylated STAT3 complex in human keratinocytes**

○ Xiuju Dai, Jun Muto, Ken Shiraishi, Ryo Utsunomiya, Hideki Mori, Masamoto Murakami, Koji Sayama

Department of Dermatology, Ehime University Graduate School of Medicine, Ehime, Japan

P05-15 [C07-03] **The ligand of epidermal growth factor receptor, betacellulin, improves Th2 cytokine-mediated impairment of tight junction barrier**

○ Saya Tsukamoto[1], Ge Peng[1,2], Saori Yoshiba[1], Ko Okumura[1], Shigaku Ikeda[1,2], Francois Niyonsaba[1,3]

[1]Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine, Tokyo, Japan, [2]Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine, Tokyo, Japan, [3]Faculty of International Liberal Arts, Juntendo University

P05-16 [O12-05] **The contribution of single nucleotide polymorphisms of AKR1C3 to susceptibility of psoriasis**

○ Yuka Nojiri[1], Motoki Nakamura[1], Kyoko Ikumi[1], Haruna Nishihara[1], Aya Nakada[1], Emi Nishida[1], Thomas Haarmann-Stemmann[2], Akimichi Morita[1]

[1]Departments of Geriatric and Environmental Dermatology, Nagoya City University, Nagoya, Japan, [2]Leibniz Research Institute for Environmental Medicine, Dusseldorf, Germany

P05-17 [O12-06] **Sphingosine 1-phosphate receptor 1 (S1PR1) negatively regulates epidermal barrier function**

○ Satomi Igawa[1], Manae Takahashi[1], Risa Matsuo[1], Mari Kishibe[1], Akemi Ishida-Yamamoto[1], Anna Di Nardo[2]

[1]The Department of Dermatology, Asahikawa Medical University, Asahikawa, Japan, [2]The Department of Dermatology, School of Medicine, University of California, San Diego, La Jolla, USA

P05-18 [O09-05] **Antimicrobial peptide AG30/5C modulates tight junction barrier function in keratinocytes via EGFR, aPKC, GSK-3 and Rac1 pathways**

○ Risa Ikutama[1,2], Ge Peng[1,2], Yoshie Umehara[1], Juan V. Trujillo Paez[1], Hainan Yue[1,2], Hai Le Thanh Nguyen[1,2], Miho Takahashi[1,2], Shun Kageyama[3], Masaaki Komatsu[3], Ko Okumura[1], Hideoki Ogawa[1], Shigaku Ikeda[1,2], François Niyonsaba[1,4]

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P05-19 [O09-06] **Mechanisms underlying the suppression of semaphorin 3A expression in atopic dermatitis**

○ Yayoi Kamata[1,2], Mitsutoshi Tominaga[1,2], Yasushi Suga[2,3], Hideoki Ogawa[1], Kenji Takamori[1,2,3]

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P05-20 [O09-07] **A skin-derived antimicrobial peptide AMP-IBP5 regulates epidermal barrier function**

○ Hai L.T. Nguyen[1,2], Juan V. Trujillo P.[1], Ge Peng[1,2], Hainan Yue[1,2], Risa Ikutama[1,2], Miho Takahashi[1,2], Yoshie Umehara[1], Hideoki Ogawa[1,2], Ko Okumura[1], Shigaku Ikeda[1,2], Francois Niyonsaba[1,3]

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P05-21 [O09-08] **Spatial distribution of KLK, SPINK, and SERPIN family proteins contributes to dense stratum corneum of normal sole skin and PPK phenotypes**

○ Aoi Ohira, Takuya Omine, Daisuke Utsumi, Sayaka Yamaguchi, Kenzo Takahashi

Department of Dermatology, University of the Ryukyus, Graduate School of Medicine, Okinawa, Japan

P05-22 [O09-09] **Detergent-induced skin inflammation and itch in a mast cell-independent and antihistamine-resistant manner in C57BL/6 mice**

○ Yurie Masutani[1,2], Toshiro Takai[1], Seiji Kamijo[1], Toru Kimitsu[1,2], Tomoko Yoshimura[1,2], Ko Okumura[1], Hideoki Ogawa[2], Shigaku Ikeda[1,2]

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P05-23 [O09-10] **Possible roles of advanced glycated end-products in pathogenesis of acquired perforating dermatosis**

○ Yuya Murase[1], Takuya Takeichi[1], Kana Tanahashi[1], Hiroyuki Takama[2], Masashi Akiyama[1]

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P05-24 [O09-11] **Functional analysis of BCL6 in epidermal cells**

○ Kaori Kanemaru[1], Kento Nagasawa[1], Asahi Tanaka[1], Yohsuke Harada[2], Yoshikazu Nakamura[1]

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Category 6 (P06): Genetic Disease, Gene Regulation and Gene Therapy

P06-01 [I-1] **CRISPR/Cas9 targeting an intronic region for retrieving Col17 expression in junctional epidermolysis bullosa model mice**

○ Hong Ha Nguyen[1], Satoru Shinkuma[1,2,3], Ryota Hayashi[1], Shota Takashima[3], Masashi Mori[4], Masahito Ikawa[4], Hiroshi Shimizu[3], Riichiro Abe[1]

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P06-02 [C08-02] **Altered replication stress response due to *CARD14* mutations induces somatic genetic reversion**

○ Toshinari Miyauchi[1], Shotaro Suzuki[1], Masae Takeda[1], Jin Teng Peh[1], Masayuki Aiba[1], Ken Natsuga[1], Yasuyuki Fujita[1], Takuya Takeichi[2], Taiko Sakamoto[3], Masashi Akiyama[2], Hiroshi Shimizu[1], Hideyuki Ujiie[1], Toshifumi Nomura[1,4]

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P06-03 [C08-03] **A novel keratin 14 mutation in epidermolysis bullosa induces more morphological abnormalities in keratin fiber than a hotspot mutation**

○ Mari Kishibe[1], Risa Matsuo[1], Satomi Igawa[1], Akiharu Kubo[2], Akemi Ishida-Yamamoto[1]

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P06-04 [C08-04] **Diversity of Mechanisms Underlying Dysregulating TGF-β Signaling in Recessive Dystrophic Epidermolysis Bullosa**

○ Eijiro Akasaka[1], Alexander Nyström[2], Leena Bruckner-Tuderman[2], Hajime Nakano[1], Daisuke Sawamura[1]

[1]Department of Dermatology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan, [2]Department of Dermatology, Faculty of Medicine and Medical Center - University of Freiburg, Germany

P06-05 [C08-05] **Psoriasis-like skin lesions in a patient carrying *MEFV* variants**

○ Takenori Yoshikawa[1], Takuya Takeichi[1], Tomoo Ogi[2], Masashi Akiyama[1]

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P06-06 [C08-06] **Transcriptional and translational interference of laminin-332 subunits in junctional epidermolysis bullosa with *LAMB3* mutations**

○ Ping-Chen Hou[1,2,3], Ken Natsuga[4], Wei-Ting Tu[1,3], Hsin-Yu Huang[1], Brandon Chen[3], Liang-Yu Chen[2,3], Wan-Rung Chen[1], Yi-Kai Hong[1,3], Yen-An Tang[5,6], Julia Yu-Yun Lee[1], Peng-Chieh Chen[7,8], H. Sunny Sun[5,6], John A. McGrath[9], Chao-Kai Hsu[1,3,7,10]

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P06-07 [O02-01] **Aberrant keratin assembly causes impaired mitochondrial movement and function: Implications for epidermolysis bullosa simplex pathogenesis**

○ Osamu Ansai[1], Ryota Hayashi[1], Satoru Shinkuma[2], Asuka Suto[3], Hiroshi Shimizu[3], Riichiro Abe[1]

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P06-08 [O02-02] **Mutations in SAM syndrome and palmoplantar keratoderma patients suggest genotype/phenotype correlations in *DSG1* mutations**

○ So Takeuchi[1], Takuya Takeichi[1], Yuta Koike[2], Hiroyuki Takama[3], Kana Tanahashi[1], Yusuke Okuno[4], Norito Ishii[5], Yoshinao Muro[1], Tomoo Ogi[6], Yasushi Suga[7], Masashi Akiyama[1]

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P06-09 [O02-03] **Atypical epidermolytic palmoplantar keratoderma caused by *KRT1* mutation is considered as mild type epidermolytic ichthyosis**

○ Ryota Hayashi[1], Osamu Ansai[1], Rei Yokoyama[1], Tatsuya Katsumi[1], Mahoko Oginezawa[1], Tomoki Nishiguchi[1], Satoru Shinkuma[2], Riichiro Abe[1]

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P06-10 [O02-04] **Delineating the functional relevance of different lamin A domains that accelerate human ageing**

○ Oliver Dreesen, Peh Fern Ong, Mattheus XR Foo

Skin Research Institute of Singapore

P06-11 [O02-05] **Evidence for a dominant-negative effect of a missense mutation in the *SERPING1* gene responsible for hereditary angioedema type I**

○ Shuichiro Yasuno[1], Osamu Ansai[2], Sawako Nakamura[1], Yutaka Shimomura[1]

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P06-12 [O02-06] **Hereditary mucoepithelial dysplasia/autosomal-dominant IFAP syndrome is a clinical spectrum due to *SREBF1* variants**

○ Chiaki Murase[1], Takuya Takeichi[1], Toshifumi Nomura[2], Tomoo Ogi[3], Masashi Akiyama[1]

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P06-13 [O02-07] **Updated allele frequencies of *SERPINB7* founder mutations in Asian patients with Nagashima-type palmoplantar keratosis/keratoderma**

○ Yasutoshi Ito[1], Takuya Takeichi[1], Kenta Ikeda[2], Kana Tanahashi[1], Takenori Yoshikawa[1], Yuya Murase[1], Yoshinao Muro[1], Yoshio Kawakami[3], Jun Muto[4], Kazumitsu Sugiura[5], Yasushi Suga[6], Mariko Seishima[7], Akira Kawada[8], Tomoo Ogi[9], Masashi Akiyama[1]

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P06-14 [O02-08] **Bradykinin pathogenesis in hereditary angioedema based on the discovery of novel genetic mutations in ACE and SERPING7 gene**

○ Takuya Omine, Takuya Miyagi, Daisuke Utumi, Sayaka Yamaguhi, Kenzo Takahashi

University of the Ryukyus

P06-15 [O02-09] **A microchip flow-chamber assay can be a powerful tool for detecting platelet function defects in Hermansky-Pudlak syndrome**

○ Satoru Shinkuma[1], Hidetaka Kinoshita[1], Kenichi Ogiwara[2], Kengo Hamada[1], Kohei Ogawa[1], Fumi Miyagawa[1], Keiji Nogami[2], Hideo Asada[1]

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Category 7 (P07): Innate Immunity, Microbiology, Microbiome

P07-01 [I-2] **Migration and local adaptation of integrinβ7-positive mast cell progenitors in murine allergic skin**

○ Yuki H Keith[1], Tetsuya Honda[2], Sachiko Ono[1], Bernett Lee[3], Satoshi Nakamizo[1], Sho Hanakawa[3], Yoshihiro Ishida[1], Kenji Kabashima[1,3]

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P07-02 [I-4] **Type I IFN derived from inflammatory monocytes controls type 2 inflammation by suppressing basophil proliferation in atopic dermatitis**

○ Fumi Miyagawa, Hideo Asada

Department of Dermatology, Nara Medical University School of Medicine, Kashihara, Japan

P07-03 [C01-01] **CCL2-CCR2 signaling in the skin drives surfactant-induced irritant contact dermatitis via IL-1β-mediated neutrophil accumulation**

○ Rintaro Shibuya[1], Yoshihiro Ishida[1], Sho Hanakawa[2], Tatsuki R. Kataoka[3], Akihiko Kitoh[2], Kenji Kabashima[1,2]

[1]Department of Dermatology, Kyoto University Graduate School of Medicine, [2]Singapore Immunology Network and Skin Research Institute of Singapore, Agency for Science, Technology and Research (A*STAR), Singapore, [3]Department of Molecular Diagnostic Pathology, Iwate Medical University

P07-04 [C01-02] **IκBζ-deficient epidermis mediates systemic autoimmune inflammation via skin dysbiosis**

○ Hitoshi Terui[1], Moyuka Wada-Irimada[1], Mayuko Onodera-Amagai[1], Naokazu Hatchome[1], Masato Mizuashi[1], Riu Yamashita[2], Setsuya Aiba[1], Kenshi Yamasaki[1]

[1]Department of Dermatology, Tohoku University Graduate School of Medicine, Miyagi, Japan, [2]Division of Translational Informatics, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Chiba, Japan

P07-05 [C01-03] **T-cell receptor signaling pathways that regulate functional reprogramming of γδ T cells in the perinatal epidermis**

○ Atsuko Ibusuki[1], Kazuhiro Kawai[1,2], Takuro Kanekura[1]

[1]Department of Dermatology, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan, [2]Department of Dermatology, Kido Hospital, Niigata, Japan

P07-06 [C01-04] **Proteomics analysis of bacterial and fungal composition in skin and serum extracellular vesicles**

○ Toru Kawai[1], Ryota Hayashi[1], Akito Hasegawa[1], Akari Sakai[1], Osamu Ansai[1], Koichi Tomii[1], Tomoki Nishiguchi[1], Jun Adachi[2,3], Takeshi Tomonaga[2,3], Riichiro Abe[1]

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P07-07 [C01-05] **TREM2/APOE-double positive macrophages as possible pathogenic cells in sarcoidosis**

○ Satoshi Nakamizo, Yoshihiro Ishida, Gyohei Egawa, Kenji Kabashima

Department of Dermatology Kyoto University Graduate School of Medicine, Kyoto, Japan

P07-08 [O05-01] **Dysbiosis mediates inflammatory destruction of the hair follicles**

○ Keiko Sakamoto[1], Seon-Pil Jin[1], Shubham Goel[1], Jay-Hyun Jo[2], Benjamin Voisin[1], Doyoung Kim[1], Vinod Nadella[1], Hai Liang[2], Tetsuro Kobayashi[1], Xin Huang[3], Clay Deming[3], Keisuke Horiuchi[4], Julia_A Segre[3], Heidi_H Kong[2], Keisuke Nagao[1]

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P07-09 [C01-06] **Purinergic molecules in murine bone marrow-derived mast cells**

○ Riko Asakawa, Youichi Ogawa, Shinji Shimada, Tatsuyoshi Kawamura

The Department of Dermatology, Faculty of Medicine, University of Yamanashi, Yamanashi, Japan

P07-10 [C01-07] **Granzyme K cleaves protease-activated receptor-2 and induces itch**

○ Sho Hiroyasu[1,2,3], Matthew R. Zeglinski[2,3], Hongyan Zhao[2,3], Aoi Hiroyasu[1], Daisuke Tsuruta[1], David J. Granville[2,3]

[1]The Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan, [2]International Collaboration On Repair Discoveries (ICORD) Centre, Vancouver, BC, Canada, [3]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada

P07-11 [C08-01] **Involvement of V δ1+ epithelial type of γδT cells in the systemic form of hydroa vacciniforme-like lymphoproliferative disorders**

○ Yoji Hirai[1], Tomoko Miyake[1], Takahide Takahashi[2], Keiji Iwatsuki[1,3,4], Shin Morizane[1]

[1]Department of Dermatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan, [2]Division of Medical Support, Okayama University Hospital, Okayama, Japan, [3]Division of Dermatology, Fukushima Rosai Hospital, Iwaki, Japan, [4]Division of Dermatology, Okazaki Medical Center, Fujita Health University, Okazaki, Japan

P07-12 [O05-02] **An antimicrobial peptide cathelicidin triggers skin inflammation with other DAMPs via multiple receptors**

○ Ryo Amagai, Toshiya Takahashi, Taku Fujimura, Kenshi Yamasaki

Department of dermatology, Tohoku University Graduate School of medicine, Miyagi, Japan

P07-13 [O05-03] **Potential role of neutrophil elastase (NE) in the development of nephrogenic systemic fibrosis (NSF) in an in vivo model of renal failure**

○ Syahla N. Amalia[1], A. Adhipatria. P Kartamihardja[2], Anu Bhattarai[3], Akiko Sekiguchi[1], Ayako Taketomi-Takahashi[2], Sei-ichiro Motegi[1], Hiroshi Koyama[4], Yoshito Tsushima[2,5]

[1]Department of Dermatology, Gunma University, Maebashi, [2]Department of Diagnostic Radiology and Nuclear Medicine, Gunma University, Maebashi, Japan, [3]National Academy of Medical Sciences (NAMS), Bir Hospital, Nepal, [4]Department of Public Health, Gunma University, Maebashi, Japan, [5]Division of Integrated Oncology Research, Gunma Initiative for Advanced Research, Japan

P07-14 [O05-04] **Coordinated expression of retrotransposon and type I interferon with distinct interferon pathways in autoimmune diseases**

○ Yuko Kuriyama[1], Akira Shimizu[1,2], Saki Kanai[1], Daisuke Oikawa[3], Fuminori Tokunaga[3], Osamu Ishikawa[1], Sei-ichiro Motegi[1]

[1]The Department of Dermatology, Gunma University Graduate School of Medicine, Gunma, Japan, [2]Department of Dermatology, Kanazawa Medical University, Ishikawa, Japan, [3]Department of Pathobiochemistry, Graduate School of Medicine, Osaka City University, Osaka, Japan

P07-15 [O05-05] **Macrophages express βKlotho in skin lesions of psoriasis patients and the skin of imiquimod-treated mice**

○ Kozo Nakai[1], Reiji Haba[2], Yoshio Kushida[2], Yasuo Kubota[3], Daisuke Tsuruta[1]

[1]Department of Dermatology, Osaka City University Graduate School of Medicine, [2]Department of Diagnostic Pathology, Kagawa University, [3]Department of Dermatology, Kagawa University

P07-16 [O05-06] **Skin Inflammation and Testicular Function**

○ Ai Umaoka[1], Hiroki Takeuchi[2], Kento Mizutani[1], Naohiro Seo[3], Yoshiaki Matsushima[1], Shohei Lida[1], Makoto Kondo[1], Koji Habe[1], Tomoaki Ikeda[2], Keiichi Yamanaka[1]

[1]Department of Dermatology Mie University, Graduate School of Medicine, Japan, [2]Obstetrics and Gynecology, Mie University Graduate School of Medicine, [3]Immuno-Gene Therapy, Mie University Graduate School of Medicine

P07-17 [O05-07] **Roles of interferon regulatory factor 3 in murine models of allergic and irritant dermatitis**

○ Risa Tamagawa-Mineoka[1], Mayumi Ueta[2], Yukiyasu Arakawa[1], Mari Nakanishi[1], Hiromi Nishigaki[1], Risa Yasuike[1], Norito Katoh[1]

[1]Departments of Dermatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, [2]Departments of Ophthalmology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine

P07-18 [O05-08] **Internalization of live atopic dermatitis-derived Staphylococcus aureus into HaCaT cells and inhibition by Staphylococcus epidermidis**

○ Tomofumi Numata, Kazumasa Iwamoto, Ryu Miyake, Michihiro Hide, Akio Tanaka

Department of Dermatology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima

P07-19 [O05-09] **Low heterogeneity among isolates of *Cutibacterium modestum*: Resident of human skin with possible infectious nature**

○ Itaru Dekio[1,2], Ken-ichi Okuda[3], Masako Nishida[4], Susumu Hamada-Tsutsumi[5], Hiroto Tamura[5], Kenichiro Ohnuma[4], Yoshiyuki Murakami[2], Yuki Kinjo[3], Akihiko Asahina[1]

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P07-20 [O05-10] **Cutaneous adverse events caused by EGFR inhibitors may result from reduced expression of human β-defensins induced by staphylococci**

○ Rie Ommori, Yuki Nishimura, Fumi Miyagawa, Chinatsu Shobatake, Kohei Ogawa, Satoru Shinkuma, Hideo Asada

The Department of Dermatology, Nara Medical University, Nara, Japan

P07-21 [O05-11] **Alternation of the cutaneous microbiome of herpes zoster lesion in a patient with severe coronavirus disease 2019**

○ Makoto Kondo[1,2], Asami Ito[2], Yoshiaki Matsushima[1], Shohei Iida[1], Ai Umaoka[1], Takehisa Nakanishi[1], Hiroshi Imai[2], Keiichi Yamanaka[1]

[1]Department of Dermatology Mie University, Graduate School of Medicine, Japan, [2]Emergency Critical Care Center, University of Mie, Mie, Japan

P07-22 [O05-12] **Postbiotics power in supporting skin**

○ Nadine Pernodet[1], Don Collins[3], Yulan Qu[2], Nan Frank Huang[2], Jian Richard Cao[2]

[1]Research & Development, The Estee Lauder Companies, Estee Lauder Research Laboratories, [2]Asia Innovation Center, the Estee Lauder Companies, [3]Research & Development, The Estee Lauder Companies

Category 8 (P08): Patient Population Research

P08-01 [III-5] **Estimation of cutaneous squamous cell carcinoma incidence attributable to arsenic in U.S. water supplies**

○ Masaoki Kawasumi

Division of Dermatology, Department of Medicine, University of Washington, Seattle, WA, United States

P08-02 [C02-01] **Plasma metabolome-wide analysis in Japanese identifies potential biomarkers of psoriasis and clinical subtypes**

○ Yukinori Okada[1,2], Toshihiro Kishikawa[1,3], Noriko Arase[4], Shigeyoshi Tsuji[5], Yuichi Maeda[6,7], Takuro Nii[6,7], Jun Hirata[1], Ken Suzuki[1], Kenichi Yamamoto[1,8], Shiro Ohshima[5], Hidenori Inohara[3], Atsushi Kumanogoh[2,5], Manabu Fujimoto[2,4]

[1]Department of Statistical Genetics, Osaka University Graduate School of Medicine, Suita, Japan, [2]Immunology Frontier Research Center (WPI-IFReC), Osaka University, Suita, Japan, [3]Department of Otorhinolaryngology-Head and Neck Surgery, Osaka University Graduate School of Medicine, Suita, Japan, [4]Department of Dermatology, Osaka University Graduate School of Medicine, Suita, Japan, [5]NHO Osaka Minami Medical Center, Kawachinagano, Osaka, Japan, [6]Department of Respiratory Medicine and Clinical Immunology, Osaka University Graduate School of Medicine, Suita, Japan, [7]Department of Immune Regulation, Osaka University Graduate School of Medicine, Suita, Japan, [8]Department of Pediatrics, Osaka University Graduate School of Medicine, Suita, Japan

P08-03 [C02-02] **Prevalence, comorbidities, and treatment patterns of Japanese patients with alopecia areata: a descriptive study using JMDC claims database**

○ Eduardo Kawasaki[1], Tomohiro Hirose[1], Manabu Ohyama[2]

[1]Medical Affairs, Pfizer Japan, [2]Department of Dermatology, Kyorin University Faculty of Medicine

P08-04 [O11-01] **Pork allergies in Japanese urban areas are predominantly classified as pork-cat syndrome**

○ Naoko Inomata, Nobuko Sagawa, Fumi Sawada, Saori Sano, Michiko Aihara

Dept. of Environmental Immuno-Dermatology Yokohama City University Graduate School of Medicine

P08-05 [C02-03] **Prevalence of malignancies in Japanese psoriasis patients and selected treatments in the West Japan Psoriasis Registry**

○ Takuya Miyagi[1,3], Kenzo Takahashi[1,3], Noriko Tsuruta[2,3], Shinichi Imafuku[2,3]

[1]Department of Dermatology, University of the Ryukyus, Graduate school of medicine, Okinawa, Japan, [2]Fukuoka University, [3]Western Japan Inflammatory Disease Research Group

P08-06 [O11-02] **The Clinical Significance of a Shortened Activated Partial Thromboplastin Time in Patients with Connective Tissue Disease**

○ Koji Habe[1], Hideo Wada[2], Kento Mizutani[1], Yoshiaki Matsushima[1], Makoto Kondo[1], Keiichi Yamanaka[1]

[1]Department of Dermatology, Mie University Graduate School of Medicine, Mie, Tsu, Japan, [2]Department of General and Laboratory Medicine, Mie Prefectural General Medical Center

P08-07 [O11-03] **Prevalence and Characteristics of Prurigo Nodules in Adults With Moderate-to-severe Atopic Dermatitis in Japan: a 2-year Observational Study**

○ Norito Katoh[1], Hidehisa Saeki[2], Yoko Kataoka[3], Takafumi Etoh[4], Satoshi Teramukai[5], Yuki Tajima[6], Parul Shah[7], Kazuhiko Arima[6]

[1]Kyoto Prefectural University of Medicine Graduate School of Medical Science, Kyoto, Japan, [2]Nippon Medical School, Tokyo, Japan, [3]Osaka Habikino Medical Care Center, Osaka, Japan, [4]Tokyo Teishin Postal Services Agency Hospital, Tokyo, Japan, [5]Kyoto Prefectural University of Medicine, Kyoto, Japan, [6]Sanofi, K.K., Tokyo, Japan, [7]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

P08-08 [O11-04] **Withdrawn**

P08-09 [O11-05] **Psoriasis Epidemiology Screening Tool (PEST) is a useful tool for psoriatic arthritis in the Japanese population**

○ Ayako Setoyama, Yu Sawada, Motonobu Nakamura

The Department of Dermatology, University of Occupational and Environmental Health, Fukuoka, Japan

P08-10 [O11-06] **The impact of atopic dermatitis on health-related quality of life in Bangladeshi adults**

○ Abir Majbauddin[1], Taheruzzaman Kazi[1], Zubaida Akter[2], Shigeki Inui[1]

[1]Department of Regenerative Dermatology, Graduate School of Medicine, Osaka University, Osaka, Japan, [2]Department of Dermatology & Venereology, Shaheed Suhrawardy Medical College Hospital, Dhaka, Bangladesh

P08-11 [O11-07] **A clinical investigation for superficial type atypical lipomatous tumor**

○ Emi Mashima, Yu Sawada, Motonobu Nakamura

The Department of Dermatology, University of Occupational and Environmental Health, Fukuoka, Japan

P08-12 [O11-08] **A single-center survey of psoriasis patients on biologics during the COVID-19 pandemic**

○ Koji Kamiya, Soichiro Kado, Megumi Kishimoto, Takeo Maekawa, Aya Kuwahara, Junichi Sugai, Mayumi Komine, Mamitaro Ohtsuki

Department of Dermatology, Jichi Medical University, Shimotsuke, Japan

Category 9 (P09): Patient-Targeted Research

P09-01 [II-5] **Basal sweating as unrecognized machinery to maintain skin hydration in the finger: a long-standing paradox in dry skin resolved**

○ Tetsuko Sato, Chieko Katayama, Yuki Hayashida, Yumiko Asanuma, Yumi Aoyama

Department of dermatology, Kawasaki Medical School, Okayama, Japan

P09-02 [II-6] **Increased serum levels ofCCL2 and IL-8 in patients with toxic epidermal necrolysis accompanied by acute respiratory distress syndrome**

○ Tomoya Watanabe, Yuko Watanabe, Michiko Aihara, Yukie Yamaguchi

Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

P09-03 [C12-01] **Decomposition of skin RNA-seq data by Non-negative matrix factorization reveals various pathways in pathogenesis of Atopic dermatitis**

○ Ayano Fukushima-Nomura[1], Hiroshi Kawasaki[1,2], Kiyoshi Yashiro[1], Keiji Tanese[1], Eiryo Kawakami[3], Masayuki Amagai[1]

[1]Department of Dermatology, Keio University School of Medicine, Tokyo, Japan, [2]RIKEN Center for Integrative Medical Sciences, [3]RIKEN Advanced Data Science Project

P09-04 [C12-02] **Automated assessment of the severity of psoriasis by AI**

○ Takashi Okamoto[1], Masataka Kawai[2], Shinji Shimada[1], Tatsuyoshi Kawamura[1]

[1]The Department of Dermatology, University of Yamanashi, Yamanashi, Japan, [2]The Department of Human Pathology, University of Yamanashi, Yamanashi, Japan

P09-05 [C12-03] **Stimulator of IFN genes (STING) expression is a prognostic marker in patients with Merkel cell carcinoma**

○ Sayaka Sato, Yu Sawada, Etsuko Okada, Motonobu Nakamura

Department of Dermatology, University of Occupational and Environmental Health, Fukuoka, Japan

P09-06 [C12-04] **Ultra high-frequency ultrasound provides a novel noninvasive diagnostic method for hair diseases complementing conventional modalities**

○ Misaki Kinoshita-Ise[1,2,3], Manabu Ohyama[1], Stuart Foster[4,5], Shachar Sade[6], Neil H. Shear[3]

[1]The Department of Dermatology, Kyorin University Faculty of Medicine, [2]The Division of Dermatology, Department of Medicine, Sunnybrook Health Sciences Centre, [3]The Division of Dermatology, Department of Medicine, University of Toronto, [4]Sunnybrook Research Institute, [5]The Department of Medical Biophysics, University of Toronto, [6]The Division of Pathology, Department of Medicine, Sunnybrook Health Sciences Centre

P09-07 [C12-05] **Persistent HHV-6 infection has an increased risk of autoimmune disorders in patients with DIHS**

○ Yuki Nishimura[1], Chinatsu Shobatake[1], Fumi Miyagawa[1], Satoru Shinkuma[1], Hideaki Watanabe[2], Masahiro Kira[3], Saeko Nakajima[4], Yuko Higashi[5], Hideo Asada[1]

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P09-08 [C12-06] **S100A2 is a potent biomarker of severe drug reaction**

○ Manabu Yoshioka, Yu Sawada, Motonobu Nakamura

Department of Dermatology, University of Occupational and Environmental Health, Fukuoka, Japan

P09-09 [C12-07] **Inflammatory type of acquired idiopathic generalized anhidrosis is characterized by dysregulation of sweat gland immune privilege**

○ Yurie Shimoda, Yoshimi Yamazaki, Yoshiko Mizukawa, Manabu Ohyama

Department of Dermatology, Kyorin University Faculty of Medicine, Tokyo, Japan

P09-10 [C12-08] **Lymphocyte count and neutrophil-to-lymphocyte ratio at the onset of herpes zoster are useful biomarker for predicting life prognosis**

○ Takenobu Yamamoto[1,2], Takuya Ohyama[1], Mariko Yamane[1], Yumi Aoyama[1]

[1]Department of Dermatology, Kawasaki Medical School, Kurashiki, Japan, [2]Department of Dermatology, Kawasaki Medical School General Medical Center, Okayama, Japan

P09-11 [O06-01] **Investigation of the involvement of TIF1γ expression in tumors in the pathogenesis of cancer-associated dermatomyositis**

○ Mai Ishikawa, Akiko Sekiguchi, Yuko Kuriyama, Yukie Endo, Sei-ichiro Motegi

The Department of Dermatology, University of Gunma, Gunma, Japan

P09-12 [O06-02] **Identification of serum biomarkers predicting the therapeutic effect of dupilumab in atopic dermatitis by a targeted metabolomics approach**

○ Shoko Miyamoto[1], Shin Nishiumi[2], Masako Matsutani[1], Makoto Nagai[1], Kiyofumi Yamanishi[1], Nobuo Kanazawa[1], Yasutomo Imai[1]

[1]Department of Dermatology, Hyogo College of Medicine, [2]Department of Omics Medicine, Hyogo College of Medicine

P09-13 [O06-03] **Predicting RNA sequences of small patch image for Treatment of Atopic Skin Disease by Deep Convolutional Neural Networks**

○ Daiki Ito[1], Yutaka Kawashima[1], Hiroto Horikawa[2], Koichi Ashizaki[3], Hiroshi Kawasaki[2], Yoshimitsu Aoki[1]

[1]Department of Engineering, Keio University School, [2]Department of Dermatology, Keio University School of Medicine, [3]Medical Sciences Innovation Hub Program, RIKEN

P09-14 [O06-04] **Dermoscopic diagnostic performance of non-dermatologists for skin tumor is improved by a computer-aided diagnosis system**

○ Akane Minagawa[1], Hiroshi Koga[1], Kazuhisa Matsunaga[2], Yuya Hayashi[2], Akira Hamada[2], Yoshiharu Houjou[2], Ryuhei Okuyama[1]

[1]The Department of Dermatology, Shinshu University School of Medicine, Matsumoto, Japan, [2]Casio Computer Co., Ltd., Tokyo, Japan

P09-15 [O06-05] **A possible role of surgical deroofing procedure to cover the disadvantage of adalimumab treatment for hidradenitis suppurativa**

○ Natsuko Sasaki, Yu Sawada, Etsuko Okada, Motonobu Nakamura

The Department of Dermatology, University of Occupational and Environmental health, Kitakyusyu, Japan

P09-16 [O06-06] **Dermcidin is a prognostic factor in patients with extramammary Paget's disease**

○ Yu Sawada, Shun Ohmori, Motonobu Nakamura

Department of Dermatology, University of Occupational and Environmental Health

P09-17 [O06-07] **Immediate impact of granulocyte and monocyte adsorption apheresis on generalized pustular psoriasis**

○ Masahiro Kamata, Hideaki Uchida, Shota Egawa, Mayumi Nagata, Saki Fukaya, Kotaro Hayashi, Atsuko Fukuyasu, Takamitsu Tanaka, Takeko Ishikawa, Takamitsu Ohnishi, Yayoi Tada

Department of Dermatology, Teikyo University School of Medicine, Tokyo, Japan

P09-18 [O06-08] **Safety and efficacy of bexarotene for Japanese patients with CTCL: Real-world experience from a result of post marketing survey**

○ Toshihisa Hamada[1], Akimichi Morita[2], Hiraku Suga[3], Hikari Boki[3], Taku Fujimura[4], Yoji Hirai[5], Takatoshi Shimauchi[6], Chiharu Tateishi[7], Eiji Kiyohara[8], Ikko Muto[9], The Japanese Bexarotene Study Group[10]

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P09-19 [O06-09] **MicroRNAs in neutrophils as markers of psoriasis**

○ Yuko Higashi[1], Munekazu Yamakuchi[2], Tomoko Fukushige[1], Teruto Hashiguchi[2], Takuro Kanekura[1]

[1]Department of Dermatology, Kagoshima University Graduate School of Medical and Dental Sciences, [2]Department of Laboratory and Vascular Medicine, Kagoshima University Graduate School of Medical and Dental Sciences

P09-20 [O06-10] **Chronic hepatitis B virus infection in dupilumab-treated atopic dermatitis patients**

○ Masako Matsutani

Department of Dermatology, Hyogo College of Medicine, Nishinomiya, Japan

P09-21 [O06-11] **Comparison of treatment goals between users of biological and non-biological therapies for treatment of psoriasis in Japan**

○ Yukari Okubo[1], Ann_Chuo Tang[2], Sachie Inoue[3], Hitoe_Torisu Itakura[2], Mamitaro Ohtsuki[4]

[1]Department of Dermatology, Tokyo Medical University, Tokyo, Japan, [2]Eli Lilly Japan K.K., Tokyo, Japan, [3]Crecon Medical Assessment INC., Tokyo, Japan, [4]Department of Dermatology, Jichi Medical University, Shimotsuke, Tochigi, Japan

P09-22 [O06-12] **A patient with atopic dermatitis and psoriasis vulgaris presenting an unusual reaction for dupilumab**

○ Yudai Tsukamoto, Toshifumi Takahashi, Miho Kabuto, Akihiko Yamaguchi, Noriki Fujimoto

Department of dermatology, Shiga university of medical science, Shiga, Japan

Category 10 (P10): Pharmacology and Drug Development

P10-01 [III-6] **Blockade of CX3CL1-CX3CR1 pathway inhibits mouse sclerodermatous chronic graft-versus-host disease model**

○ Akira Utsunomiya[1], Vu Huy Luong[1], Takenao Chino[1], Noritaka Oyama[1], Takashi Matsushita[2], Naoto Ishii[3], Hideaki Ogasawara[3], Toshio Imai[3], Minoru Hasegawa[1]

[1]Dermatology, University of Fukui, [2]Dermatology, Kanazawa University, [3]KAN Research Institute. Inc.

P10-02 [C02-04] **Vitamins and their derivatives synergistically promote hair shaft elongation *ex vivo* via PlGF/VEGFR-1 signaling activation**

○ Liuying Hu[1], Shun Kimura[1], Sayo Kashiwagi[1], Kyoko Takagi[1], Takashi Shimizu[1], Tsuyoshi Ishii[1], Manabu Ohyama[2]

[1]Basic Research Development Division, ROHTO Pharmaceutical Co., LTD., Kyoto, Japan, [2]Department of Dermatology, Kyorin University Faculty of Medicine, Tokyo, Japan

P10-03 [C02-05] **Formyl peptide receptor 1 triggers cell death signals in keratinocyte as SJS/TEN model**

○ Tomoki Nishiguchi, Akito Hasegawa, Riichiro Abe

Department of dermatology, Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Japan

P10-04 [C02-06] **Konjac-ceramide (kCer) induces semaphorin 3A production in normal human epidermal keratinocytes**

○ Mirei Fujita[1], Yayoi Kamata[1], Mitsutoshi Tominaga[1], Seigo Usuki[2], Katsuyuki Mukai[3], Nobuaki Takahashi[1], Hideoki Ogawa[1], Yasuyuki Igarashi[2], Kenji Takamori[1,4]

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P10-05 [C02-07] **A calpain inhibitor ALLN attenuates bleomycin-induced skin fibrosis in a mice model**

○ Hiroshi Kasamatsu[1], Takenao Chino[1], Takumi Hasegawa[1], Natsuko Utsunomiya[1], Akira Utsunomiya[1], Noritaka Oyama[1], Masami Yamada[2], Minoru Hasegawa[1]

[1]Department of Dermatology, University of Fukui, Fukui, Japan, [2]Department of Cell Biology and Biochemistry, University of Fukui, Fukui, Japan

P10-06 [O04-08] **Spesolimab improves patient-reported outcomes (PROs) in patients with generalized pustular psoriasis (GPP) in the Effisayil 1 study**

○ Akimichi Morita[1], Alexander A Navarini[2], Manuelle Viguier[3], Tsen-Fang Tsai[4], Kristian Reich[5], Eva Kleine[6], Mogana Sivalingam[6], Christian Thoma[7], Mark G Lebwohl[8]

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P10-07 [O04-09] **Induction of Type XVII collagen decreases cellular senescence in Human hTert/KER-CT keratinocytes**

○ Tuba M. Ansary, Koji Kamiya, Md. Razib Hossain, Mayumi Komine, Mamitaro Ohtsuki

Department of Dermatology, Jichi Medical University, Tochigi, Japan

P10-08 [O04-10] **An antimicrobial peptide derived from insulin-like growth factor-binding protein 5 alleviates imiquimod-induced psoriatic skin inflammation**

○ Saori Yoshiba[1], Ge Peng[1,2], Saya Tsukamoto[1,2], Ko Okumura[1], Hideoki Ogawa[1], Shigaku Ikeda[2], Francois Niyonsaba[1,3]

[1]Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine, Tokyo, Japan, [2]Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine, Tokyo, Japan, [3]Faculty of International Liberal Arts, Juntendo University

P10-09 [O04-11] **Difamilast, a novel PDE4B inhibitor, topically improves chronic idiopathic dermatitis induced by persisting psychological stress in mice**

○ Hidetaka Hiyama, Naoya Arichika, Masafumi Shibamori, Hiroki Urashima

Biology and Translational Research Unit, Department of Medical Innovations, New Drug Research Division, Otsuka Pharmaceutical Co., Ltd. Tokushima, Japan

P10-10 [O04-12] **Investigation of *in-vitro* antibacterial activity of selected plant extracts and its combination with a view of developing a face wash**

○ N. A. Sanjeewani[1], H. M. G. M. Dissanayake[1], U. H. W. De Silva[1], W. D. Ratnasooriya[2], P. B. V. Navaratne[3]

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Category 11 (P11): Photobiology

P11-01 [I-6] **Skin regulatory T cells producing proenkephalin expand upon ultraviolet B exposure without ST2-IL33 axis and promote keratinocyte outgrowth**

○ Sayuri Yamazaki[1], Hiroaki Shime[1], Mizuyu Odanaka[1], Makoto Tsuiji[2], Takuma Matoba[1,3], Masaki Imai[1], Yoshiaki Yasumizu[4], Ryuta Uraki[1], Kiyoshi Minohara[1,3], Maiko Watanabe[1], Anthony Bonito[5], Hidehiro Fukuyama[6], Naganari Ohkura[4,7], Shimon Sakaguchi[4], Akimichi Morita[8]

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P11-02 [C09-02] **Analysis of anti-inflammatory effects and the underlying mechanisms of CO2 on skin**

○ Keimon Sayama[1,2], Katsuyuki Yuki[1], Keiichi Sugata[1], Satoko Fukagawa[1], Tetsuji Yamamoto[1], Natsumi Nagamori[1], Takayoshi Inoue[1], Shigaku Ikeda[2], Takatoshi Murase[1]

[1]Biological Science Research, Kao Corporation, Tochigi, Japan, [2]Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine, Tokyo, Japan

P11-03 [C09-03] **Epigenetic regulation in melanocytes differentiated from induced pruripotent stem cells originated from xeroderma pigmentosum**

○ Chihiro Takemori[1], Takeshi Fukumoto[1], Michiyo Koyanagi-Aoi[2,3], Makoto Kunisada[1], Chieko Hosaka[1], Takashi Aoi[2,3], Chikako Nishigori[1,3]

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P11-04 [C09-04] **Identification and Quantification of Senescent Cells In UV-induced Skin Pathologies**

○ Audrey Wang[1], Satoshi Nakamizo[2], Yoshihiro Ishida[2], Genevieve Klassen[3], Priscilla Chong[3], John Lim[4], Graham Wright[4], Oliver Dreesen[1], Kenji Kabashima[1,2]

[1]Skin Research Institute Singapore, [2]Kyoto University Graduate School of Medicine, Japan, [3]School of Biological Sciences, Nanyang Technology University, [4]A*STAR Microscopy Platform

P11-05 [O09-01] **Deficiency of epidermal ferroportin enhances UV dermatitis in mice**

○ Naokazu Hatchome, Hitoshi Terui, Mayuko Onodera-Amagai, Masayuki Asano, Kenshi Yamasaki, Setsuya Aiba

The Department of Dermatology, University of Tohoku, Miyagi, Japan

P11-06 [C09-05] **Rapid pustule fixation of palmoplantar pustulosis by UVA1-LED phototherapy**

○ Kyoko Ikumi[1], Tomohiko Kio[2], Kan Torii[1], Hideyuki Masuda[2], Akimichi Morita[1]

[1]Department of Geriatric and Environmental Dermatology Nagoya City University Graduate Schol of Medical Sciences, [2]R&D Group, Biomedical Division, USHIO INC, Tokyo, Japan

P11-07 [C09-06] **Switching the light source of phototherapy from a lamp to a deep ultraviolet light-emitting diodes**

○ Hideyuki Masuda[1,2], Akimichi Morita[1]

[1]Department of Geriatric and Environmental Dermatology, Nagoya City University, Graduate School of Medical Sciences, Nagoya, Japan, [2]Ushio Inc. Tokyo, Japan

P11-08 [O09-02] **Effect of M1 and M2 Macrophages on Production and Degradation of Extracellular Matrix in Dermal Fibroblasts**

○ Munetaka Kawamoto, Ryota Kami, Satoshi Horiba

MIRAI Technology Institute, Shiseido Co.,Ltd

P11-09 [O09-03] **Downregulation of IL-34 Associated with the Skewing of M1/M2 Balance of Macrophages Induces Senescence in Human dermal fibroblasts**

○ Satoshi Horiba, Ryota Kami, Taiki Tsutsui, Junichi Hosoi

Shiseido Co., Ltd MIRAI Technology Institute

P11-10 [C09-07] **Bath-PUVA therapy targets keratinocytes to suppress the secretion of pathogenic chemokines**

○ Yoshifumi Kanayama, Kan Torii, Kyoko Ikumi, Akimichi Morita

Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

P11-11 [O09-04] **Non-invasive assessment of diameter-dependent cutaneous vascular alterations with age using Optical Coherence Tomography Angiography**

○ Takuma Hoshino[1], Yusuke Hara[1], Masato Ninomiya[1], Toyonobu Yamashita[1], Motoki Oguri[1], Masako Katsuyama[1], Chika Katagiri[1], Yuandong J. Li[2], Yuxuan Cheng[2], Nhan M. Le[2], Ruikang Wang[2]

[1]MIRAI Technology Institute, Shiseido Corporation Limited, [2]Department of Bioengineering, University of Washington, Seattle, United States

P11-12 [O03-01] **Excimer light downregulates interleukin-17 production and induces regulatory T cells in imiquimod-induced psoriasiform dermatitis**

○ Shota Egawa, Masahiro Kamata, Hideaki Uchida, Teruo Shimizu, Makoto Ito, Ryosuke Takeshima, Itsumi Mizukawa, Ayu Watanabe, Yayoi Tada

Department of Dermatology, Teikyo University School of Medicine, Tokyo, Japan

P11-13 [O03-02] **Characterization of the DNA damage response in human skin cell types**

○ Chin Yee Ho[1], A.L Soon[1], C Tan[2], P.F Ong[1], M Ehrman[3], J Oblong[4], S Bellanger[2], O Dreesen[1]

[1]Skin Research Institute of Singapore, A*STAR, Singapore, [2]Stemness, Differentiation and Aging in Human Epidermis, Skin Research Institute of Singapore, A*STAR, Singapore, [3]Proctor & Gamble International Operations SA, Singapore, [4]Beauty Technology Division, The Procter & Gamble Company, Cincinnati, Ohio, USA

P11-14 [O03-03] **A role of elastogenic factors in the pathogenesis of Solar Elastosis**

○ Teruhiko Makino[1], Ko Kagoyama[1], Chisato Murabe[2], Tomoyuki Nakamura[2], Tadamichi Shimizu[1]

[1]Department of Dermatology, University of Toyama, Toyama, Japan, [2]Department of Pharmacology, Kansai Medical University, Osaka, Japan

P11-15 [O03-04] **Photodynamic therapy using portable devices**

○ Rie Teranishi[1], Toshiyuki Ozawa[1], Tsuyoshi Goya[3], Kenji Kuwada[3], Katsuyuki Morii[3,4], Takahiro Nishimura[2], Kunio Awazu[2], Daisuke Tsuruta[1]

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P11-16 [O03-05] **Usefulness of UVA lamps for the diagnosis of green nail syndrome with or without onychomycosis**

○ Tomotaka Sato, Kazuhiro Aoyama, Norihito Fukada, Akihiko Kinjo

The Department of Dermatology, Teikyo University Chiba Medical Center

Category 12 (P12): Pigmentation and Melanoma

P12-01 [II-4] **A mechanism of cooling hot tumors: lactate and its induced EGR1 are novel key factors that turn hot tumors into cold tumors**

○ Hisashi Kanemaru, Yukari Mizukami, Akira Kaneko, Hidemi Tagawa, Toshihiro Kimura, Haruka Kuriyama, Soichiro Sawamura, Ikko Kajihara, Katsunari Makino, Jun Aoi, Satoshi Fukushima

Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University

P12-02 [C05-01] **TIGIT/CD155 axis mediates resistance to immunotherapy in cancer patients with the inflamed tumor microenvironment**

○ Shusuke Kawashima[1,2], Takashi Inozume[1,2,3], Masahito Kawazu[4], Toshihide Ueno[4], Etsuko Tanji[1], Tatsuyoshi Kawamura[3], Yasuhiro Nakamura[5], Tomonori Kawasaki[6], Yukiko Kiniwa[7], Hiroyoshi Nishikawa[8,9], Hiroyuki Matsue[2], Yosuke Togashi[1,8,10]

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P12-03 [C05-02] **IPS cell-derived myeloid cells expressing OX40 ligand amplify tumor-infiltrating T cells in advanced melanoma**

○ Toshihiro Kimura[1], Haruka Kuriyama[1], Hisashi Kanemaru[1], Yosuke Kubo[1], Satoshi Nakahara[1], Azusa Miyashita[1], Jun Aoi[1], Hirotake Tsukamoto[2], Yasuharu Nishimura[3,4], Takashi Inozume[5], Rong Zhang[6], Yasushi Uemura[6], Satoru Senju[3], Hironobu Ihn[1], Satoshi Fukushima[1]

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P12-04 [C05-03] **Impact of a *SLC24A5* novel mutation identified in the first Japanese patient with oculocutaneous albinism 6 on retinal pigment epithelium**

○ Toru Saito[1], Ken Okamura[1], Rika Kosaki[2], Kazumasa Wakamatsu[3], Shosuke Ito[3], Osamu Nakajima[4], Hidetoshi Yamashita[5], Yutaka Hozumi[1], Tamio Suzuki[1]

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P12-05 [C05-04] **Molecular and functional characterization of melanocyte subpopulations in the human hairy skin epidermis based on single-cell RNA sequencing**

○ Fumihito Noguchi, Peinan Zhao, Mark Shackleton

Cancer Development and Treatment Group, Department of Medicine Research Laboratories, Alfred Hospital, Monash University, Melbourne, Victoria, Australia

P12-06 [C05-05] **Melanocyte stem cell dynamics underlie de novo melanomagenesis**

○ Sally Eshiba[1], Takeshi Namiki[2], Yasuaki Mohri[1], Tomomi Aida[3,4], Naotaka Serizawa[1], Takakazu Shibata[5], Hironobu Morinaga[1], Daisuke Nanba[1], Keiko Miura[6], Masaru Tanaka[7], Hisashi Uhara[8], Hiroo Yokozeki[2], Toshiaki Saida[9], Emi K. Nishimura[1,10]

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P12-07 [C05-06] **Liquid biopsy-based analysis by CAPP-Seq and ddPCR in patients with melanoma**

○ Akira Kaneko, Hisashi Kanemaru, Ikko Kajihara, Haruka Kuriyama, Toshihiro Kimura, Soichiro Sawamura, Katsunari Makino, Azusa Miyashita, Jun Aoi, Takamitsu Makino, Shinichi Masuguchi, Satoshi Fukushima

Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

P12-08 [O11-09] **NUMB inhibits melanoma migration, invasion, and metastasis**

○ Takeshi Fukumoto[1], Denitsa M Hristova[2], Xia Hua[2], Haruki Jimbo[1], Chihiro Takemori[1], Chikako Nishigori[1,3], Zhi Wei[4], Rajasekharan Somasundaram[2], Mizuho Fukunaga-Kalabis[2], Meenhard Herlyn[2]

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P12-09 [O11-10] **Nucleosome assembly protein 1-like 4, a new therapeutic target for melanoma**

○ Satoru Mizuhashi[1], Takayuki Ishibashi[1], Haruka Kuriyama[1], Toshihiro Kimura[1], Hisashi Kanemaru[1], Ikko Kajihara[1], Katsunari Makino[1], Azusa Miyashita[1], Jun Aoi[1], Kanako Kita[2], Hironobu Ihn[1], Satoshi Fukushima[1]

[1]Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan, [2]Department of Comprehensive Molecular Medicine, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

P12-10 [O11-11] **Investigation the mechanism of novel lncRNAs, LncRNA00094, involved in metformin-inducing inhibition of melanoma cells**

○ Hui-Wen Tseng[1,2], Kuo-Wang Tsai[3]

[1]The Department of Dermatology, Kaohsiung Veterans General Hospital, [2]Institute of Biomedical Sciences, National SunYet-sen University, [3]Department of Research, Taipei Tzu Chi Hospital, NewTaipei, Taiwan

P12-11 [O11-12] **Increased expression of SPARC and TIMP3 in epidermotropic melanoma metastasis**

○ Maureen.T Meling, Yukiko Kiniwa, Eisaku Ogawa, Yuki Sato, Ryuhei Okuyama

Department of Dermatology, Shinshu University School of Medicine, Matsumoto, Japan

P12-12 [O03-06] **Attenuation of melanocyte reoccupation in long-lasting rhododendrol-induced guinea pig model of vitiligo**

○ Yasutaka Kuroda[1,2], Lingli Yang[1], Fei Yang[1,2], Sylvia Lai[1], Tetsuya Sayo[1,2], Yoshito Takahashi[1,2], Daisuke Tsuruta[3], Ichiro Katayama[1]

[1]Department of Pigmentation Research and Therapeutics, Osaka City University Graduate school of medicine, [2]Biological Science Research Laboratories, Kao Corporation, [3]Department of Dermatology, Osaka City University Graduate school of medicine

P12-13 [O03-07] **Methyl-CpG binding domain protein 3 is a new diagnostic marker and potential therapeutic target of melanoma**

○ Takayuki Ishibashi[1], Ikko Kajihara[1], Satoru Mizuhashi[1], Haruka Kuriyama[1], Toshihiro Kimura[1], Hisashi Kanemaru[1], Katsunari Makino[1], Azusa Miyashita[1], Jun Aoi[1], Takamitsu Makino[1], Satoshi Fukushima[1], Kanako Kita[2], Hironobu Ihn[1]

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P12-14 [O03-08] **NUAK2 is an important factor in acral melanomas development and progression**

○ Kohei Nojima[1], Masahiro Hayashi[2], Masakazu Kawaguchi[2], Tamio Suzuki[2], Masashi Ishikawa[3], Yasuhiko Kaneko[4], Atsushi Tanemura[5], Ichiro Katayama[6], Taisuke Mori[7], Naoya Yamazaki[8], Hiroki Mori[9], Hiroo Yokozeki[1], Takeshi Namiki[1]

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P12-15 [O03-09] **Protective efficacy of Sanqi-derived compound K on melanocytes against oxidative stress: in vitro and in vivo evaluation**

○ Suwei Tang[1,5], Lingli Yang[1], Yasutaka Kuroda[2], Sylvia Lai[1], Shaoqiong Xie[5], Huimin Zhang[4], Daisuke Tsuruta[3], Ichiro Katayama[1]

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P12-16 [O03-10] **Genipin contained in gardenia fruit enhanced melanogenesis**

○ Megumi Mizawa[1], Tsugunobu Andoh[2], Tadamichi Shimizu[1]

[1]Department of Dermatology, Faculty of Medicine, Academic Assembly, University of Toyama, Toyama, Japan, [2]Department of Pharmacology and Pathophysiology, College of Pharmacy, Kinjo Gakuin University, Aichi, Japan

P12-17 [C05-07] **Genome-scale DNA methylation analysis identifies regulatory region and repeat element alterations that modulate the genomic stability of melanocytic nevi**

Meghan E. Muse[1], Drew T. Bergman[1], Lucas A. Salas[1], Lisa N. Tom[2], Jean-Marie Tan[2], Antonia Laino[2], Duncan Lambie[3,4], Richard A. Sturm[2], Helmut Schaider[2,5], H. Peter Soyer[2,6], Brock C. Christensen[1,7,8], ○ Mitchell S. Stark[2]

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Category 13 (P13): Skin, Appendages, and Stem Cell Biology

P13-01 [III-3] **Development of molecular atlas of the human nail unit and hair follicle with spatially resolved transcriptomics**

Dongyoun Lee, ○ Joonho Shim, Ji-Hye Park, Gulimila Abudureyimu, Jong Hee Lee

Department of Dermatology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

P13-02 [C03-02] **Antifibrotic effects and mechanisms of miR-196b-5p of mesenchymal stem cell-derived exosomes in a systemic sclerosis mouse model**

Hritu Baral[1], ○Akihiko Uchiyama[1], Yoko Yokoyama[1], Akiko Sekiguchi[1], Sahori Yamazaki[1], Syahla Nisaa Amalia[1], Yuta Inoue[1], Sachiko Ogino[1], Ryoko Torii[1], Mari Hosoi[1], Toshiyuki Matsuzaki[2], Sei-ichiro Motegi[1]

[1]Department of Dermatology, Gunma University Graduate School of Medicine, [2]Department of Anatomy and Cell Biology, Gunma University Graduate School of Medicine

P13-03 [C03-03] **Obesity accelerates hair thinning by stem cell-centric converging mechanisms**

○Hironobu Morinaga[1], Emi K. Nishimura[1], Yasuaki Mohri[1], Kyosuke Asakawa[1], Hiroyuki Matsumura[1], Andrzej_A Dlugosz[2], Atsushi Iwama[3]

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P13-04 [C03-04] **Therapeutic potential of adipose-derived stem cells for the treatment of recessive dystrophic epidermolysis bullosa**

○Akinori Matsuda, Toshio Hasegawa, Akino Wada, Shigaku Ikeda

Department of Dermatology and Allergology Juntendo University Graduate School of Medicine, Tokyo, Japan

P13-05 [C03-05] **Perivascular adipose tissue in dermis induces infiltration of immune cells in the murine imiquimod (IMQ)-induced psoriasis model**

○Riko Takimoto-Ito, Satoshi Nakamizo, Gyohei Egawa, Kenji Kabashima

Department of Dermatology, Kyoto University Graduate school of medicine, Kyoto, Japan

P13-06 [C03-06] **Label-free quality control and identification of human keratinocyte stem cells by deep learning-based automated cell tracking**

Takuya Hirose[1], Jun'ichi Kotoku[1], Fujio Toki[2], Emi K. Nishimura[2,3], ○Daisuke Nanba[2]

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P13-07 [C03-07] **Ahed has crucial roles as a spliceosomal protein for cell proliferation of epidermal keratinocytes**

○Mikiro Takaishi[1], Tatsushi Ishimoto[1], Masahiro Tokunaga[2], Chikara Kokubu[3], Junji Takeda[4], Shigetoshi Sano[1]

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P13-08 [O08-01] **Dynamic stem cell selection safeguards the genomic integrity of the epidermis**

○Tomoki Kato[1], Nan Liu[1], Kyosuke Asakawa[1], Taichi Muraguchi[1], Yuko Muroyama[1], Hironobu Morinaga[1], Mariko Shimokawa[1], Yuriko Nishimori[1], Li Jing Tan[1], Yasuaki Mohri[1], Emi K. Nishimura[1,2]

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P13-09 [O08-02] **Impaired holocrine cell rupture of sebocytes in comedo: Revisiting the mechanism of comedo formation in the study with excised human skins**

○Toru Atsugi[1], Takashi Teramura[2], Hiroki Ota[3], Tomoko Aida[3], Mika Yamashita[3], Mathieu Lacroix[4], Anne-Laure Desroches[4], Nico Forraz[4], Colin McGuckin[4], Eiji Naru[1]

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P13-10 [O08-03] **Immunological Properties of Atopic Dermatitis-Associated Alopecia Areata**

○Reiko Kageyama[1], Taisuke Ito[1], Shiho Hanai[2], Naomi Morishita[1], Shinsuke Nakazawa[1], Toshiharu Fujiyama[1], Tetsuya Honda[1], Yoshiki Tokura[3]

[1]Department of Dermatology, Hamamatsu University School of Medicine, [2]Seirei Hamamatsu General Hospital, [3]Chutoen General Medical Center

P13-11 [O08-04] **Time course changes in peripheral blood mononuclear cell subsets during intravenous corticosteroid pulse therapy for severe alopecia areata**

○Ryo Takahashi[1], Yohei Sato[2], Momoko Kimishima[2], Manabu Ohyama[1,2]

[1]Flow Cytometry Core Facility, Kyorin University Graduate School of Medicine, Tokyo, Japan, [2]Department of Dermatology, Kyorin University Faculty of Medicine, Tokyo, Japan

P13-12 [O08-05] **Distinct types of stem cell divisions orchestrate organ regeneration and aging in hair follicles**

○Hiroyuki Matsumura[1], Nan Liu[1], Daisuke Nanba[1], Shizuko Ichinose[2], Aki Takada[1], Sotaro Kurata[3], Hironobu Morinaga[1], Yasuaki Mohri[1], Adèle De Arcangelis[4], Shigeo Ohno[5], Emi K. Nishimura[1]

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P13-13 [O08-06] **Mu-opioid ligand endomorphin induces alloknesis at the periphery**

○ Eriko Komiya[1], Mitsutoshi Tominaga[1,2], Ryo Hatano[3], Takumi Itoh[3], Kotaro Honda[1], Sumika Toyama[1], Yayoi Kamata[1,2], Haruna Otsuka[3], Kei Ohnuma[3], Chikao Morimoto[3], Kenji Takamori[1,2,4]

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P13-14 [O08-07] **Monocytic lineage cells distributed along sweat glands modulate sweat function**

○ Tadatsune Iida[1], Daisuke Kobayashi[2], Tomoki Tamura[2], Hiroo Yokozeki[1], Takeshi Namiki[1]

[1]Department of dermatology, Tokyo Medical and Dental University, Tokyo, [2]Department of human pathology, Tokyo Medical and Dental University, Tokyo

P13-15 [O08-08] **The potential of hair-follicle-associated pluripotent (HAP) stem cells to treat Parkinson's disease**

○ Michiko Yamane[1], Nanako Takaoka[1,2], Koya Obara[2], Kyoumi Shirai[2], Yuko Hamada[2], Nobuko Arakawa[2], Ryoichi Aki[2], Robert M. Hoffman[3,4], Yasuyuki Amoh[2]

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P13-16 [O08-09] **The potential of hair-follicle-associated pluripotent (HAP) stem cells for heart regeneration**

○ Nanako Takaoka[1,2], Michiko Yamane[1], Koya Obara[2], Kyoumi Shirai[2], Yuko Hamada[2], Nobuko Arakawa[2], Ryoichi Aki[2], Robert M. Hoffman[3,4], Yasuyuki Amoh[2]

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P13-17 [O08-10] **Exploring the impact of ovariectomy on hair growth; Is ovariectomized mouse a model for investigating female pattern hair loss in human?**

○ Sayaka Togo, Hisayoshi Imanishi, Koji Sugawara, Daisuke Tsuruta

Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan

Category 14 (P14): Tissue Regeneration and Wound Healing

P14-01 [III-2] **CCL5/CCR5 feedforward loop by FLI1 deficiency in microvascular endothelial cells contributes to SSc vasculopathy**

○ Tetsuya Ikawa, Takuya Miyagawa, Yuki Fukui, Satoshi Toyama, Jun Omatsu, Kentaro Awaji, Yuta Norimatsu, Yusuke Watanabe, Ayumi Yoshizaki, Shinichi Sato, Yoshihide Asano

The Department of Dermatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

P14-02 [C07-04] **Ninjurin-1 contributes to skin wound healing through the formation of functional blood vessels**

○ Risa Matsuo, Mari Kishibe, Shin Iinuma, Mizue Fujii, Satomi Igawa, Masaru Homma, Akemi Ishida-Yamamoto

The Department of Dermatology, Asahikawa Medical University, Hokkaido, Japan

P14-03 [C07-05] **Odorant-dependent Merkel cell chemosensation: implications for wound healing**

Ilaria Piccini[1], Jeremy Cheret[1,2], Moe Tsutsumi[3], S Sakaguchi[3], Leslie Ponce[1], Luis Almeida[1], K Funk[4], Max Kueckelhaus[5], Kentaro Kajiya[3], Ralf Paus[1,2,6], ○ Marta Bertolini[1]

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P14-04 [C07-06] **Adipose derived stem cells inhibits fibrotic effect of keloid derived dermal fibroblasts**

○ Yuki Nukui, Toshio Hasegawa, Akino Wada, Shigaku Ikeda

Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine

P14-05 [C07-07] **Skin-derived human β-defensin-3 promotes wound healing and angiogenesi**

○ Miho Takahashi[1,2], Yoshie Umehara[1], Hainan Yue[1,2], Juan Valentin Trujillo[1], Ge Peng[1,2], Hai Le Thanh Nguyen[1,2], Risa Ikutama[1,2], Ko Okumura[1], Hideoki Ogawa[1], Shigaku Ikeda[1], Francois Niyonsaba[1,3]

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P14-06 [O01-03] **Calcitriol, the active form of vitamin D, regulates epidermal tight junction barrier function in diabetes**

○ Juan V. Trujillo[1], Le Thanh Hai Nguyen[1,2], Yoshie Umehara[1], Hainan Yue[1,2], Lisa Ikutama[1,2], Miho Takahashi[1,2], Ge Peng[1,2], Hideoki Ogawa[1], Shigaku Ikeda[2], Ko Okumura[1], Francois Niyonsaba[1,3]

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P14-07 [O01-04] **Trehalose-induced senescence-associated secretory phenotype accelerates organotypic skin culture development**

○ Jun Muto[1], Shinji Fukuda[2], Kenji Watanabe[3], Xiuju Dai[1], Teruko Tsuda[1], Hideki Mori[1], Ken Shiraishi[1], Masamoto Murakami[1], Shigeki Higashiyama[4,5], Yoichi Mizukami[3], Koji Sayama[1]

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P14-08 [O01-05] **Antioxidant protein Peroxiredoxin 4 uniquely improved aging-related delayed wound healing in mice**

○ Reimon Yamaguchi[1,2], Xin Guo[2], Jianbo Zheng[2], Jing Zhang[2], Jia Han[2], Akihiro Shioya[2], Hidetaka Uramoto[3], Takashi Mochizuki[1], Akira Shimizu[1], Sohsuke Yamada[2]

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P14-09 [O01-06] **AMP-IBP5, an antimicrobial peptide derived from insulin-like growth factor-binding protein 5, promotes diabetic wound healing**

○ Hainan Yue[1,2], Yoshie Umehara[2], Juan Valentin Trujillo-Paez[2], Ge Peng[1,2], Hai Le Thanh Nguyen[1,2], Miho Takahashi[1,2], Risa Ikutama[1,2], Ko Okumura[2], Hideoki Ogawa[2], Shigaku Ikeda[1,2], Francois Niyonsaba[2,3]

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P14-10 [O01-07] **Determination of host defense peptide inducers for their therapeutic use in diabetic foot ulcers**

○ Alan Santos[1], Bruno Rivas[1,2]

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P14-11 [O01-08] **Effects of antimicrobial peptide human β-defensins on the expression of angiogenin in human dermal fibroblasts**

○ Yoshie Umehara[1], Miho Takahashi[1,2], Hainan Yue[1], Juan Valentin Trujillo-Paez[1], Ge Peng[1], Le Thanh Hai Nguyen[1], Risa Ikutama[1,2], Ko Okumura[1], Hideoki Ogawa[2], François Niyonsaba[1,3]

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Category 15 (P15): Translational Studies

P15-01 [O01-09] **Spinal cholecystokinin 2 receptor is involved in induction of alloknesis**

○ Mitsutoshi Tominaga[1], Kotaro Honda[1], Fumiya Kusube[1], Eriko Komiya[1], Masafumi Yokota[1], Masaru Kurosawa[1], Nobuaki Takahashi[1], Sumika Toyama[1], Yayoi Kamata[1], Mirei Fujita[1], Qiao Feng Zhao[1], Yasushi Suga[2], Hideoki Ogawa[1], Kenji Takamori[1,2]

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P15-02 [C03-01] **Early-onset female pattern hair loss: a case-control study for analyzing clinical features and genetic variants**

○ Jungyoon Ohn[1,2], Ho-Young Son[3,4], Kyu Han Kim[1,2], Ohsang Kwon[1,2,4], Jong-Il Kim[3,4]

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P15-03 [C09-01] **A deep learning framework enables prompt and objective scoring of Nail Psoriasis Severity Index**

○ Hiroto Horikawa, Keiji Tanese, Ryoko Hosokawa, Julia Miyamoto, Kaori Murakami, Risa Kakuta, Hitomi Matsuzaki, Yuhei Kawashima, Masayuki Amagai, Masataka Saito

Department of Dermatology, Keio University School of Medicine, Tokyo, Japan

P15-04 [O01-10] **The effectivity of metformin solution as a melanogeneis inhibitor: A chromameter analysis on human**

○ Ivan Kurniadi[1], Asnawi Madjid[1], Farida Tabri[1], Arifin Seweng[2], Husaini Umar[3], Firdaus Hamid[4]

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P15-05 [O01-11] **Predicting regional Eczema Area and Severity Index from the images of atopic dermatitis using deep convolutional networks**

○ Yutaka Kawashima[1], Daiki Ito[1], Hiroto Horikawa[2], Ayano Nomura[2], Koichi Ashizaki[2,3], Hiroshi Kawasaki[2,4], Masayuki Amagai[2], Yoshimitsu Aoki[1]

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P15-06 [O01-12] **Serum biomarkers correlate with disease response in Moderate to Severe Atopic Dermatitis patients treated with baricitinib**

○ Takeshi Nakahara[1], Jonathan_T. Sims[2], Robert Bissonnette[3], Stephanie Colvin[2], Jonathan Janes[2], Venkatesh Krishnan[2], Jason_R. Chan[2], Ferda Cevikbas[2]

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Late abstract submission

L-01 **Histone deacetylase 4 reverses cellular senescence via DDIT4 in dermal fibroblasts**

Yuri Lee[1,2,3], Ji Hwan Park[5], Hye Sun Shin[1,2,3], Mi Hee Shin[1,3], Min-Kyoung Kim[1,3], Daehee Hwang[6], ○ Dong Hun Lee[1,3], Jin Ho Chung[1,2,3,4]

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L-02 **Metabolic reprogramming defines myeloid cell function in skin repair**

○ Sebastian Willenborg[1], David E. Sanin[2], Alexander Jais[3], Xiaolei Ding[1], Milica Popović[4], Edward J. Pearce[2], Jens C. Brüning[3], Aleksandra Trifunovic[4], Sabine A. Eming[1]

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L-03 **Application of microdissection-based spatial transcriptomics for mechanistic and biomarker investigations in dermatology**

○ Tomohiro Miyai[1,2], Hiroshi Kawasaki[2,3], Masahito Hosokawa[4], Hiroko Matsunaga[4], Rumi Satoh[1], Aiko Sekita[1], Haruko Takeyama[4], Masayuki Amagai[2,3], Haruhiko Koseki[1,5]

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L-04 **Anti-staphylococcus aureus effect of the hot spring water via metal accumulation**

○ Duerna Tie[1], Saeko Nakajima[1,2], Ichiro Nakagawa[3], Kenji Kabashima[1,4]

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L-05 **Particulate matter triggers Th17 polarization in atopic dermatitis in association with increased pregnane X receptor signaling**

○ Ji Su Lee[1], Sunhyae Jang[2,3,4], Dong Hun Lee[1,3,4], Youngae Lee[1,3,4], Soyun Cho[3,4,5]

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L-06 **Bird's-eye viewing of dermatologists' research trends using a natural language processing approach: the contribution of Japanese researchers**

○ Yasushi Ogawa[1,2], Takeya Adachi[3,4], Jun Hirako[5], Ryohei Sasano[5], Masashi Akiyama[2]

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L-07 **Expression of TAM receptors in melanoma of Korean patients**

Min Young Lee[2], ○ Yoon Jin Choi[1], You Won Choi[2], Hae Young Choi[1], Ji Yeon Byun[1]

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L-08 **Autophagy is a defense mechanism rescuing hair loss against particulate matter exposure**

○ Da-Ae Yu[1], Sunhyae Jang[1,2,3], Jungyoon Ohn[1,2,3], Tommy Sungjoo Hwang[4], Kyu Han Kim[1,2,3], Ohsang Kwon[1,2,3]

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L-09 **Skin Microbiome Analysis using Postally-Delivered Tape-Stripped Material for General Consumers**

○ Yutaka Shimokawa[1], Osamu Funatsu[1], Nozomi Kajihara[1], Fukashi Inoue[2], Sumiko Ohashi[2], Atsuko Asano[2], Itaru Dekio[3]

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L-10 **Comprehensive morphological observation of epidermal Merkel cells in human skin**

○ Moe Tsutsumi, Saito Sakaguchi, Kazuki Takagaki, Kentaro Kajiya

MIRAI Technology Institute, Shiseido Co., Ltd., Yokohama, Japan

L-11 **Withdrawn**

L-12 **Evaluation of anti-pigmentation cassette to other anti-pigmentation ingredients**

○ Thomas Mammone, Jaimie Jerome

The Estee Lauder Companies, Melville, New York

L-13 **Unmet educational needs and clinical practice gaps in the management of generalized pustular psoriasis: Global insights from the front line**

○ Yukari Okubo[1], Joyce Leman[2], Maja Mockenhaupt[3], Juliana Nakano de Melo[4], Ahmed Nassar[5], Lee Yoong Wei[6], Masahito Yasuda[7], Ning Yu[8], Ana Cristina Hernandez Daly[9], Bruce Strober[10]

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Tanioku Kihei Memorial Lecture

The 46th Annual Meeting of the Japanese Society for Investigative Dermatology

Tanioku Kihei Memorial Lecture

Howard Y. Chang

Stanford University School of Medicine

Howard Y. Chang M.D., Ph.D. is Director of the Center for Personal Dynamic Regulomes and the Virginia and D.K. Ludwig Professor of Cancer Research at Stanford University. He is a Howard Hughes Medical Institute Investigator; he is also Professor of Dermatology and of Genetics at Stanford University School of Medicine. Chang earned a Ph.D. in Biology from MIT, M.D. from Harvard Medical School, and completed Dermatology residency and postdoctoral training at Stanford University. His research addresses how large sets of genes are turned on or off together, which is important in normal development, cancer, and aging. Chang discovered a new class of genes, termed long noncoding RNAs, can control gene activity throughout the genome, illuminating a new layer of biological regulation. He invented ATAC-seq and other new methods for defining DNA regulatory elements genome-wide and in single cells. The long term goal of his research is to decipher the regulatory information in the genome to benefit human health.

Dr. Chang's honors include the NAS Award for Molecular Biology, Outstanding Investigator Award of the National Cancer Institute, Paul Marks Prize for Cancer Research, Judson Daland Prize of the American Philosophical Society, and the Vilcek Prize for Creative Promise. He is a Member of the National Academy of Sciences, National Academy of Medicine, American Academy of Arts and Sciences, American Society for Clinical Investigation and Academia Sinica. His work was honored by the journal *Cell* as a Landmark paper over the last 40 years and by *Science* as "Insight of the decade".

RNA origin of sex biased immunity

Howard Y. Chang
Stanford University School of Medicine

Many autoimmune diseases involving the skin show a striking female bias. The response to viruses and many other diseases suggest sex difference is fundamental to biology and medicine. The discovery of extensive transcription of long noncoding RNAs (lncRNAs) provide an important new perspective on the centrality of RNA in gene regulation. I will discuss genome-scale strategies to discover and characterize lncRNAs, specifically XIST, the female-specific lncRNA that silences one of two X chromosomes in female cells. An emerging theme from multiple model systems is that lncRNAs form extensive networks of ribonucleoprotein (RNP) complexes with numerous chromatin regulators, and target these enzymatic activities to appropriate locations in the genome. Consistent with this notion, long noncoding RNAs can function as modular scaffolds to specify higher order organization in RNP complexes and in chromatin states. LncRNAs use distinct mechanisms to first establish and then maintain a chromatin state over time, providing gene memory over the lifetime in different cell types of the body. The importance of these modes of regulation is underscored by the newly recognized roles of long RNAs in human diseases.

JSID Award Lecture / JSID Kisaragi Award

The 46th Annual Meeting of the Japanese Society for Investigative Dermatology

JSID Award Lecture

December 4 (Sat) 10:45-11:15
Chair and Presenter: Kenji Kabashima

Autoimmune mechanisms in dermatology

Naoko Okiyama
Department of Dermatology, Faculty of Medicine, University of Tsukuba

I am very honored for the opportunity to introduce our research for this prestigious award. Recently, our team has performed clinical and basic scientific investigations on autoimmune mechanisms in dermatology, including (1) dermatomyositis, (2) mucocutaneous graft-versus-host disease (GVHD) presenting interface dermatitis, and (3) the blockade of programmed cell death-1 (PD-1) signaling-induced immune-related adverse events (irAE). Here, I would like to speak on these three research projects.

(1) Dermatomyositis is an idiopathic inflammatory myopathy and an autoimmune collagen disease, in which some myositis-specific autoantibodies (MSAs) have been identified. As we found these MSA-characterized clinical and histopathological features in our clinical research, we have advocated that dermatomyositis consists of some clinical subgroups classified according to MSAs. In addition, our research findings explained whether these MSAs are pathogenic. The immunization of transcription intermediary factor-1γ (TIF1γ) recombinant protein induced a new murine model of dermatomyositis-like experimental myositis depending on TIF1γ-specific CD8 T cells but not autoantibodies. We are developing murine models for each MSA to investigate the pathogenesis in each dermatomyositis subgroup.

(2) Interface dermatitis is histologically characterized by keratinocyte death and is observed in many severe skin disorders, such as mucocutaneous GVHD, lupus erythematosus, lichen planus, and Stevens-Johnson syndrome. Our second project on GVHD-like mucocutaneous disease with interface dermatitis indicated that granzyme B-perforin axis on cytotoxic CD8 T cells is the main pathogenesis of interface dermatitis and that skin-resident Langerhans cells exert inhibitory effects on the interface dermatitis via B7 family molecules. Moreover, our investigation showed that chronic GVHD-like cutaneous fibrosis is induced by tumor growth factor-β produced from apoptotic keratinocytes in the interface dermatitis.

(3) PD-1 blockade-induced irAEs include various types of dermatitis. Our third project on the PD-1-PD-ligands axis clarified that the T-helper (Th)-1-type immune responses, including contact hypersensitivity, lichen planus, Stevens-Johnson syndrome, and Th17 response with psoriasis, are mediated by the PD-1-PD-L1 axis. In contrast, the Th2 response, including atopic dermatitis, is mediated by the PD-1-PD-L2 axis. Our clinical and basic research also revealed that Th17-type psoriasis is accelerated by the blockade of PD-1 signaling on CD8 T cells and that interleukin-6 is a potential treatment target for irAE such as psoriasis.

Biography

Experience

Jul. 2014 - Present	Assistant Professor, Department of Dermatology, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan
Feb. 2011 - Jun. 2014	Visiting Fellow, Dermatology Branch, National Cancer Institute, National Institutes of Health, Maryland, USA
Apr. 2010 - Jun. 2012	Staff Clinician and Assistant Professor, Department of Dermatology, Hospital Faculty of Medicine, Tokyo Medical and Dental University, Tokyo, Japan
Apr. 2008 - Mar. 2010	Research Fellow, the Japan Society for the Promotion of Science, Ministry of Education, Culture, Sports, Science and Technology-Japan
Apr. 2005 - Mar. 2007	Trainee and Junior Research Associate, Laboratory for Clinical Immunology, RCAI, RIKEN, Kanagawa, Japan
Apr. 2005 - Jun. 2009	Graduate Student, Department of Dermatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan
Apr. 1999 - Mar. 2005	Resident, Clinical Fellow and Staff Clinician at Department of Dermatology of 2004-2005 Tokyo Metropolitan Bokutoh Hospital, Tokyo, Japan 1999-2000 and 2002-2004 Hospital Faculty of Medicine, Tokyo Medical and Dental University, Tokyo, Japan 2001-2002 Sayama Hospital, Saitama, Japan 2000-2001 Yokosuka City Hospital, Kanagawa, Japan

Education

July 2009	Ph.D. in Medical Science, Tokyo Medical and Dental University
March 1999	M.D., Yamanashi Medical University

JSID Kisaragi Award

December 4 (Sat) 10:40-10:45
Chair and Presenter: Kenji Kabashima

The role of Ninjurin-1 in pericytes during skin wound healing: effects on capillary maturation

Risa Matsuo
Department of Dermatology, Graduate School of Medicine, Asahikawa Medical University, Japan

Pericytes (PCs), which wrap around endothelial cell (EC) tube in microvessels, contribute to structural integrity and blood flow regulation. During wound healing, PCs participate in angiogenesis, involving early endothelial sprouting and subsequent vascular maturation. In the early stages of angiogenesis, PCs separate from the basement membrane, followed by budding of EC tubes. On the other hand, in the late stage of angiogenesis, PCs reattach to immature new blood vessels to form functional vessels with blood flow. Although there is no specific marker for PCs, NG2 is one of the common markers for PCs in various tissues including skin.
Nerve injury-induced protein-1 (Ninjurin-1: Ninj1) was originally identified as a transmembrane homophilic adhesion molecule in Schwann cells and neurons induced in nerve injury. A recent study has shown that Ninj1 in PCs is involved in the maturation of vessels through PC-EC interaction during hindlimb ischemia. Although Ninj1 presumably contributes to the regeneration of various tissues, its role in skin injury remains unclear. We aimed to elucidate the role of Ninj1 in wound healing using an *in vivo* mouse wound model.
To investigate the function of Ninj1, we assessed wound healing in NG2-specific Ninj1 knockout (KO) mice. Ninj1 KO mice showed delayed wound healing and reduced PC coverage in new microvessels compared with control mice. To analyze the effect of reduced PC coverage in cutaneous angiogenesis, we administered FITC-Lectin to the tail vein of mice and visualized functional vessels with blood flow. Furthermore, we performed whole-mount CD31 staining in the cleared tissue and evaluated the proportion of functional vessels in all vessels three-dimensionally. In this evaluation method, functional vessels were significantly reduced in Ninj1 KO mice. These findings indicate that Ninj1 in PCs is involved in angiogenesis during cutaneous wound healing through the formation of matured blood vessels.

Biography

2003-2009	M.D. course, School of Medicine, Asahikawa Medical University
2009-2011	Resident, Asahikawa Medical University
2012	M.D., Department of Dermatology, Asahikawa Medical University
2018-present	Ph.D. course, Department of Dermatology, Graduate School of Medicine, Asahikawa Medical University

World Showcase of Investigative Dermatology

The 46th Annual Meeting of the Japanese Society for Investigative Dermatology

Early Life Imprinting of a Th2-Stromal Cell Niche in Skin

Michael D. Rosenblum
UCSF, Department of Dermatology

Inflammation early in life can prime the local immune milieu of peripheral tissues, causing lasting changes in immunologic tone that confer disease protection or susceptibility. The cellular and molecular mechanisms that confer changes in immune tone in many nonlymphoid tissues remain largely unknown. We find that time-limited neonatal inflammation induced by transient reduction of neonatal regulatory T cells (Tregs) causes a dramatic dysregulation of subcutaneous tissue in murine skin, accompanied by the selective accumulation of Th2 cells within a distinct microanatomic niche. Th2 cells are maintained into adulthood through interactions with a fibroblast population in skin fascia that we refer to as Th2-interacting fascial fibroblasts (TIFFs), which expand in response to Th2 cytokines to form subcutaneous fibrous bands. Activation of the Th2-TIFF niche by neonatal inflammation primes skin for altered reparative responses to wounding. We further identify fibroblasts in healthy human skin expressing the TIFF transcriptional signature and find these cells at high levels in eosinophilic fasciitis, an orphan fibroinflammatory disease. Taken together, these data define a novel Th2 niche in skin, functionally characterize a disease-associated fibroblast population, and suggest a mechanism of immunologic priming whereby inflammation early in life creates networks between adaptive immune cells and stromal cells, thereby establishing an immunological set-point in tissues that is maintained throughout life.

Biography

Dr. Rosenblum's research focuses on understanding the fundamental mechanisms of how immune responses are regulated in peripheral tissues, and how this knowledge can be exploited to treat human disease. Using transgenic mouse model systems to mechanistically dissect how regulatory T cells (Tregs) function in tissues, Dr. Rosenblum has discovered that Tregs can differentiate into memory cells that utilize unique pathways for their establishment and long-term maintenance. In skin, these cells play major roles in wound healing and mediating tolerance to commensal microbes. He has discovered that skin-resident Tregs augment the function of epithelial stem cells during both hair follicle regeneration and epidermal barrier repair. Dr. Rosenblum also functionally investigates Tregs in human tissues and has discovered that human skin contains a unique population of tissue-resident Tregs. He has found that these Tregs are dysfunctional in patients with psoriasis, scleroderma, and melanoma. Through Delinia Bio., Dr. Rosenblum generated and validated a novel therapeutic molecule that selectively activates human Tregs. Currently, he has authored 85 basic science research papers.

Neuronal control of cutaneous inflammation

Daniel Kaplan
University of Pittsburgh, Department of Dermatology/Secondary Appointment Department of Immunology/Cutaneous Biology Research Center/Dermatology Medical Student Research

The skin functions as a protective physical barrier as well as an immunologic organ that protects the host from pathogens but is also subject to autoinflammatory disease. Immunity in the skin involves the development of inflammatory cytokine cascades between different cell types that both promote host defense but are pathogenic in disease. For example, IL-23 from dermal dendritic cells drives production of IL-17 from T cells resulting host defense against extracellular pathogens but this cascade is also pathogenic in diseases such as psoriasis vulgaris and hidradenitis suppurativa. Recently, it has become appreciated that cutaneous sensory neurons, in particular pain-sensing nociceptors expressing the ion channel TRPV1, are a key cell type involved in the inflammatory cytokine cascade and are required for the development of Type-17 inflammation in skin in both patients and mouse models. In mice, we and others have demonstrated that Type-17 inflammation in the psoriasis-like imiquimod and C. albicans infection models requires TRPV1-expressing neurons. Using optogenetics, we found that multiple rounds of activation of TRPV1-expressing neurons with laser light was sufficient to trigger expression of IL-6, IL-23 and IL-17 by immune cells (Type-17 inflammation) which was dependent on the neuropeptide CGRP released from sensory nerve terminals and dermal dendritic cells (dDC2). Host defense against epicutaneous C. albicans and S. aureus infection was augmented, and both the Type-17 inflammation and host defense extended beyond the site of stimulation through a nerve reflex arc providing regional anticipatory immunity. Another type of cutaneous sensory afferent identified based on expression of the protein MrgprD actively suppresses cutaneous inflammation. We have found that the neurotransmitter glutamate released from MrgprD-expressing neurons actively suppresses mast cell transcription resulting in reduced degranulation. Taken together, these findings demonstrate that sensory neurons in the skin play an important role in the development and regulation of cutaneous inflammation and host defense.

Biography

GRADUATE

1991-1998	Washington University St. Louis, MO	PhD, 1998	Immunology
1991-1998	Washington University St. Louis, MO	MD, 1998	Medicine

POST-GRADUATE: RESIDENCIES and FELLOWSHIPS

2002-2004	Yale Unversity, New Haven CT Department of Dermatology	Post Doctoral Fellowship Mark Shlomchik, MD, PhD
1999-2002	Yale University, New Haven CT Departent of Dermatology	Residency Michael Girardi, MD
1998-1999	Beth Israel Hospital, Boston MA Department of Medicine	Internship

APPOINTMENTS AND POSITIONS

2018- present	Professor, University of Pittsburgh Department of Dermatology/Secondary Appointment Department of Immunology/Director, Cutaneous Biology Research Center/Director, Dermatology Medical Student Research
2015- 2018	Visiting Associate Professor, University of Pittsburgh, Department of Dermatology/Secondary Appointment Department of Immunology/Director, Cutaneous Biology Research Center/Director, Dermatology Medical Student Research
2012-2015	Associate Professor with Tenure, University of Minnesota, Department of Dermatology
2007-2011	Assistant Professor, University of Minnesota, Department of Dermatology
2005-2007	Assistant Professor, Yale University School of Medicine, Department of Dermatology
2004-2005	Instructor, Yale University School of Medicine, Department of Dermatology

Neuroimmune Regulation of Itch

Brian S. Kim
Department of Medicine, Division of Dermatology, Center for the Study of Itch and Sensory Disorders, Department of Anesthesiology, Department of Pathology and Immunology, Division of Biology and Biomedical Sciences, Washington University School of Medicine

Classically, skin was considered a mere structural barrier protecting organisms from a diversity of environmental insults. In recent decades, the cutaneous immune system has become recognized as a complex immunologic barrier involved in both antimicrobial immunity and homeostatic processes like wound healing. To sense a variety of chemical, mechanical, and thermal stimuli, the skin harbors one of the most sophisticated sensory networks in the body. However, recent studies in itch biology suggest that the cutaneous nervous system is highly integrated with the immune system to encode specific sensations into evolutionarily conserved protective behaviors such as scratching. We uncovered novel neuroimmune functions of type 2 cytokines and associated JAK1 in sensory neurons in promoting chronic itch. These studies have directly informed drug development and the design of multiple clinical trials for chronic itch disorders such as atopic dermatitis. Recently, we have further unveiled how basophils, in response to environmental allergens, mediate a previously unrecognized form of acute itch flare in atopic dermatitis. Collectively, our studies highlight how the diverse and dynamic type 2 immune response dictates the quality, scope, and intensity of various itch responses in mammals. We propose that itch represents a broad paradigm of neuroimmune physiology that may underlie a variety of chronic inflammatory disorders at multiple barrier surfaces.

Biography

Present Position

Associate Professor of Medicine
Associate Professor of Anesthesiology
Associate Professor of Pathology and Immunology
Co-Director, Center for the Study of Itch and Sensory Disorders

Education

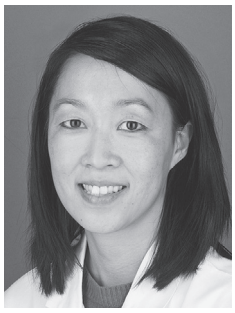
Undergraduate	2001	BS	Haverford College (Chemistry, Honors)
Graduate	2007	MD	University of Washington School of Medicine (AOA)
Graduate	2014	MTR	Perelman School of Medicine at the University of Pennsylvania
Postdoctoral	2010-2014		Laboratory of David Artis at Perelman School of Medicine at the University of Pennsylvania

Academic Positions/Employment

2011 - 2014	Instructor of Dermatology, Department of Dermatology, Perelman School of Medicine at the University of Pennsylvania
2014 - 2018	Assistant Professor of Medicine, Division of Dermatology, Department of Medicine, Washington University School of Medicine
2019 -	Associate Professor of Medicine, Division of Dermatology, Department of Medicine, Washington University School of Medicine

University and Hospital Appointments and Committees

2011 - 2012	Attending Physician, Division of Dermatology, Children's Hospital of Philadelphia
2011 - 2014	Attending Physician, Department of Dermatology, Perelman School of Medicine at the University of Pennsylvania
2011 - 2014	Attending Physician, Dermatology Clinic, Philadelphia VA Medical Center
2012 - 2014	Institutional Review Board Member, University of Pennsylvania
2014 -	Attending Physician, Center for Advanced Medicine, Barnes-Jewish Hospital



Cell therapy for pemphigus: entering the precision medicine era

Aimee Payne
Dermatology, University of Pensylvania

Chimeric antigen receptor (CAR) T cells have transformed the paradigm for cancer treatment by genetically engineering a patient's own immune system to eradicate previously refractory B cell cancers, raising hope that precision medicine cures can be extended beyond B cell cancers to other life-threatening diseases. We re-designed CAR technology for autoimmune disease therapy by utilizing an autoantigen as the extracellular domain of a chimeric autoantibody receptor (CAAR), linked to T cell receptor cytoplasmic signaling domains. CAARs target T cell cytotoxicity against autoantigen-specific B cells, which express a surface-bound autoantibody (B cell receptor) that defines the pathogenic autoimmune B cell population. We established preclinical proof-of-concept for CAAR safety and efficacy in achieving antigen-specific B cell depletion in experimental models of pemphigus vulgaris (PV), a potentially fatal blistering disease caused by autoantibodies to the skin cell adhesion protein desmoglein 3 (DSG3). If CAARs for autoimmunity prove to be as effective as CARs for B cell cancers, CAAR T cells may represent a one-time treatment leading to autoimmune disease cure. We will discuss the preclinical development pathway leading to a landmark first-in-human trial of DSG3 CAAR T cells for mucosal pemphigus vulgaris.

Biography

Education

1989-1993	B.S.	Stanford University (with Honors in Biology)
1993-2001	M.D.	Washington University School of Medicine
1993-2001	Ph.D.	Washington University School of Medicine (Molecular and Cellular Biology)

Postgraduate Training and Fellowship Appointments

2001-2002	Internal Medicine, Pennsylvania Hospital
2002-2005	Dermatology, Hospital of the University of Pennsylvania
2004-2006	Postdoctoral Fellow, University of Pennsylvania

Faculty Appointments

2005-2006	Clinical Instructor, Dermatology, University of Pennsylvania
2006-2015	Assistant Professor, Dermatology, University of Pennsylvania
2015-2020	Associate Professor with tenure, Dermatology, Univ. of Pennsylvania
2020-	Professor with tenure, Dermatology, University of Pennsylvania

Hospital and Administrative Appointments

2005-	Attending physician, Presbyterian Hospital
2005-	Attending physician, Hospital of the University of Pennsylvania

Translational research in vitiligo: Launching a new era of targeted treatments

John E. Harris[1,2,3]
[1]Department of Dermatology UMass Medical School, Worcester, MA,
[2]Vitiligo Clinic and Research Center,
[3]Autoimmune Therapeutics Institute

Vitiligo is a common autoimmune disease of the skin characterized by the appearance of white spots that result from the elimination of melanocytes by T cells. There are no FDA-approved medical treatments to reverse disease, however improved treatments are on the horizon. We determined that IFNg drives vitiligo progression through chemokines that promote T cell recruitment into the skin and hypothesized that targeting this pathway could be an effective treatment for patients. Early proof-of-concept studies demonstrated that JAK inhibitors, which block IFNg signaling, reversed vitiligo in a small number of vitiligo patients, and now Phase 2 and Phase 3 trials are reporting exciting results. However, treatment responses from either conventional therapies or JAK inhibitors are not durable, with relapses frequently occurring shortly after discontinuing treatment. We recently reported that autoreactive resident memory T cells form within vitiligo lesions and are responsible for the relapse of disease. We also discovered that IL-15 is required for the maintenance of these cells in lesional skin, and that targeting IL-15 signaling reverses vitiligo in our mouse model, with durable, long-lasting results. Clinical trials are ongoing to test this promising, and potentially durable, treatment strategy in patients with vitiligo.

Biography

Education

1998-2005	Ph.D., (Molecular Medicine), UMass Medical School, Worcester, MA Thesis Title: "The Molecular Mechanisms of T cell Clonal Anergy" Advisors: Dr. Aldo Rossini, Dr. Michael Czech
1998-2005	M.D., UMass Medical School, Worcester, MA
1994-1998	B.S., Premedicine, Gordon College, Wenham, MA

Postdoctoral Training

2008-2010	Postdoctoral Fellowship, University of Pennsylvania, Philadelphia, PA Research: "Development of a Mouse Model to Study Vitiligo Pathogenesis" Advisors: Dr. Laurence Turka, Dr. John Wherry, Dr. Christopher Hunter
2006-2009	Dermatology Residency, University of Pennsylvania, Philadelphia, PA
2005-2006	Medical Internship, UMass Medical School, Worcester, MA

Academic Appointments

2021	Professor, Department of Dermatology, UMass Medical School, Worcester, MA
2018	Tenured
2016-present	Associate Professor, Department of Dermatology, UMass Medical School, Worcester, MA
2010-2016	Assistant Professor, Department of Medicine, Division of Dermatology, UMass Medical School, Worcester, MA

Major Leadership Positions

2021-present	Chair, Department of Dermatology, UMass Medical School, Worcester, MA
2021-present	Founding Director, Autoimmune Therapeutics Institute
2017-2021	Vice Chair, Department of Dermatology, UMass Medical School, Worcester, MA
2016-present	Associate Director, MD/PhD Program, UMMS

Computational systems medicine approach towards personalised treatment design of atopic dermatitis

Reiko J Tanaka
Department of Bioengineering, Imperial College London

Atopic dermatitis (AD) is the most common inflammatory skin disease, whose pathogenesis includes a combination of skin barrier abnormalities, skin dysbiosis and immunological dysregulations. Given a considerable variation in the clinical phenotype and responses to treatments among patients, designing personalised treatment strategies is of high clinical relevance.

Designing personalised treatment strategies requires a systems-level understanding of AD pathogenesis that changes dynamically over time. However, its understanding may lie beyond the ethical and practical reach permitted by clinical and experimental studies and could be supported by a systematic and extensive investigation of the disease dynamics by using computational models.

As we all observed abandonedly since last year when many computational simulations were used to decide the governmental decision on interventions for COVID-19, computational models can be used to test hypothetical scenarios that are often difficult to be tested in real experiments or clinical trials. The model results are expected to explain complex pathogenesis, system-level dynamical changes and patient variability.

In this talk, I will provide an overview of computational models of AD that have been developed so far, what they aim for and how they could help towards designing personalised treatment strategies. The computational systems medicine approach is applicable to a wide range of disease, not only to AD, and is expected to be integrated as a part of the experimental and clinical trial design.

Biography

Dr Reiko J Tanaka is Reader in Computational Systems Biology & Medicine in the Department of Bioengineering at Imperial College London. She is one of the pioneers of an emerging area of systems dermatology. Her group developed mathematical models to understand pathogenesis of atopic dermatitis (AD), machine learning models for personalised prediction of AD severity and for automatic assessment of AD severity scores. Her core expertise covers the fields of systems biology, machine learning and control engineering.
She obtained her PhD in mathematical engineering at the University of Tokyo, and was an Assistant Professor in the Department of Applied Physics at Keio University, a Visiting Associate at California Institute of Technology, and a Research Scientist in RIKEN, before joining Imperial as a PI in 2009.

The ultrastructure of a novel and dynamic endoplasmic reticulum-desmosome complex: Implications for skin disease

Bharathan NK[1], Giang W[1], Aaron J[2], Khuon S[2], Chew TL[2], **Kowalczyk Andrew P.**[1]
[1]Departments of Dermatology and Cellular and Molecular Physiology, Pennsylvania State College of Medicine, Hershey, PA, USA,
[2]Advanced Imaging Center, Janelia Research Campus, Howard Hughes Medical Institute, Ashburn, Virginia

Desmosomes are adhesive intercellular junctions that participate in signaling and gene expression programs that drive epidermal differentiation. These functions underscore a key desmosome role in the ability of the epidermis to resist mechanical stress and to form a protective barrier. Genetic and autoimmune disorders that target desmosomes further highlight the importance of these adhesive junctions in skin pathophysiology. It has been known for some time that mutations in the gene encoding the SERCA2 calcium-ATPase on the endoplasmic reticulum (ER) cause desmosome defects that underlie the skin disorder, Darier's disease. However, the mechanism by which a non-desmosomal gene mutation causes desmosome defects has remained elusive. We reasoned that the functional integration between ER and desmosomes as revealed by Darier's disease might be explained by an unappreciated structural relationship between these organelles. To test this possibility, we examined desmosomes and peripheral ER tubules using fluorescently-tagged desmoplakin to mark desmosomes and VAPB to identify ER tubules. We observed frequent ER tubule-desmosome interactions that exhibited variable dwell times ranging from transient to over two minutes of continuous contact. Similar results were observed in A 431 carcinoma cells, HaCaTs, and primary human keratinocytes. ER tubule-desmosome contacts were frequently observed during desmosome assembly and fusion, suggesting a role for ER in desmosome dynamics. Transmission electron microscopy (EM) of untransfected cells confirmed ER tubule proximity to desmosomes. Both optical imaging and EM identified numerous mirror image arrangements of ER tubules extending perpendicularly to the cell membrane at sites of desmosome formation, suggesting that desmosomes organize peripheral ER morphology. These mirror image ER arrangements were absent in desmoglein-null cells where ER tubules were observed running parallel to the plasma membrane, confirming a role for desmosomes in ER organization. To resolve the three dimensional ultrastructure of the ER-desmosome complex, focused ion beam milling and scanning EM (FIB SEM) were conducted to achieve 4nm isotropic resolution. Reconstruction and segmentation of FIB SEM images revealed that ER tubules travel along keratin filament bundles as they extend toward desmosomes. ER tubules then diverge away from keratin filaments at the desmosome inner dense plaque forming branches that "cup" the desmosome as they extend to the plasma membrane. FIB SEM revealed close apposition between keratin filaments and ER tubules, suggesting molecular interactions between these structures. Optical imaging confirmed that ER tubule extension and keratin filament polymerization are temporally coupled during initiation of cell-cell contact. Overall, these findings reveal a previously unknown structural relationship between keratin filaments and the ER, and highlight a role for desmosomes in organizing peripheral ER tubule organization and dynamics. The ER-desmosome associations revealed here provide a structural explanation for Darier's disease and other epidermal disorders that involve activation of ER signaling pathways associated with desmosome dysfunction.

Biography

Current Titles and Affiliations

1. Primary Appointments: 2020-present Professor, Department of Dermatology, Penn State College of Medicine
2. Joint Appointment: 2020-present Professor, Cellular and Molecular Physiology, Penn State College of Medicine

Previous Academic and Professional Appointments

1994-1996	Research Associate, Department of Pathology, Northwestern University Medical School, Chicago, IL
1996-1998	Research Assistant Professor, Department of Dermatology, Northwestern University Medical School, Chicago, IL
1998-2005	Assistant Professor, Departments of Dermatology and Cell Biology, Emory University School of Medicine, Atlanta, GA
2005-2015	Associate Professor, Departments of Cell Biology and Dermatology, Emory University School of Medicine, Atlanta, GA
2015-2020	Professor, Department of Cell Biology, Emory University, Atlanta, GA
2015-2020	Professor, Department of Dermatology, Emory University, Atlanta, GA
2005-2020	Member, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA

Chromatin Dynamics for Diagnosis and Therapy

Annie Collier, Angela Liu, Hanson Zhen, Jessica Torkelson, Kelly McCarthy, Tiffany Patel,
Anthony Oro
Program in Epithelial Biology Stanford University School of Medicine, Stanford, CA

Proper ectodermal patterning during human development requires the concerted action of regional mesodermal and ectodermal transcription factors (TFs) that provide precise spatial and temporal regulatory information; however, the mechanism by which these factors act to stably pattern gene expression and lineage commitment remains poorly understood. We have taken a multi-dimensional genomics approach to detail the chromatin dynamics of skin using an embryonic stem differentiation method that leads to graftable human skin. We find initiation factors TFAP2, GRHL2, and GATA3 act to pattern the early genome and induce the master regulator p 63, which matures the early chromatin to the definitive tissue. We have now used this skin chromatin dynamic map to improve the efficiency and specificity of cellular manufacturing of CRISPR-corrected autologous induced pluripotent cell-derived skin to heal the wounds of patients with Recessive Dystrophic Epidermolysis Bullosa. Along with the regenerative therapies, we have used the map to identify and dissect the mechanism of disease genes involved in cleft lip/cleft palate. One example is Gibbin, encoded by the Xia-Gibbs AT-hook DNA Binding Motif Containing 1 (*AHDC1*) disease gene, that acts with GATA3 to regulate skin development. The Gibbin protein-protein interactome network is enriched for sequence-specific zinc-finger transcription factors and methyl-CpG binding proteins, and Gibbin acts on target genes by blocking DNA methylation maintenance. Novel *in vivo* chimeric CRISPR mouse mutants reveal a spectrum of surface ectoderm patterning defects affecting craniofacial structure, abdominal wall closure, epidermal adhesion, and hair follicle development that mirror patient phenotypes. Iterative increases in the resolution of the chromatin dynamic map within different skin lineages and novel informatic approaches will facilitate additional disease diagnoses and therapies for previously incurable epithelial diseases.

Biography

Education

9/81-6/85	Stanford University, Stanford, California. B.S. degree in Biological Sciences, with Honors and Departmental Distinction, June 1985 (emphasis in molecular biology and biochemistry).
9/85-6/93	University of California, San Diego, School of Medicine. La Jolla, California. Medical Scientist Training Program, M.D./Ph.D. Ph.D, Department of Biology, Molecular Genetics.
7/93-6/94	Stanford University Hospital, internship in Internal Medicine.
7/94-11/98	Stanford University Hospital, residency/fellowship in Dermatology.

Academic and Research Experience

6/85-6/93	Ph.D. thesis, Dr. Ronald Evans, Salk Institute, Gene Expression Lab and Howard Hughes Medical Institute. Title: Molecular and genetic analysis of two *Drosophila* nuclear receptors, knirps-related and ultraspiracle
6/96-11/98	Post-doctoral Fellowship, Dr. Matthew P. Scott, Department of Genetics and Developmental Biology, Howard Hughes Medical Institute, Stanford University school of Medicine. Genetics of vertebrate skin development
11/98-9/06	Assistant Professor, Department of Dermatology, Stanford University, School of Medicine. Genetics of vertebrate skin development Stanford Cancer Institute
9/06-10/11	Associate Professor, Department of Dermatology, Stanford University, School of Medicine. Genetics of vertebrate skin development
10/11-6/17	Professor, Department of Dermatology, Stanford University, School of Medicine. Epithelial regeneration and carcinogenesis
6/17-	Eugene and Gloria Bauer Endowed Professor of Dermatology Stanford University
6/17-	Associate Director, Center for Definitive and Curative Medicine Stanford University
6/17-	Co-Director, Stanford Child Health Research Institute

Scaling the Impact of Research-Based Innovation

William Ju
Advancing Innovation in Dermatology, Inc.

The tragic emergence of COVID-19 has emphatically reinforced to us the incredible power of innovation and also the profound need for it.
Dermatology-oriented research by its nature can be at the forefront of innovations in health. As an inspiring example, fundamental discoveries in bovine and human papillomaviruses foundationally created HPV vaccines. Follow on research & development and commercialization efforts then enabled this scientific invention, which prevents cervical and other cancers, to have a monumental impact on benefiting global health.
Over recent years, avenues have expanded, so that scientists and clinicians have more ways to translate their research into products that can have impact at scale. We will review some of opportunities.

Biography

EMPLOYMENT HISTORY

2011 - present	Advancing Innovation in Dermatology, Inc. (Mendham, NJ)
	Co-founder, president, and trustee
2018 - present	Zoomi, Inc. (Malvern, PA)
	Co-founder and board observer
2012 - 2018	Co-founder and board director
2018 - present	RxThat, Inc. (Castle Rock, CO)
	Co-founder and board director
2014 - 2018	Brickell Biotech, Inc./BBI (Boulder, CO)
	Board director
2009 - 2012	Follica, Inc. (Mendham, NJ)
	Chief executive officer, president, and board director
2003 - 2009	PTC Therapeutics, Inc. (South Plainfield, NJ)
	Chief operating officer
2001 - 2003	Pharmacia (Bedminster, NJ)
	Vice president, Research & Development
	(as of April 2003, Pharmacia became a wholly-owned subsidiary of Pfizer Inc.
	Declined an offer to become Therapeutic Area Head Oncology, Worldwide Medical
	Affairs at Pfizer)
2000 - 2001	Merck & Co., Inc. (Rahway, NJ)
	Director, Project Planning & Management and Head, Resource & Research Planning Merck Research Laboratories
1999 - 2000	Director, Project Planning and Management
1997 - 1999	Director, Clinical Pharmacology
1995 - 1997	Associate director, Clinical Pharmacology
1994 - 1995	Associate director, Regulatory Affairs Liaison International
1992 - 1994	Hoffmann-La Roche (Nutley, NJ)
	Assistant medical director, International Clinical Research - Dermatology

Principles of regeneration captured by imaging the skin of live mice

Greco Valentina
Department of Genetics, Cell Biology and Dermatology, Yale University

My lab tackles fundamental principles of organ regeneration during homeostasis and the emergence of aberrant tissue growth. For a long time, a major challenge in the mammalian stem cell field was the inability to follow the same cells in vivo. This limitation obscured insight into the dynamics of these processes, the contributions of intercellular interactions to tissue growth, and the initial events leading to malignancy. To overcome this challenge, my lab established the ability to visualize skin epithelial stem cells in an intact animal over prolonged periods of time by two-photon microscopy. Looking at the skin epithelium, we have studied regeneration in real time by labeling, manipulating and tracking stem cells. Our studies have expanded to understanding the skin as a whole organ and the crucial functions that other cells, such as fibroblasts and immune cells, play in supporting skin function. These approaches have repeatedly led us to a significant number of discoveries, including but not limited to 1) stem cell position dictates their fate in the hair follicle, 2) a stem cell-mediated phagocytic clearance mechanism that regulates the size of the hair follicle stem cell pool and 3) the unanticipated plasticity of the skin epithelium to correct aberrant tissue growths induced by mutational and non-mutational insults. Moving ahead, we continue our commitment to a holistic approach to both scientists and science in order to understand how different tissue types in the skin both sustain their homeostasis as well as interact with epithelial stem cells that harbor cancerous mutations.

Biography

EDUCATION

B.S.	Molecular Biology, University of Palermo, Italy, 1996
Ph.D.	Cell & Developmental Biology, EMBL/MPI-CBG, Heidelberg, Germany, 2002

CAREER/ACADEMIC APPOINTMENTS

2018-present	Carolyn Walch Slayman Professor of Genetics, Department of Genetics, Cell Biology and Dermatology, Yale University
2016-2018	Associate Professor with Tenure, Department of Genetics, Cell Biology and Dermatology, Yale University
2015-2016	Associate Professor, Department of Cell Biology, Yale University
2014-2016	Associate Professor, Department of Genetics and Dermatology, Yale University
2012-2014	Assistant Professor, Department of Dermatology, Yale University
2009-2014	Assistant Professor, Department of Genetics, Yale University
2003-2009	Postdoctoral Fellow, Rockefeller University, New York
1998-2003	PhD student, EMBL/MPI-CBG, Heidelberg/Dresden, Germany

Skin regeneration during wound healing

Mayumi Ito
The Ronald O. Perelman Department of Dermatology and Cell Biology, NYU Grossman School of Medicine, New York, USA

Mammalian wounds typically heal by fibrotic repair without hair follicle (HF) regeneration. Fibrosis and regeneration are currently considered the opposite end of wound healing. We asked if scar could be remodeled to promote healing with HF regeneration. We found that activation of the Sonic hedgehog (Shh) pathway reinstalls a regenerative dermal niche, called dermal papilla, which is required and sufficient for HF neogenesis (HFN). Epidermal Shh overexpression or constitutive Smoothened dermal activation resulted in extensive HFN in wounds in contrast to control experiments that did not lead to HFN. While long-term Wnt activation is associated with fibrosis, Shh signal activation in Wnt active cells promotes the dermal papilla fate in scarring fibroblasts. We found that SHH signaling functions to transform fibroblasts into dermal papilla depending upon WNT signaling and BMPR signaling. These studies demonstrate that mechanisms of scarring and regeneration are not distant from one another and that wound repair can be redirected to promote regeneration following injury by modifying a key dermal signal.

Biography

Mayumi Ito PhD is an Associate Professor in The Ronald O. Perelman Department of Dermatology at New York University School of Medicine (NYU). Dr. Ito received Ph.D from Nagoya University, and then performed her postdoctoral studies in the laboratory of Dr. George Cotsarelis in the University of Pennsylvania before joining the faculty at NYU (2003-2008). Her research focuses on understanding tissue regeneration in mammals with particular interest in epimorphic regeneration, which is rarely seen in mammalian organs. Her research team identified signaling pathways that govern regenerative behaviors of melanocyte stem cells and hair follicle stem cells for hair follicle pigmentation and neogenesis, which has unique implications for treatment of alopecia and wound healing.

Developmental cell programs in inflammatory skin disease

Muzlifah Haniffa
Dermatology and Immunology, Newcastle University

Muzlifah has used functional genomics, comparative biology and more recently single cell RNA sequencing to study human mononuclear phagocytes. In this seminar, she will discuss the power and utility of single cell RNA sequencing to understand the functional organisation of the human skin.

Biography

Education and qualifications

1999	BSc. (First Class Hons), MBBCh (Hons), University of Wales College of Medicine
2002	MRCP, Royal College of Physicians London
2007	Diploma in Epidemiology, London School of Hygiene and Tropical Medicine
2009	PhD, Newcastle University
2010	Certificate of Completion of Training in Dermatology

Professional appointments

1/10/15-current	Wellcome Trust Senior Research Fellow in Clinical Science, Professor of Dermatology and Immunology, Newcastle University
2019-current	Associate Faculty, Wellcome Sanger Institute
1/03/10-31/09/15	Wellcome Trust Clinical Intermediate Fellow in Dermatology, Newcastle University
1/10/05-30/09/08	Clinical Research Training Fellow, Newcastle University
1/11/02-3/01/10	Specialist Registrar in Dermatology, Royal Victoria Infirmary, Newcastle
1/08/02-31/10/02	Senior House Officer in Dermatology, Queens' Medical Centre, Nottingham
1/08/00-31/7/02	Cambridge Teaching Hospitals Medical Senior House Officer Rotation
1/08/99-31/07/00	Pre-registration House Officer, Medicine and Surgery, Univ Hosp of Wales, Cardiff

SARS-CoV2-driven immunopathology: lessons learned from the skin

Michel Gilliet
Lausanne University Hospital CHUV, Switzerland

Detrimental SARS-COV2 lung pathology is driven by a yet poorly-understood hyperinflammatory response. Recent evidence suggests that type I interferons (IFNs) play a critical role in this process: whereas rapid induction of type I IFNs limits virus propagation, the aberrant expression of type I IFNs in the late phases of the infection is associated with hyperinflammation and poor clinical outcomes. Because SARS-CoV2 also spreads to the skin, we performed in-depth analysis of skin lesions from severe COVID-19 patients to further elucidate these mechanisms. Profiling of skin lesions revealed a role of the cyclic GMP-AMP synthase (cGAS)-Stimulator of interferon genes (STING)-pathway, which controls immunity to cytosolic DNA in the context of cell damage, as the central driver of the aberrant type I IFN response in COVID-19. The STING-dependent type I IFN expression was primarily mediated by skin macrophages adjacent to areas of endothelial cell damage. Similarly, we found prominent cGAS-STING activity associated with tissue destruction in post-mortem lung samples of COVID-19 patients. A lung-on-chip model revealed that SARS-CoV-2 infection of the epithelium indirectly triggered STING activation in both endothelial cells and macrophages, leading to cell death and type I IFN production. In mice, pharmacological inhibition of STING reduced the severity of lung inflammation induced by SARS-CoV-2 and improved disease outcome. Collectively, our study establishes the mechanistic basis of pathological type I IFN responses in COVID-19 and provides the basis for the development of novel treatment approaches.

Biography

PRESENT POSITION (since 2010)

Professor and Chairman, Department of Dermatology, University of Lausanne CHUV

PAST POSITIONS

2008 - 2010	Associate Professor (with tenure) in Dermatology, Melanoma Medical Oncology and Immunology (triple appointment), The University of Texas M.D. Anderson Cancer Center, Houston (TX) Co-Director of the Center for Cancer Inflammation, The University of Texas M.D. Anderson Cancer Center, Houston (TX)
2004 - 2008	Assistant Professor (tenure-track) in Melanoma Medical Oncology and Immunology, The University of Texas, M.D. Anderson Cancer Center, Houston (TX)
2001 - 2004	Clinical Resident in Dermatology, Zürich University Hospital, Zürich, Switzerland
1999 - 2001	Post-Doctoral Research Fellow in Immunology, DNAX Research Institute, Schering Plough, Palo Alto (CA)
1998 - 1999	Clinical Resident in Dermatology, Zürich University Hospital, Zürich, Switzerland
1996 - 1998	Postgraduate Research Fellow, Department of Internal Medicine, Zürich University Hospital, Zürich, Switzerland

EDUCATION, ACADEMIC DEGREES, CERTIFICATIONS

1989	Swiss Matura, Bellinzona, Switzerland
1995	Swiss Federal Diploma in Medicine, University of Zurich, Switzerland
1998	Doctorate in Medicine, University of Zürich, Switzerland
2004	Swiss Board Certification in Dermatology
2008	Texas Medical Board License to practice Dermatology

Potency and activity of endovascular progenitors in wound healing and scarring

Kiarash Khosrotehrani
The University of Queensland Diamantina Institute, Brisbane, Australia

The endothelium possesses a profound regenerative capacity to adapt and reorganise in homeostasis and disease. The capacity to regenerate is increasingly attributed to a population of vessel-resident endovascular progenitor (EVP) cells that governs an endothelial hierarchy. Using functional stem cell assays and fate map analysis, we show that two transcription factors *Sox9* and *Rbpj* specifically demarcate the EVP population and regulate progenitor fate choice. EVPs can adopt an endothelial phenotype, forming new vessels, contributing to wound healing or they adopt a mesenchymal phenotype, disorganising vessels, forming myofibroblasts and contributing to fibrosis. Conditional knock-out of *Sox9* from the endothelium drove the depletion of EVP to a mature differentiated endothelial phenotype and enhanced *Rbpj* expression and Notch signalling. Additionally, skin wound analysis from *Sox9* knock-out mice demonstrated a significant reduction in endothelial to mesenchymal transition (EndMT), reducing scar area. The converse was observed with *Rbpj* conditionally knocked-out from the vasculature, with enhanced *Sox9* and key EndMT gene (*Snail*, *Slug*, *Twist1*, *Twist 2*, *TGF-β*) expression. Concurrently, vascular sonic hedgehog activation upregulates the expression *Sox9* and is key in driving pathological EndMT and vascular fibrosis, resulting in over 3-fold increase in scar area in skin wound healing. In this scenario, we see EVP transitioning towards a mesenchymal fate; with increased *Sox9*, reduced *Rbpj* and enhanced EndMT gene expression. Importantly, using topical administration of siRNA against *Sox9* on skin wounds significantly reduced scar area by blocking pathological EndMT. Finally, we explored the role of high-fat diet as a major contributor to EndMT establishing the importance of this duality between RBPJ and Sox9 in this clinically relevant scenario. The understanding of how vascular resident EVP function opens exciting new avenues for more effective therapies in blocking fibrotic disease.

Biography

Professor Khosrotehrani is a clinician-scientist, practicing dermatologist with a focus on delivering state of the art concept and technologies to real-world clinical problems. He leads the Experimental Dermatology Group at the University of Queensland Diamantina Institute in Brisbane, Australia and is the deputy director of the Australian Skin and Skin Cancer Research Centre in Brisbane. Prof Khosrotehrani is passionate about the development of academic medicine and future academic clinicians and leads this effort in dermatology as the chair of Academic Research Committee at the Australasian College of Dermatologists, the President of the Australasian Society for Dermatology Research and the co-Editor in Chief of the Australasian Journal of Dermatology and a board member of the International Society for Investigative Dermatology.

Prof Khosrotehrani obtained his MD in Paris, France, where he specialized in Dermatology. He is a former graduate of the Ecole Normale Supérieure and the Institut Pasteur of Paris (Université Paris VI, Pierre et Marie Curie) where he obtained a PhD in Physiology and Physiopathology. He completed his post-doctoral training in stem cell biology and clinical genetics at Tufts-New England Medical Centre in Boston, USA. He is a fellow of the Australian College of Dermatologists and a practising dermatologist at the Princess Alexandra Hospital and the Skin and Cancer Foundation's Queensland Institute of Dermatology.

His research is fundamentally based on regenerative medicine concepts applied at basic, translational and clinical levels to melanoma, keratinocyte cancers and skin wounds. The breadth of expertise established in his research team allows the multidisciplinary approach required for these difficult questions. This unique expertise and leadership in research is witnessed by a record of highly cited articles (over 3700 citations, H index 33). The originality of this body of work was acknowledged by the National Health and Medical Research Council (NHMRC) of Australia through an achievement award (2011) and an NHMRC excellence award (2016).

State-of-the-Art Symposium of Skin Research

The 46th Annual Meeting of the Japanese Society for Investigative Dermatology

Interclonal competition for active TGFb preferentially enrich antigen-specific tissue resident memory T cells in the epidermal niche

Toshiro Hirai[1,2]

[1]BIKEN Innovative Vaccine Research Alliance Laboratories, Institute for Open and Transdisciplinary Research Initiatives/Research Institute for Microbial Diseases, Osaka University,

[2]Departments of Dermatology, University of Pittsburgh

Tissue-resident $CD8^+$ memory T (Trm) cells are a highly abundant, non-blood-circulating subset of memory T cells that provide efficient peripheral immune surveillance. In the skin, cutaneous viral infection, such as vaccinia virus (VV) or herpes simplex virus infection, is well described to result in the development of large numbers of Trm cells that preferentially reside in the epidermis. In these models, viral-derived antigen is initially brought to skin-draining lymph nodes by dendritic cells or through lymph that drives the expansion of $CD8^+$ T cell effectors. These effectors are then recruited into the sites of infected skin, where they re-encounter antigen, and some differentiate into long-lived Trm cells. Although re-encounter with cognate antigen in peripheral tissue is required for Trm cells differentiation in certain tissue, it appears not to be the case for skin. Thus epicutaneous application of the inflammatory chemicals, such as 1-Fluoro-2,4-dinitrobenzene (DNFB), can efficiently recruit non-antigen-specific, bystander effector cells activated by, in some cases, even not skin relevant antigen (e.g. influenza virus) where they then differentiate into epidermal Trm cells. Both Trm that have seen cognate antigen in skin (antigen-specific Trm) and that have not seen antigen in skin (bystander Trm cells) are maintained by skin local factors, such as TGFb, and might compete for them within a given niche but the potential competition of the local resources and the impact for Trm persistence have not been well explored. Here we found antigen-specific Trm cells and bystander Trm cells both displayed long-term persistence in the epidermis under steady-state conditions. However, when active TGFb was limited by administration of antibodies blocking TGFb-activating integrins or by a small molecule inhibitor, antigen-specific Trm cells were able to persist in the epidermis while bystander Trm cells were depleted. Notably, when new T cells were recruited into the skin by a subsequent challenge, bystander Trm cells being preferentially replaced by newly recruited $CD8^+$ T cells. Genetically enforced TGFbR signaling rescued this phenotype and allowed bystander Trm cells to persist in the epidermis as efficiently as antigen-specific Trm cells in both contexts. Thus, T cell interclonal competition for active TGFb results in an unexpected selective pressure promoting the retention of antigen-specific Trm cells within the epidermal niche.

Biography

Education

2010 March	B.S. in Pharmaceutical Sciences at Osaka University
2012 March	M.S. in Pharmaceutical Sciences at Osaka University
2015 March	Ph.D. in Pharmaceutical Sciences at Osaka University

Appointments

2012 April - 2015 March	JSPS Research Fellow
2015 April - 2017 March	JSPS Overseas Research Fellow
2015 April - 2015 October	Postdoctoral Associate (Daniel H. Kaplan lab, Department of dermatology, University of Minnesota)
2015 November - 2020 August	Postdoctoral Associate/Research Instructor (Daniel H. Kaplan lab, Departments of dermatology and immunology, University of Pittsburgh)
2020 September - present	Specially Appointed Associate Professor (Vaccine Creation Group, BIKEN Innovative Vaccine Research Alliance Laboratories, Institute for Open and Transdisciplinary Research Initiatives/Research Institute for Microbial Diseases, Osaka University)

Tracing the origin of hair follicle stem cells

Hironobu Fujiwara
RIKEN Center for Biosystems Dynamics Research, Kobe, Japan

Tissue stem cells are generated from an embryonic progenitor population through organ-specific morphogenetic events. Although tissue stem cells are central to organ homeostasis and regeneration, it remains unclear how they are induced during development, mainly owing to the lack of specific markers that exclusively label prospective stem cells. Here, by combining marker-independent long-term 3D live imaging and single-cell transcriptomics, we captured cellular dynamics, cell lineages, and transcriptome changes in the entire epithelium of developing mouse hair follicles. We found that different epithelial lineage precursors were aligned in a 2D concentric manner in the basal layer of the hair placode. Each concentric ring zone acquired unique transcriptomes and telescoped out to form longitudinally aligned 3D cylindrical compartments. Prospective bulge stem cells were derived from the peripheral ring zone of the placode, irrespective of cell division orientation. We also identified 13 gene clusters in which their ensemble expression dynamics drew the entire transcriptional landscape of epithelial lineage diversification, coinciding with cell lineage data. Combining these findings with insect appendage development, we provide a generalized model termed the 'telescope model' wherein 2D concentric zones in the placode telescope out to form 3D longitudinally aligned cylindrical compartments.

Biography

2019-	JST CREST Investigator
2018-	Team Leader, RIKEN Center for Biosystems Dynamics Research (BDR)
2012-2018	Team Leader, RIKEN Center for Developmental Biology (CDB)
2007-2012	Post-doc, Cancer Research UK Cambridge Research Institute (Fiona Watt laboratory)
2006-2007	Post-doc, Institute for Protein Research, Osaka University (Kiyotoshi Sekiguchi laboratory)
2003-2006	Post-doc, JST ERATO Sekiguchi Project
2003	Ph.D., Osaka University Graduate School of Science
2001-2003	JSPS Research Fellow (DC2), Osaka University
2000	Master, Osaka University Graduate School of Science
1998	Bachelor, Kyoto Pharmaceutical University

Specialty and present interests: skin development and regeneration, cellular microenvironment, stem cell, live imaging

A unique mode of functional keratinocyte death, *corneoptosis* requires intracellular acidification

Takeshi Matsui[1,2]
[1]School of Bioscience and Biotechnology, Tokyo University of Technology, Tokyo, Japan,
[2]RIKEN Center for Integrative Medical Sciences

The stratum corneum (SC), the outermost epidermal layer, consists of non-viable anuclear keratinocytes (corneocytes), which serve as a protective barrier. The exact modes of functional cell death executed by keratinocytes of the upper stratum granulosum (SG1 cells) remain unclear. Using intravital imaging combined with intracellular Ca^{2+}- and pH-responsive fluorescent probes, we aimed to dissect the SG1 death process in vivo. We found that SG1 cell death was preceded by prolonged (~60min) Ca^{2+} elevation and rapid induction of intracellular acidification. Once this intracellular ionic changes were initiated, they became sustained, irreversibly committing the SG1-to-corneocyte conversion. Time-lapse imaging of isolated murine SG1 cells revealed that intracellular acidification was essential for the elimination of keratohyalin granules and nuclear DNA, phenomena specific to corneocyte formation. Furthermore, intravital imaging showed that the number of SG1 cells exhibiting Ca^{2+} elevation and the timing of intracellular acidification were both tightly regulated by the transient receptor potential cation channel V3 (TRPV3). These findings provide an improved theoretical framework of the unique molecular mechanisms underlying keratinocyte-specific functional death mode, termed *corneoptosis*.

Biography

Educations

1990-1994	Undergraduate Course, Faculty of Agriculture, Tohoku University
1994-1996	Master's Course, Graduate School of Biological Sciences, Nara Institute of Science and Technology
1996	Master's Degree (Nara Institute of Science and Technology, Prof. Kozo Kaibuchi)
1996-2000	Doctoral Course, Faculty of Medicine, Kyoto University
2000	Ph.D. (Kyoto University, Prof. Shoichiro Tsukita)

Positions

2000-2006	Group Leader, Research Group of Dermatology, KAN Research Institute, Inc., Kyoto, Japan
2006-2007	Assistant Professor, Prof. Sachiko Tsukita's laboratory, Graduate School of Frontier Biosciences, Osaka University, Osaka, Japan
2007-2011	Lecturer, Medical Top Track Program, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan
2011-2013	Assistant Professor, Prof. Takashi Hiiragi's laboratory, Institute for Integrated Cell-Material Sciences, Kyoto University, Kyoto, Japan
2013-	Senior Research Scientist, Laboratory for Skin Homeostasis, (Team Leader: Masayuki Amagai), RIKEN Center for Integrative Medical Sciences (IMS)
2016-	Deputy Team Leader, Laboratory for Skin Homeostasis, RIKEN Center for Integrative Medical Sciences (IMS)
2021-	Professor, Laboratory for Evolutionary Cell Biology of the Skin, School of Bioscience and Biotechnology, Tokyo University of Technology

Dysbiosis leads to inflammatory destruction of the hair follicles mediated by innate lymphoid cells

Keisuke Nagao
Dermatology Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health

The hair follicles (HF) harbor HF stem cells and are capable of self-renewal, producing hair shafts that provide the first line of physical defense of the mammalian body. HFs also function as control towers of skin immunity. We have found over the years that HFs are important sources of chemokine and cytokines that guide the localization and survival of tissue-resident immune cells. Furthermore, HFs provide niches for commensal microbes to reside in, highlighting them as hubs for stem cells, immune cells and microbes. Understanding the functional interaction between stem cells, immune cells and commensal microbes residing on the skin surface is critical for unraveling mechanism that underlie host-microbial symbiosis at barrier surfaces, which may further enable us to understand the pathophysiology of hair loss disorders. In this talk, I will present our recent study on how the HFs regulate commensal bacteria and how the disruption of this function leads to the inflammatory destruction of the HFs.

Biography

EDUCATION

1994	M.B., M.D. Keio University School of Medicine, Tokyo, Japan
2005	Ph.D. in Microbiology (medical mycology), Keio University School of Medicine, Tokyo, Japan

PROFESSIONAL POSITIONS AND EMPLOYMENT

1994-1996	Residency, Department of Dermatology, Keio University School of Medicine, Tokyo, Japan
1996-1997	Staff Surgeon, Plastic and Reconstructive Surgery, Shizuoka Red Cross Hospital, Shizuoka, Japan
1997-2001	Staff Dermatologist, Department of Dermatology, Shimizu Municipal Hospital, Shizuoka
2001-2005	Instructor, Department of Dermatology, Keio University School of Medicine
2005-2008	Visiting Fellow, Mark Udey Lab, Dermatology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health (NIH)
2008-2010	Instructor, Department of Dermatology, Keio University School of Medicine
2010-2014	Senior Assistant Professor, Department of Dermatology, Keio University School of Medicine
2014-2017	Earl Stadtman Investigator, Dermatology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health
2017-2019	Earl Stadtman Investigator, Dermatology Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health
2020-present	Senior Investigator, Dermatology Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health

Stem cell-centric mechanisms of skin aging

Emi K. Nishimura
Institute of Medical Science, University of Tokyo, Tokyo, Japan

Somatic stem cells underlie tissue regeneration and homeostasis, yet the actual stem cell dynamics and fates during the life cycle and their relevance to organ aging had been largely unknown. Our previous studies revealed that the age-associated depletion of melanocyte stem cells, the reservoir of pigment cells in the skin causes hair graying, suggesting that actual stem cell dynamics during a life cycle could be a clue to understand tissue regeneration and aging. We thus have performed fate-tracing of multiple stem cells in the skin in vivo during a life cycle as well as under various environmental factors. This approach enabled us to visualize the spatio-temporal fates and dynamics of those stem cells and revealed that stem cells limit their self-renewal by promoting their commitment to differentiation under genomic or oxidative stress, thereby dynamically eliminating stressed stem cells and driving organ aging. Through those studies, we demonstrated the existence of a stem cell-centric organ aging program. Further, we recently found that environmental factors such as indued by high fat diet feeding directly modify and accelerate the program by targeting stem cells. In contrast to hair follicles that miniaturize and are lost by aging, large organs such as the skin maintain their integrity and functions throughout life. To understand the mechanism, we performed multi-color clone tracing studies and revealed that epidermal stem cells compete with each other through a cell competition mechanism to maintain the tissue youthfulness. We have identified stem cell divisions based on hemidesmosomal proteins as the underlying molecular and cellular mechanism for stem cell competition. That mechanism is effective in maintaining the epithelial tissue/organ quality yet eventually fails to prevent tissue/organ aging and allows tumor development. Thorough those studies we have demonstrated that tissue stem cells play a central role not only in tissue homeostasis and aging, but also in disease pathogenesis.

Biography

Education and Training

1994	M.D., Shiga University of Medical Science
1994-1995	Resident, Department of Dermatology, Kyoto University Hospital
1995-1996	Resident, Department of Dermatology, Kurashiki Hospital, Japan
2000	Ph.D., Medicine, Kyoto University Graduate School of Medicine
2000	Medical Staff, Department of Dermatology, Kyoto University Hospital

Current and Past Professional Positions

1997-2000	Research Fellow of the Japan Society for the Promotion of Science (JSPS, DC1)
2000-2003	Research Fellow, Department of Pediatric Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
2003-2004	Instructor of Pediatrics, Department of Pediatric Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
2004-2006	Associate Professor, Creative Research Institute Sousei (CRIS), Hokkaido University
2006-2009	Professor and Chair, Division of Stem Cell Medicine, Cancer Research Institute, Kanazawa University
2009-present	Professor and Chair, Department of Stem Cell Biology, Medical Research Institute, Tokyo Medical and Dental University
2021-present	Professor, Division of Aging and Regeneration, Department of Cancer Biology, The Institute of Medical Science, The University of Tokyo

JDS Symposium

The 46th Annual Meeting of the Japanese Society for Investigative Dermatology

Introduction of Journal of Dermatological Science Symposium

Riichiro Abe
Division of Dermatology, Niigata University Graduate School of Medical and Dental Sciences, Japan

Journal of Dermatological Science, or JDS is the official journal of the Japanese Society for Investigative Dermatology (JSID), which now comprises more than 1300 dermatologists and skin researchers from Japan and other countries. JDS has increasingly upgraded its value among the dermatological journals. The Impact Factor in 2020 is 4.438, ranked the 14th highest among 89 dermatology journals. Manuscripts are being submitted from over the world, including other Asian countries, European countries, and the United States. High quality editorial process is essential for JDS, and the system composed of 18 well-known Section Editors plays an essential role for a rapid but qualified review and decision-making process.
In this seminar, skin researchers present their experience and opinion about success of basic research and publication of their work. In addition, Executive Publisher of JDS will explain about medical journal publication process. I also attempt to provide relevant insights and advice based on my involvement in the editorial process for JDS.

Biography

1994-1998	Hokkaido University Graduate School of Medicine
1998-2000	Research fellow, Picower Institute for Medical Research, NY
2000-2002	Staff dermatologist, Hokkaido University Graduate School of Medicine
2002-2007	Instructor, Hokkaido University Graduate School of Medicine
2007-2010	Assistant Professor, Hokkaido University Graduate School of Medicine
2010-2015	Associate Professor, Hokkaido University Graduate School of Medicine
2015-present	Professor and Chair, Division of Dermatology, Niigata University Graduate School of Medical and Dental Sciences
2018-present	Editor-in-Chief, Journal of Dermatological Science

What we can do to patch the "leaky pipeline": Issues revealed by the first national survey

Mari Kishibe
Department of Dermatology, Asahikawa Medical University

A wide gender gap exists in many fields in Japan, and it can be a barrier to hinder the development of an organization. While the number of women doctors has been increasing, we need to clarify the current gender gap in academic dermatology. In 2019, we performed a survey of faculty members' academic productivity at the dermatology departments of all the educational institutions in Japan. Japanese female dermatologists had significantly lower academic productivity than male dermatologists. A significant gender difference in academic productivity was found in lecturers and assistant professors but not in associate professor and professor positions, even after normalizing the productivity for career length. The gender gap was also seen in the total number of governmental Grant-in-Aid for Scientific Research. However, being male is advantageous for promotion in the group with lower research output in Japan. The main reason for the low percentage of Japanese female dermatologists at higher academic positions is not overt gender discrimination ("glass ceiling"), but the tendency that female faculty members leave academic institutions before they can achieve further advancement ("leaky pipeline"). To patch the "leaky pipeline" on their career path, we need to take adequate measures. First, we need to support the research activity of female dermatologists at the position of lecturer or below in their efforts to enhance their academic achievements. Second, we need to help female doctors with child-bearing responsibilities become aware of and overcome their own unconscious biases. Based on ancient patriarchy in Japan, the division of gender roles, the idea that men should go out and women should stay at home has taken root. In fact, many Japanese women prefer to take responsibility for their own families. Providing role models and educational programs may be effective to overcome the bias.

Biography

1998	M.D., Asahikawa Medical University
1998-1999	Residency, Department of Dermatology, Asahikawa Medical University
1999-2001	Clinical fellow, JA Asahikawa Kosei Hospital
2001-2002	Clinical fellow, Kitami Red Cross Hospital
2002-2006	Ph.D., Department of Functional Anatomy and Neuroscience, Asahikawa Medical University
2006-2007	Clinical fellow, Asahikawa Medical University
2007-2008	Clinical fellow, Asahikawa City Hospital
2008-2013	Clinical fellow, Asahikawa Medical University
2014-2015	Post-Doctoral Fellow, Burn Shock and Trauma Institute, Department of Surgery, Loyola University Chicago
2016-2020	Assistant Professor, Department of Dermatology, Asahikawa Medical University
2020-present	Associate Professor, Department of Dermatology, Asahikawa Medical University

Dissecting the molecular mechanism of acne keloidalis by single-cell transcriptomics

Chao-Kai Hsu
Department of Dermatology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Chinese Taipei

Acne keloidalis (AK) is one of the primary cicatricial alopecias and predominantly affects men of African descent. We recently retrospectively reviewed the clinical and histopathological features of AK patients in southern Taiwan and identify the pathognomonic features of AK, i.e., the segments of hair shafts remained in the upper to mid-dermis and induced chronic inflammation and extensive fibrosis, resulting in the clinical keloid-like appearance. To explore the molecular mechanism of AK, single-cell transcriptomics was applied to scalp biopsy samples. We performed unbiased clustering on ~5,000 cells from subacute inflammatory AK and ~3,000 cells from the adjacent control skin, and 18 distinct populations were identified based on their differentially expressed genes. We found hair follicle stem cells (*SOX9*, *FOXC1*) were reduced in AK, while a lineage of keratinocytes expressing *CCL18* were found in AK. Among the five distinct myeloid subsets, SPP1+ cells belonging to M2 macrophages were increased in AK. There were four distinct fibroblast subsets, from which POSTN+ cells with enriched extracellular matrix signatures were increased in AK. Pseudotime trajectory and immunofluorescence revealed that POSTN+ fibroblasts were potentially differentiated from SPP1+ myeloid cells. These findings will help us better understand the pathogenesis of AK and develop the potential prevention and treatment.

Biography

EDUCATION

1996-2003	MD, Department of Medicine, Medical College of Medicine, National Cheng Kung University
2000-2017	PhD, Institute of Clinical Medicine, College of Medicine, National Cheng Kung University

AFFILIATION & WORKING EXPERIENCE

Aug 2018 to present	Associate Professor, Department of Dermatology, College of Medicine, National Cheng Kung University, Taiwan
Aug 2018 to present	Associate Professor, Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Taiwan (Joint Appointment)
Aug 2014 to Aug 2018	Assistant Professor, Department of Dermatology, National Cheng Kung University Hospital, Taiwan
Dec 2014 to Dec 2016	Research fellow, St John's Institute of Dermatology, Department of Dermatopathology & Department of Genetics and Molecular Medicine King's College London, UK
Feb 2008 to Apr 2008	Research fellow, Department of Dermatology, Hokkaido University Graduate School of Medicine, Japan

How to publish our work in a decent journal

Shuai Shao, Gang Wang
Department of Dermatology, Xijing Hospital, Fourth Military Medical University, Xi'an, China

For this topic, I will take one of our published articles for example, to talk about how to conclude questions from clinical problems or phenomenon, how to address this problem and dig into it using a series of in vivo and in vitro experiments, and how to wrap up the interesting story. The experience of scientific writing and publishing is also included.

Biography

Dr. Shuai Shao, M.D, PhD is an attending dermatologist of the Department of Dermatology, Xijing hospital. During 2018-2019, Dr. Shao went to the Department of Dermatology, University of Michigan for joint education. In recent years, Dr. Shao has been devoted to the immunological and genetic work on psoriasis in the Xijing hospital and U-M. Until now, Dr. Shao has published her works as the first author on Journals including *Science Translational Medicine*, *Journal of Investigative Dermatology*, *Theranostics*, *The Journal of Pathology*, etc.

How age and sex shape the skin cancer landscape

Amaya Viros Usandizaga[1,2]
[1]Cancer Research UK Manchester Institute,
[2]Salford Royal NHS Foundation Trust

Age and sex are known modifiers of skin cancer onset and progression. Most skin cancers and skin cancer deaths occur in older patients, and mortality is specifically increasing in the elderly. There is additionally a male sex bias in incidence and mortality. We have found the mutation processes underpinning melanoma differ by sex and age. Specifically, the rate of mutations associated with cell division declines in the melanoma with age, and men present a higher rate of mutations associated with cell division compared to women. Our data shows an additional critical factor modifying primary melanoma outcome in old age is the rate of destruction of the extracellular matrix in the dermis, which impedes melanoma single cell invasion into deeper dermal structures. However, some melanomas that arise over severely sun-damaged skin can deposit new collagen fibres at the invasive front of the tumour in the dermis to restore invasion, driving increased death. We show in a mouse model of squamous cell carcinoma that sex profoundly alters the onset, progression and immune-fighting responses to external carcinogens, such as UV light, explaining the increased incidence and higher morbidity of male cSCC patients.

Biography

Amaya obtained her degree in Medicine and Surgery at the University of Barcelona. She completed her training as a dermatologist and venereologist at Vall d'Hebrón University Hospital, Spain. She then obtained a Fulbright Scholarship to become a Fellow in the Department of Dermatology and Pathology at the University of California, San Francisco, in the laboratory of Boris Bastian. She then moved to Richard Marais' laboratory, first to the Institute of Cancer Research and then at the CRUK Manchester Institute where she obtained a PhD. Amaya has combined her research with clinical work as a dermatologist at St. George's Hospital in London, and Salford Royal Foundation Trust in Manchester. Her research has focused on the mechanisms driving secondary keratinocytic tumours in metastatic melanoma patients treated with the BRAF inhibitor vemurafenib, as well as on dissecting the specific contribution of ultraviolet radiation to distinct subtypes of melanoma defined by their driver oncogene. In 2016, she became a Wellcome Trust Intermediate Clinician Scientist Fellow and won the Wellcome-Beit Award. Her lab focuses on how ageing influences melanoma initiation and progression, and on developing rationales of adjuvant care for patients at high risk for melanoma progression. Amaya was most recently awarded the 2018 European Society for Dermatological Research Rising Star.

Revertant mosaicism in inherited disorders of keratinization

Toshifumi Nomura
Department of Dermatology, University of Tsukuba, Ibaraki, Japan

Revertant mosaicism refers to a condition in which a pathogenic germline mutation is spontaneously corrected in somatic cells, resulting in the presence of two or more cell populations with different genotypes in an organism arising from a single fertilized egg. If the revertant cells are clonally expanded due to a survival advantage over the surrounding mutant cells, patients benefit from this self-healing phenomenon which leads to the development of milder-than-expected clinical phenotypes; in genetic skin diseases, patients with revertant mosaicism present with small islands of healthy skin. To date, revertant mosaicism has been reported in ˜50 genetic diseases involving the skin, blood, liver, muscle, and brain. In this lecture, I briefly summarize current knowledge on revertant mosaicism in inherited disorders of keratinization, including ichthyosis with confetti and loricrin keratoderma, and pityriasis rubra pilaris type 5, where patients develop numerous revertant skin patches. Notably, homologous recombination is the major mechanism underlying the reversion of pathogenic mutations in these diseases, and this was identified following the analysis of ˜50 revertant epidermis samples. All the samples showed long-tract loss of heterozygosity that originated at regions centromeric to pathogenic mutations and extended to the telomere of the mutation-harboring chromosomes. Elucidating the molecular mechanisms underlying revertant mosaicism, especially how mutant proteins induce long-tract loss of heterozygosity, would potentially expand the possibility of manipulating homologous recombination to induce the reversion of disease-causing mutations and help devising novel therapies not only for these diseases but also for other intractable genetic diseases.

Biography

Education

1996-2002	Hokkaido University School of Medicine (M.D)
2006-2009	Hokkaido University Graduate School of Medicine (Ph.D)

Work experience

May 2002 - Mar 2004 (Resident)	Hokkaido University Hospital (Prof. Hiroshi Shimizu)
Apr 2004 - Mar 2005 (Medical Staff)	Kushiro City General Hospital (Dr. Hiroyuki Nakamura)
Apr 2005 - Jan 2008 (Medical Staff)	Hokkaido University Hospital (Prof. Hiroshi Shimizu)
Feb 2008 - Aug 2010 (Visiting Researcher)	University of Dundee (Prof. W.H. Irwin McLean)
Sep 2010 - Aug 2016 (Assistant Professor)	Hokkaido University Hospital (Prof. Hiroshi Shimizu)
Sep 2016 - Oct 2020 (Associate Professor)	Hokkaido University Hospital (Prof. Hiroshi Shimizu)
Nov 2020 - present (Professor and Chair)	University of Tsukuba

An Update on Scholarly Publishing in the Wake of the Pandemic in its Second Year

Helen Habernickel
Executive Publisher, Health & Medical Sciences Elsevier, Berlin, Germany

Following up on last year's presentation, now nearly two years into the COVID-19 pandemic, radical shifts in day-to-day operations and strategic planning have become necessary for scholarly publishers.

Changes include rapid peer-review and sped-up publishing workflows as well as the wider acceptance of preprints. Conferences are now taking place virtually, which also allows for new ways to link to content. Furthermore, transformative changes in the publishing market with regards to Open Access are accelerating.

Long-term implications for publishers, learned societies, editors, reviewers and authors will become more apparent in the course of next year.

Biography

Following her Master's in International Publishing Management, Helen joined Elsevier, first based in Amsterdam, as a Publishing Editor and later as a Publisher. In her current role as Executive Publisher in Berlin, Helen is focused on managing a portfolio of peer-reviewed medical journals, assuring their ideal positioning in the global market, coordinating on a daily basis with journal editors, authors and learned societies.

JSID-Asia-Oceania-Forum

The 46th Annual Meeting of the Japanese Society for Investigative Dermatology

Metabolic Control of Epithelial-Immune Interaction in Skin Inflammation

Srikala Raghavan
A*Star Skin Research Lab (ASRL), Agency for Science, Technology and Research (A*STAR)

Inflammatory diseases in skin have been shown to develop from aberrant interactions between skin immune cells and resident cells of the tissue. The innate immune arm, specifically macrophages have been shown to play critical role in driving the disease conditions since depletion of macrophages significantly reduces inflammatory burden in skin. While the crosstalk between macrophages and skin compartments has been studied largely at the level of cytokines and chemokines, much less has been understood at the level of metabolic crosstalk between macrophages and other skin compartments.

Metabolic factors have been shown to play supportive, instructive and permissive roles, essential for regulating fate decision in immune cells. The acquired metabolic state depends on the functional requirements of the immune cells and the local availability of carbon and nitrogen sources. Innate immune cells especially macrophages have been shown to exhibit remarkable functional and metabolic flexibility, capable of acquiring distinct M1 and M2 fates, *in vitro*. Interestingly, these M1 and M2 macrophages have been shown to be associated with distinct metabolic states where M1 macrophages have preferential dependence on glycolysis and M2 macrophages on tricarboxylic acid cycle (TCA) and oxidative phosphorylation (OXPHOS). While these metabolic pathways are well understood in vitro, much less is known about their states in tissues. This is in part due to a wide range of cues received from the microniches, which is in turn complicated by tissue specific metabolic diversity. In inflammatory skin conditions such as wounding, atopic dermatitis and psoriasis macrophages have been shown to acquire distinct functional states which exacerbate disease condition. Consistently, loss of macrophages lead to remarkable rescue of the diseased skin. However, much less is understood about how the metabolic crosstalk between different skin cells and macrophages bring about these switches. This is specifically due to additional network of crosstalk of the macrophages with the adaptive immune arm.

In our work, we have used embryonic skin specific integrin β1 KO model of inflammation to investigate the metabolic crosstalk between skin compartments with macrophages to understand the initial event that drive inflammatory responses in skin. This allows us a rather simplified system since the embryonic skin lacks the adaptive immune arm.

Biography

Dr. Srikala Raghavan obtained her Ph.D from the University of Cambridge and did her post-doctoral training with Prof. Elaine Fuchs at the University of Chicago and later at The Rockefeller University. In 2005, Dr. Raghvan established her lab at Columbia University NY, at the College of Dental Medicine and Dept of Dermatology. In 2012, she was recruited to inStem Bangalore to establish the Centre for Inflammation and Tissue Homeostasis where she is an Associate Professor. In January 2020, Prof. Raghavan joined A*SRL, A*STAR as a Principle Investigator. The Raghavan Lab studies stem cell homeostasis and immune regulation in the skin.

IKK/NF-κB signaling in keratinocytes regulates necroptosis-mediated skin inflammation

Snehlata Kumari[1,2], Trieu-My Van[2], Manolis Pasparakis[2]
[1]The University of Queensland Diamantina Institute, Translational Research Institute, Brisbane, Australia,
[2]CECAD Research Center, University of Cologne, Cologne, Germany

IKK/NF-kappaB signaling controls inflammation and cell death and is important to maintain tissue homeostasis. Keratinocyte-specific deletion of IKK2 (IKK2$^{E\text{-}KO}$) leads to TNFR1-dependent Psoriasis-like skin inflammation in mice. IKK2$^{E\text{-}KO}$ mice showed increased numbers of apoptotic and necrotic keratinocytes, and upregulation of inflammatory cytokines mediators in the epidermis. We proposed that keratinocyte death could trigger inflammation.

Receptor Interacting Protein Kinase (RIPK1) induces cell death via kinase activity-dependent functions. To address the kinase-dependent role of RIPK1 in IKK2$^{E\text{-}KO}$ mice, we generated IKK2$^{E\text{-}KO}$ mice expressing kinase inactive RIPK1 (IKK2$^{E\text{-}KO}$;*Ripk1*$^{D138N/D138N}$). We observed that IKK2$^{E\text{-}KO}$;*Ripk1*$^{D138N/D138N}$ mice did not develop skin lesions, demonstrating an essential role of RIPK1 kinase activity in skin inflammation. We further dissected out whether apoptosis or necroptosis drives skin inflammation in IKK2$^{E\text{-}KO}$ mice by crossing them to the mice lacking RIPK3 or MLKL, which are essential mediators of necroptosis. We found that the IKK2$^{E\text{-}KO}$;*Ripk3*$^{-/-}$ or IKK2$^{E\text{-}KO}$;*Mlkl*$^{-/-}$ mice were strongly protected from skin lesion development, showing the important role of necroptosis in triggering skin inflammation. Since inhibition of necroptosis strongly ameliorated but could not fully prevent the skin lesions, we generated IKK2$^{E\text{-}KO}$ mice lacking both apoptosis and necroptosis pathways to assess whether the remaining inflammation in IKK2$^{E\text{-}KO}$;*Ripk3*$^{-/-}$ mice is due to apoptosis. We observed that these mice were fully protected from the development of skin lesions. Furthermore, combined deficiency of NF-κB subunits, cRel and RelA, also resulted in TNFR1-mediated, RIPK1 kinase- dependent skin inflammation, strengthening the role of NF-κB signaling in inhibiting RIPK1 kinase activity-dependent cell death and skin inflammation.

Collectively, we identified the mechanisms by which TNFR1 triggers necroptosis and apoptosis and drives skin inflammation.

Biography

Work Experiences

11/2020-Present	Senior Research Fellow/Group Leader
	The University of Queensland Diamantina Institute, Translational Research Institute, Brisbane, Australia
2013 -2020	Postdoctoral Research Fellow
	CECAD Research Center, Institute for Genetics, University of Cologne, Cologne, Germany
2012 -2012	Postdoctoral Research Fellow
	Center for Molecular Medicine, Cologne, Germany
2006 -2008	Research Fellow, International MD/PhD program in 'Molecular Medicine'
	Medizinische Hochschule Hannover, HBRS, Hannover, Germany

Education

2008 - 2012	PhD in Biological Sciences (Dr. rer. nat.)
	Graduate School for Biological Sciences, University of Cologne, Germany

Immune mechanism of immune checkpoint inhibitors-induced Stevens-Johnson syndrome and toxic epidermal necrolysis

Chun-Bing Chen
The Department of Dermatology, Chang Gung Memorial Hospital

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a life-threatening adverse immune reactions, mostly caused by medications. Immune checkpoint inhibitors (ICPi), including anti-PD-1/PDL-1 and anti-CTLA-4, have been widely used to treat with advance cancers and may cause irAE (immune-related adverse events), from mild to severe systemic reactions. Skin toxicities are the most common and usually the earliest-onset irAE, consisting mainly of maculopapular rash, pruritus, eczematous dermatitis, lichenoid dermatitis, psoriasis vulgaris, vitiligo, delayed type hypersensitivity, and bullous disorders. There are more and more reports showing ICPi also induce SJS/TEN with high mortality that interrupt ICPi treatment. To date, the immune pathomechanism of ICPi-induced SJS/TEN remains unclear. Moreover, the intervention with immunomodulating agents especially corticosteroid is commonly used, but evidence-based of treatment efficacy of immunomodulants is limited. Also, the use of corticosteroid may influence the efficacy of immunotherapy. We performed a comprehensive single-cell transcriptome analysis and observed an over activation of macrophage that recruited cytotoxic T lymphocytes in blister cells from skin lesions of ICPi-induced SJS/TEN. Gene expression profiling further identified IFN and TNF signaling as the key pathways responsible for the pathogenesis, which was further confirmed by *ex vivo* assay. Our findings may provide an effective therapeutic strategy to manage ICPi-induced SJS/TEN and prevent occurrence of severe immune reactions from continuous ICPi therapy.

Biography

Education and positions:

2003-2010	Chang Gung University College of Medicine, Taoyuan, Taiwan (M.D.)
2011-2012	Resident, Department of Medicine, Taipei Veterans General Hospital, Taiwan
2012-2016	Resident, Department of Dermatology, Chang Gung Memorial Hospital, Linkou, Taipei and Keelung Branches, Taiwan
2016-	Attending physician, Department of Dermatology, Drug Hypersensitivity Clinical and Research Center, Immune-Oncology Center of Excellence, Chang Gung Memorial Hospital, Linko, Taipei and Keelung Branch, Taiwan
2016-	Graduate Institute of Clinical Medical Sciences, Chang Gung University, Taiwan
2019.7-	Deputy Director, Drug Hypersensitivity Clinical and Research Center, Chang Gung Memorial Hospital, Taiwan

Mechanisms of melanocyte death in vitiligo

Chunying Li
Department of Dermatology, Xijing Hospital, Fourth Military Medical University, China

Vitiligo is an autoimmune depigment skin disease that results from epidermal melanocytes destruction. The destruction of melanocyte is thought to be of multifactorial causation. Firstly, vitiligo patients are thought to have vulnerable genetic structure. Genome-wide associated studies have identified single-nucleotide polymorphisms in a panel of susceptible loci as risk factors in melanocyte death, most of which encode immune and apoptotic regulators and some regulate melanocyte function. But vitiligo onset can't be solely attributed to a susceptive genetic background. Secondly, oxidative stress, triggered by environmental stress and aberrant reactive oxygen species-removing mechanisms, might functionally disrupt and even murder melanocytes. More importantly, the disrupted melanocyte releases damage-associated molecular patterns molecules, which might further elicit autoreactive innate and adaptive immune response. Thirdly, the self-responsive immune function directly contributes to the bulk of melanocyte deaths in vitiligo. The aberrantly heightened innate immunity, type-1-skewed T helper, and incompetent regulatory T cells tip the balance toward autoreaction and CD8+ cytotoxic T lymphocytes finally execute the killing of melanocytes. In addition to the well-established apoptosis and necrosis, we discuss several death modalities like oxeiptosis, ferroptosis, necroptosis, parthanatos and autophagy-associated death that are probably employed in melanocyte destruction, which might play their unique role in vitiligo pathogenesis. This lecture aims to combine the cutting-edge progress in the various mechanisms of melanocytic death in vitiligo pathogenesis to demonstrate a panorama of that and provide new insights into vitiligo pathogenesis and therapeutic strategies.

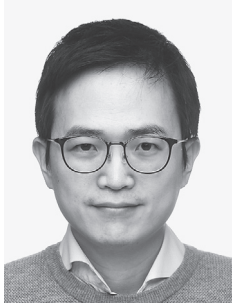
Biography

Education

1993.09-1998.06	M.D., Fourth Military Medical University, China
1998.09-2000.06	M. Phil., Dermatology, Graduate School, Fourth Military Medical University, China
2000.09-2003.07	Ph.D., Dermatology, Graduate School, Fourth Military Medical University, China

Professional Experience

1998.09-2000.07	Resident and Teaching Assistant, Department of Dermatology, Xijing Hospital, Fourth Military Medical University, China
2000.09-2007.09	Attending Physician and Lecturer, Department of Dermatology, Xijing Hospital, Fourth Military Medical University, China
2005.02-2007.02	Post-doctoral Fellow, Department of Epidemiology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas
2007.09-2011.09	Associate Professor, Department of Dermatology, Xijing Hospital, Fourth Military Medical University, China
2007.09-2012.09	Associate Chief Physician, Department of Dermatology, Xijing Hospital, Fourth Military Medical University, China
2010.04-present	Vice Chair, Department of Dermatology, Xijing Hospital, Fourth Military Medical University, China
2011.09-present	Professor, Department of Dermatology, Xijing Hospital, Fourth Military Medical University, China
2012.09-present	Chief Physician, Department of Dermatology, Xijing Hospital, Fourth Military Medical University, China



The Significance of $CD4^+$ T cells in the Pathogenesis of Pemphigus

Jong Hoon Kim
Yonsei University College of Medicine, Gangnam Severance Hospital, Seoul, Korea

Pemphigus is an intraepidermal form of autoimmune bullous diseases characterized by autoantibodies against desmoglein 1 and/or 3. In many years, the role of autoreactive B cells has been studied to understand the pathogenesis of pemphigus. The use of rituximab, a B-cell depleting anti-CD20 antibody, is a good strategy and is nowadays approved for the treatment of pemphigus in many countries. However, clinical issues such as relapse or chronic lesions still remain in patients with pemphigus. We have focused on T cells to find out the pathogenic role during the disease course of pemphigus. The production of anti-desmogelin 3 antibody is associated with desmoglein 3-specific $ICOS^+$ T follicular helper cells in active pemphigus vulgaris mouse model and Th2-type $ICOS^+PD\text{-}1^+$ circulating Tfh cells in patients with pemphigus vulgaris. We showed that $ICOS^+$ T follicular helper cells, required for the pathogenicity of pemphigus, are expanded without B cells. These findings indicated that remaining pathogenic Tfh cells can contribute relapse after B-cell depleting therapy. We also found tertiary lymphoid structures (TLSs) in chronic skin lesions of patients with pemphigus, and CXCL13, a chemokine recruiting CXCR5-expressing Tfh cells and naïve B cells, is predominantly produced by activated $CD4^+$ T cells with cytotoxic features in these TLSs. Taken together, these data suggest that $CD4^+$ T cells indeed play pathogenic role at various stage of disease progression in pemphigus.

Biography

Education

3/2013-8/2016	Ph.D. in Medical Sciences, Major in Immunology, Graduate School of Medical Science and Engineering, KAIST, Daejeon, Korea Advisor: Eui-Cheol Shin, M.D., Ph.D. Thesis: The Role of Programmed Cell Death Ligand 1 in the Regulation of Psoriatic Inflammation
9/2010-8/2012	M.S. in Medical Sciences, Major in Dermatology, Graduate School of Medicine, Yonsei University, Seoul, Korea Advisor: Soo-Chan Kim, M.D., Ph.D. Thesis: Serum Levels of Anti-Type VII Collagen Antibodies Detected by Enzyme-Linked Immunosorbent Assay in Patients with Epidermolysis Bullosa Acquisita are Correlated with the Severity of Skin Lesions
3/2002-2/2008	M.D. Yonsei University College of Medicine, Seoul, Korea

Experiences

3/2020-present	Assistant Professor, Department of Dermatology, Gangnam Severance Hospital, Yonsei University College of Medicine Seoul, Korea
9/2018-2/2020	Clinical Assistant Professor, Department of Dermatology, Gangnam Severance Hospital, Yonsei University College of Medicine Seoul, Korea
3/2018-8/2018	Clinical Research Assistant Professor, Department of Dermatology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
3/2017-2/2018	Medical Fellowship, Department of Dermatology, Gangnam Severance Hospital, Yonsei University College of Medicine Seoul, Korea
8/2016-2/2017	Post-doctoral Associate, Natural Science Research Institute, KAIST, Daejeon, Korea
3/2009-2/2013	Residency, Department of Dermatology, Gangnam Severance Hospital, Korea
3/2008-2/2009	Internship, Gangnam Severance Hospital, Seoul, Korea

JSID's Fellowship
Shiseido Research Grant

The 46th Annual Meeting of the Japanese Society for Investigative Dermatology

2020 JSID's Fellowship Shiseido Research Grant SE-1[O01-01]

Observation of tight junction formation using cultured keratinocytes

○Hiroaki Iwata
Department of Dermatology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

Tight junctions (TJs) are structures that firmly bond epithelial cells to each other. A TJ is not composed of a single molecule, but is formed by the interaction of multiple molecules. Typical examples are occludin and claudin, which are cell membrane proteins, and zonula occludens (ZO) molecules, which are intracellular scaffold proteins. Most research on TJs has used the Madin-Darby Canine Kidney (MDCK-2) cell line, which is a proximal tubular cell that is a monolayer epithelium cell, and Caco2, which is an intestinal epithelium cell. TJs in the skin have received less scholarly attention. This may be mainly due to the stratified structure of the squamous epithelium. The simple epithelium is relatively easily reproduced by a monolayer cell culture, whereas the stratified squamous epithelium is difficult to reproduce by such a culture. In this study, we aimed to establish a monolayer keratinocyte culture in order to observe TJ formation. First, we observed the TJ-related proteins claudin 1, occludin and ZO-1 in normal skin and in normal buccal mucosa. Interestingly, ZO-1 staining in the buccal mucosa differed significantly from that in the skin. To establish TJ formation conditions in a monolayer culture, we focused on the calcium shift in the culture medium. TJ-like structures were clearly observed by the staining of claudin 1 and ZO-1. In a high-calcium condition, the expression of both proteins was increased dose-dependently. We tried to produce keratinocytes expressing fluorescent labeled proteins and to observe TJ formation by time-lapse. In the future, we plan to screen compounds for the treatment of TJ disruption using a cell culture system.

2020 JSID's Fellowship Shiseido Research Grant SE-2[O01-02]

Dynamics of epigenetic environment in skin inflammatory diseases

○Sayaka Shibata
Department of Dermatology, University of Tokyo Graduate School of Medicine

The skin is the outermost organ of the body and is susceptible to external stimuli. In order to respond quickly to external stimuli, epidermal cells effectively utilize the epigenetic system to regulate gene expression, which does not involve sequence changes. Psoriasis or atopic dermatitis is a chronic skin inflammatory disease, and the onset and development of the disease are greatly influenced by environmental factors including external stimuli. In this study, we focused on CHD4, one of the epigenetic regulators, to investigate the pathogenesis of skin inflammatory diseases through epigenetic mechanisms. CHD4 binds to DNA in the nucleus and regulates gene expression by reorganizing chromatin structure in response to stimuli. CHD4 is bound to a number of gene regulatory regions associated with inflammation and differentiation in epidermal cells, including Ccl20, Il36, Cxcl1, Tslp, Il33, Vegf, and Il4r. These genes contribute to the pathogenesis of psoriasis or atopic dermatitis. We found that CHD4 in the epidermis mostly forms a closed chromatin environment in the steady state. Upon an epidermal activation, CHD4 is unbound from DNA and induces an open chromatin environment. The exception was il33, in which CHD4 loss of function resulted in the formation of more tightly closed chromatin. Mice lacking epidermis-specific CHD4 showed an exacerbation of dermatitis with epidermal thickening and inflammatory cell infiltration. The epidermis of psoriasis patients has reduced expression of CHD4, suggesting that the pathogenesis of psoriasis may be regulated through epigenetic mechanisms.

The 22nd Maruho Research Award
Presentations by award winners and award ceremony

The 46th Annual Meeting of the Japanese Society for Investigative Dermatology

Glucose-6-Phosphate Dehydrogenase Correlates with Tumor Immune Activity and Programmed Death Ligand-1 Expression in Merkel Cell Carcinoma

Motoki Nakamura[1], Kotaro Nagase[2], Maki Yoshimitsu[1], Tetsuya Magara[1], Yuka Nojiri[1], Hiroshi Kato[1], Tadahiro Kobayashi[3], Yukiko Teramoto[4], Masahito Yasuda[5], Hidefumi Wada[6], Toshiyuki Ozawa[7], Yukie Umemori[8], Dai Ogata[9], Akimichi Morita[1]

[1]Departments of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Aichi, Japan,
[2]Division of Dermatology, Department of Internal Medicine, Faculty of Medicine, Saga University, Saga, Japan,
[3]Department of Molecular Pathology of Skin, Faculty of Medicine, Kanazawa University, Kanazawa, Ishikawa, Japan,
[4]Department of Skin Oncology/Dermatology, Saitama Medical University International Medical Center, Hidaka, Saitama, Japan,
[5]Department of Dermatology, Gunma University, Maebashi, Gunma, Japan,
[6]Environmental Immuno-Dermatology, Yokohama City University, Yokohama, Kanagawa, Japan,
[7]Department of Dermatology, Osaka City University, Abeno-ku, Osaka, Japan,
[8]Division of Dermatology, Nagaoka Red Cross Hospital, Nagaoka, Niigata, Japan,
[9]Department of Dermatology, Saitama Medical University, Iruma-gun, Saitama, Japan

Merkel cell carcinoma (MCC) is a rare and highly malignant skin cancer. Some cases have a good prognosis and spontaneous regression can occur. Reported prognostic markers, such as Merkel cell polyoma virus infection or programmed death ligand-1 (PD-L1) expression, remain insufficient for precisely estimating the vastly different patient outcomes. We performed RNA sequencing to evaluate the immune response and comprehensively estimate prognostic values of immunogenic factors in patients with MCC.

We collected 90 specimens from 71 patients and 53 blood serum samples from 21 patients with MCC at 10 facilities. The mRNA was extracted from formalin-fixed paraffin-embedded tissues. Next-generation sequencing, immunohistochemical staining, and blood serum tests were performed.

Next-generation sequencing results classified MCC samples into 2 types: the “immune active type” was associated with better clinical outcomes than the “cell division type”. Expression of the glucose-6-phosphate dehydrogenase (G6PD) gene was highly significantly upregulated in the “cell division type”. Among 395 genes, G6PD expression correlated with the presence of lymph node or distant metastases during the disease course and significantly negatively correlated with PD-L1 expression. Immunohistochemical staining of G6PD also correlated with disease-specific survival and exhibited less heterogeneity compared with PD-L1 expression. G6PD activity could be measured by a blood serum test. The detection values significantly increased as the cancer stage progressed and significantly decreased after treatment.

G6PD expression was an immunohistochemically and serum-detectable prognostic marker that negatively correlated with immune activity and PD-L1 levels, and could be used to predict the immunotherapy response.

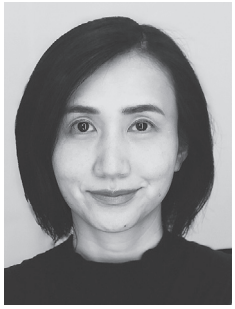
Biography

2007-2008	Senior Resident, Department of Geriatric and Environmental Dermatology, Nagoya City University Hospital
2008-2009	Assistant Professor, Division of Skin Oncology, Comprehensive cancer center, Saitama Medical University International Medical Center
2009-2012	Commissioned Doctor, Department of Dermatology, Komono Kosei Hospital
2012-2015	Assistant Professor in Department of Geriatric and Environmental Dermatology, Nagoya City University Hospital
2015-2017	Guest Researcher, IUF -Leibniz Research Institute for Environmental Medicine, Duesseldorf, Germany
2017-2019	Assistant Professor, Department of Geriatric and Environmental Dermatology, Nagoya City University Hospital
2019-Present	Lecturer, Department of Geriatric and Environmental Dermatology, Nagoya City University Hospital

The 22nd Maruho Research Award Presentations by award winners and award ceremony

Maruho Co., Ltd.

December 4 (Sat) 12:30-13:30
Chairs: Masayuki Amagai
Shinichi Sato
Kenji Kabashima



Inhibition of endoglin exerts antitumor effects through the regulation of non-Smad TGF-β signaling in angiosarcoma

Ryoko Sakamoto[1], Ikko Kajihara[1], Hitomi Miyauchi[1], Saki Maeda-Otsuka[1], Saori Yamada-Kanazawa[1], Katsunari Makino[1], Jun Aoi[1], Takamitsu Makino[1], Satoshi Fukushima[1], Mamiko Masuzawa[2], Mikio Masuzawa[3], Yasuyuki Amoh[2], Daichi Hoshina[4], Riichiro Abe[5], Hironobu Ihn[1]

[1]Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan,
[2]Department of Dermatology, Kitasato University School of Medicine, Kanagawa, Japan,
[3]Department of Molecular Diagnostics, School of Allied Health Sciences, Kitasato University, Kanagawa, Japan,
[4]Department of Dermatology, Hokkaido University Graduate School of Medicine, Hokkaido, Japan,
[5]Department of Dermatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Angiosarcoma is a rare malignant tumor derived from endothelial cells, and its prognosis is poor because advanced angiosarcoma is often resistant to taxane therapy. Endoglin (CD105) acts as a coreceptor for transforming growth factor-β (TGF-β) signaling, and is overexpressed in tumor-associated endothelial cells and enhances tumor angiogenesis. Numerous clinical trials are testing the effectiveness of anti-endoglin antibodies in various types of malignancies. In this study, we investigated the role of endoglin in the pathogenesis of angiosarcoma and whether endoglin inhibition results in antitumor activity.

The protein level of endoglin in angiosarcoma tissues and cell lines was examined using immunohistochemistry and Western blot analysis. The effect of inhibition of endoglin was assessed for the ability of apoptosis/migration/invasion/tube formation/Warburg effect in angiosarcoma cells treated with endoglin siRNA. To investigate the effect of overexpression of endoglin on cell proliferation, we performed endoglin plasmid transfection in HDMECs. Furthermore, to clarify the molecular mechanism of the anti-tumor effect of endoglin inhibition, we examined whether endoglin siRNA affected the downstream TGF-β signaling.

Endoglin was overexpressed in angiosarcoma and its inhibition was effective in the induction of apoptosis and the suppression of migration/invasion/tube formation/Warburg effect in angiosarcoma cells. Overexpression of endoglin in HDMECs suppressed apoptosis and enhanced migration and invasion. Knockdown of endoglin activated caspase 3/7 and decreased survivin and the phosphorylation of paxillin and VE cadherin. And it activated MMP-2 and MMP-9 in angiosarcoma cells.

Although endoglin is a coreceptor that regulates TGF-b signaling, the antitumor effect of endoglin in angiosarcoma was not based on Smad signaling regulation but on non-Smad TGF-b signaling. Endoglin could be a novel therapeutic target for angiosarcoma.

Biography

Education

1997-2003	M.D., Kagoshima University Faculty of Medicine, Japan
2015-current	in Graduate School of Medical Sciences Kumamoto University, Japan

Work experience

2020-current	Staff Doctor, Kumamoto Kenhoku Hospital
2018-2020	Ph.D. student, Dept. of Dermatology and Plastic Surgery, Graduate School of Medical Sciences Kumamoto University
2015-2016	Staff Doctor, Dept. of Dermatology and Plastic Surgery, Kumamoto University Hospital
2003-2005	Resident, Dept. of Dermatology, Kagoshima University Hospital

Extramammary Paget's disease patient-derived xenografts harboring ERBB2 S310F mutation show sensitivity to HER2-targeted therapies

Takuya Maeda[1], Shinya Kitamura[1], Hiroshi Nishihara[2], Teruki Yanagi[1]
[1]Department of Dermatology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan,
[2]Genomics Unit, Keio Cancer Center, Keio University School of Medicine, Tokyo, Japan

Extramammary Paget's disease (EMPD) is a rare adnexal neoplasm and no curative treatments have existed for advanced EMPD. Although development of novel therapeutic strategy against EMPD has been desired, there are no preclinical research models available. This study aims to establish a preclinical research model for EMPD. In recent years, the usefulness of patient-derived xenograft (PDX) models has been reported in many types of cancers. PDX models have demonstrated an ability to maintain the characteristics of the original tumor and to be useful for preclinical therapeutic studies in certain cancers. These models have shown to be predictive of clinical outcomes and are being used for preclinical drug evaluation, biomarker identification, biological studies, and personalized medicine strategies. To establish the EMPD-PDX model, we transplanted a piece of resected metastatic lymph nodes of the EMPD patient into immunodeficient NOD/Scid mice. Transplanted tissue from the EMPD patient was enlarged in NOD/Scid mice and was transplanted into further generations. Histopathological and genetic analyses using a comprehensive cancer panel were performed. Histopathologically, the xenografted tumors were positive for CK7, which was consistent with the patient's tumors. Genetically, the pathogenic mutation *ERBB2* S310F was detected in the patient's tumors (both primary *in situ* lesion and metastatic lymph node) and was observed in the xenografted tumors even after continued passages. Both the transplantation of PDX into nu/nu mice and the reanimation of the cryopreserved xenografted tumors in NOD/Scid mice were successful. In addition, we also established an EMPD-PDX-derived primary cell culture. For *in vivo* preclinical treatments, PDX models were treated with cytotoxic agents (docetaxel or eribulin) or HER2-targeted therapy (trastuzumab or lapatinib) since HER2-targeted therapy is effective against lung, colon, and other cancers harboring the *ERBB2* S 310F mutation. The xenografted tumors responded well to docetaxel and eribulin. Also, trastuzumab and lapatinib were effective against the xenografted tumors. Thus, we generated a novel EMPD PDX model that maintained the original patient's tumors both histopathologically and genetically. Our therapeutic experiments revealed *in vivo* tumor growth inhibition by anti-HER2 therapies and cytotoxic agents. Our novel PDX model could be a powerful tool for developing effective therapies for EMPD.

Biography

Education

2019 - current: Graduate School of Medicine, Hokkaido University
- 2015: School of Medicine, Hokkaido University

Work experience

April 2015 - March 2018, April 2019 -March 2021:
Department of Dermatology, Hokkaido University Hospital

April 2018 - March 2019, April 2021- current:
Department of Dermatologic Oncology, Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital

Clinical characteristics and treatment of 50 cases of Blau syndrome in Japan confirmed by genetic analysis of the *NOD2* mutation

Tomoko Matsuda[1], Yoko Ueki[1], Nobuo Kanazawa[2], Naotomo Kambe[1,3]
[1]Department of Dermatology, Kansai Medical University, Hirakata, Osaka, Japan,
[2]Department of Dermatology, Hyogo Medical University, Nishinomiya, Hyogo, Japan,
[3]Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Kyoto, Japan

Introduction; Blau syndrome is an autoinflammatory granulomatosis disease, characterized by a distinct triad of skin, joint and eye disorders. *NOD2* has been identified as the gene responsible for Blau syndrome.

Objectives; To collect clinical information and *NOD2* mutation data on patients with Blau syndrome in Japan and to evaluate their current treatments and prognosis.

Methods; Fifty patients with *NOD2* mutations were analyzed. The activity of each *NOD2* mutant was evaluated in HEK293 cells by reporter assay. Clinical information was collected from medical records through the attending physicians.

Results; The study population comprised 26 males and 24 females aged 0-61 years. 32 cases were sporadic, and 18 were familial from 9 unrelated families. 15 different mutations in *NOD2* were identified, including 2 novel mutations (p.W490S and D512V); all showed spontaneous NF-kappa B activation, and the most common mutation was p.R334W. 26 patients had fever at relatively early timepoints in the disease course. 43 of 47 patients had a skin rash. The onset of disease in 9 patients was recognized after BCG vaccination. 45 of 49 patients had joint lesions. 38 of 50 patients had ocular symptoms, 7 of which resulted in blindness. The primary diagnosis other than Blau syndrome was juvenile idiopathic arthritis (JIA) in 16 cases, and most cases experienced fever. After the diagnosis of Blau syndrome, 26 patients were treated with biologics; all were anti-TNF agents. Only 3 patients were treated with biologics alone; the others received a biologic in combination with MTX and/or prednisolone. None of the patients treated with biologics from a young age was blind.

Discussion; Our study revealed that fever is an important clinical feature of Blau syndrome. In many cases of Blau syndrome, skin lesions occur as the initial symptom. However, we speculate that skin eruptions may be overlooked because they are asymptomatic and often resolve spontaneously. Some cases in our study were initially diagnosed with JIA, but based on relatively mild symptoms as JIA, in some of these cases joint and eye involvement progressed irreversibly, probably because the amount of glucocorticoid was insufficient for Blau syndrome. In contrast, none of the patients who had been treated with biologics from a younger age was blind when they became older.

Conclusions; From our survey of 50 cases of mutation-positive Blau syndrome in Japan, early biologic treatment for joint involvement is essential to avoid the irreversible symptoms of joint contracture and to prevent eyesight impairment and blindness. We also believe that dermatologists play an important role in the early diagnosis of Blau syndrome because skin symptoms are the first signs of this disease. We are grateful for the valuable cooperation of the physicians who kindly allowed us to study their patients, as well as for the assistance of the members and Prof. Okamoto and Tanizaki of Kansai Medical University.

Biography

Medical School (2008-2014): Nara Medical University, Nara, Japan
Internship (2014-2016): Hirakata City Hospital, Osaka, Japan
Residency (2016-2020): Kansai Medical University, Osaka, Japan
2021- Assistant Professor of Kansai Medical University, Osaka, Japan

Sun Pharma
RISING SUN AWARD 2021

The 46th Annual Meeting of the Japanese Society for Investigative Dermatology

Sun Pharma RISING SUN AWARD 2021

Sun Pharma Japan Ltd.

December 3 (Fri) 13:30-14:10
Chairs: Kenji Kabashima
Tatsuyoshi Kawamura
Manabu Fujimoto

Neutrophils initiate and exacerbate Stevens-Johnson syndrome and toxic epidermal necrolysis

Youichi Ogawa
Department of Dermatology, University of Yamanashi, Yamanashi, Japan

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening mucocutaneous adverse drug reactions characterized by massive epidermal detachment. Cytotoxic T cells and associated effector molecules are known to drive SJS/TEN pathophysiology, but the contribution of innate immune responses is not well understood. We found a mechanism by which neutrophils triggered inflammation during early phases of SJS/TEN. Skin-infiltrating $CD8^+$ T cells produced lipocalin-2 in a drug-specific manner, which triggered the formation of neutrophil extracellular traps (NETs) in early lesional skin. Neutrophils undergoing NETosis released LL-37, an antimicrobial peptide, which induced formyl peptide receptor 1 (FPR1) expression by keratinocytes. FPR1 expression caused keratinocytes to be vulnerable to necroptosis that caused further release of LL-37 by necroptotic keratinocytes and induced FPR1 expression on surrounding keratinocytes, which likely amplified the necroptotic response. The NETs-necroptosis axis was not observed in less severe cutaneous adverse drug reactions, autoimmune diseases, or neutrophil-associated disorders, suggesting that this was a process specific to SJS/TEN. Initiation and progression of SJS/TEN keratinocyte necroptosis appear to involve a cascade of events mediated by innate and adaptive immune responses, and understanding these responses may contribute to the identification of diagnostic markers or therapeutic targets for these adverse drug reactions.

Biography

2002-2003	Resident, Department of Dermatology, Faculty of Medicine, University of Yamanashi, Japan
2003-2004	Resident, Dermatology, Yamanashi Kosei Hospital, Yamanashi, Japan
2004-2007	Medical staff, Department of Dermatology, Faculty of Medicine, University of Yamanashi, Japan
2007-2011	Assistant professor, Department of Dermatology, Faculty of Medicine, University of Yamanashi, Japan
2011-2014	Visiting fellow (Dr. Udey laboratory), Dermatology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, U.S.A.
2014-2020	Assistant professor, Department of Dermatology, Faculty of Medicine, University of Yamanashi, Japan
2020-present	Senior Lecturer, Department of Dermatology, Faculty of Medicine, University of Yamanashi, Japan

Sun Pharma RISING SUN AWARD 2021

Sun Pharma Japan Ltd.

December 3 (Fri) 13:30-14:10
Chairs: Kenji Kabashima
Tatsuyoshi Kawamura
Manabu Fujimoto

Role of host-microbe interactions in the pathogenesis of inflammatory skin diseases

Yumi Matsuoka-Nakamura
Cutaneous Immunology, Immunology Frontier Research Center, Osaka University, Osaka, Japan

Our research has been focused on skin pathobionts that can cause disease only when specific environmental conditions are altered in the host. One of the important skin pathobionts, *Staphylococcus aureus*, is a part of human commensal microbiota but causes not only the majority of skin and soft tissue infections but also induces skin inflammation in atopic dermatitis/eczema (AD). AD is a devastating and common chronic skin disease affecting 15-30% of children and 2-10% of adults. The pathogen *S. aureus* selectively colonizes the lesional skin of AD patients while this bacterium is absent in the skin of the majority of healthy individuals. However, the role of *S. aureus* in the pathogenesis of AD had remained poorly understood. We previously found that colonization of lesional skin by *S. aureus* resulted in a severe allergic skin phenotype which depended on the expression of δ-toxin by *S. aureus* (Nakamura et al. ***Nature.*** 2013). We also found that PSMα cytotoxic peptide produced by *S. aureus* via quorum-sensing, induces keratinocyte damage and the release of the alarmins, IL-1α and IL-36. Alarmin release elicited the induction of IL-17-producing γδT cells and ILC3 via Myd88 signaling, which is critical for skin inflammation in response to epicutaneous *S. aureus* infection (Nakagawa et al. ***Cell Host Microbe.*** 2017). Most recently, we found that infants who developed atopic dermatitis early in life were more likely to have cheek skin colonized by *S. aureus* while infants harboring *S. aureus* with acquired loss-of-function mutations in Agr quorum-sensing were more likely to remain healthy, despite the presence of this bacterium on their skin. Then, cutaneous acquisition of loss-of-function mutations in *S. aureus agr* virulence loci reduces skin colonization in healthy skin and protects against the development of AD. (Nakamura et al. ***Sci Transl Med.*** 2020).
Another interest of our research has been focused on pathobiont fungi. *Malassezia* yeasts are human commensal fungi that are found most abundantly in the skin, but also in the gut of healthy individuals. *Malassezia* species have been implicated in several skin diseases including dandruff, seborrheic dermatitis, pityriasis versicolor, folliculitis, psoriasis, and AD. The pathophysiology of *Malassezia*-associated skin disease is poorly understood, due in part to the lack of appropriate animal models to study *Malassezia*-host interactions in vivo. Therefore, we established a novel *Malassezia* skin infection model without skin barrier disruption and in the absence of lipid supplementation. Using this model, we found that *Malassezia* yeasts induce IL-17-dependent skin inflammation, which was mediated through IL-36/MyD88 signaling in keratinocytes (Miyachi et al. ***J Infect Dis.*** 2021).
We believe that unraveling the role of skin pathobionts will provide new insight into our current knowledge of the pathogenesis of inflammatory skin diseases as well as aid the development of novel treatment options for these diseases.

Biography

Employment:

2020-	Associate Professor, Cutaneous Immunology, Immunology Frontier Research Center, Osaka University
2018-19	Associate Professor, Department of Dermatology, Chiba University Graduate School of Medicine
2014-17	Assistant Professor, Department of Dermatology, Chiba University Graduate School of Medicine
2013-14	Research Fellow, General Foundation Japan Preventive Medicine Association
2009-13	Postdoctoral Fellow, Department of Pathology, University of Michigan, Medical School, USA. Sponsor: Gabriel Nunez
2006-09	Clinical Fellow, Department of Dermatology, Chiba University Hospital
2005-06	Clinical Fellow, Department of Dermatology, Yamanashi University Hospital
2003-05	Resident, Department of Dermatology, Yamanashi University Hospital

Sun Pharma RISING SUN AWARD 2021

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December 3 (Fri) 13:30-14:10
Chairs: Kenji Kabashima
Tatsuyoshi Kawamura
Manabu Fujimoto

Genetic and epigenetic research of skin diseases

Masatoshi Jinnin
Department of Dermatology, Wakayama Medical University Graduate School of Medicine, Wakayama, Japan

Inherited genetic factors and environmental factors are involved in the pathogenesis of human diseases in different proportions. Recent researches have suggested that epigenetics play a role by mediating influence of the environmental factors.

We have demonstrated that epigenetics, such as microRNA and yRNA expression abnormalities, contributes to the pathogenesis of collagen diseases and inflammatory skin diseases by regulating the key molecules of each disease. In addition, we identified novel fusion genes in tumors including dermatofibrosarcoma, angiosarcoma, and squamous cell carcinoma, and proved their potential as the causative genes by genetics research.

The clarification of the mechanism by which epigenetic abnormalities and fusion genes contribute to the pathogenesis of skin diseases may lead to the development of new diagnostic tools and new treatments.

Biography

Educational Background & Professional Experience

1993-1999	Tokyo University (MD)
1999-2000	Resident, Department of Dermatology, Tokyo University Hospital
1999-2001	Resident, Department of Dermatology, Tokyo Teishin Hospital
2001-2005	Department of Dermatology, Graduate School of Medicine, University of Tokyo (PhD)
2005-2006	Assistant Professor, Department of Dermatology, Tokyo University Hospital
2006-2008	Research associate, Department of Developmental Biology, Harvard School of Dental Medicine
2008-2014	Lecturer, Kumamoto University
2014-	Associate Professor, Kumamoto University
2017-	Professor, Department of Dermatology, Wakayama Medical University

Sponsored Seminar

The 46th Annual Meeting of the Japanese Society for Investigative Dermatology

Morning Seminar 1

Mitsubishi Tanabe Pharma Corporation/Teikoku Seiyaku Co., Ltd.

December 4 (Sat) 8:00-9:00
Chair: Shinichi Imafuku

Chronic spontaneous urticaria and itch: a "Cinderella" disease with the Devil's itch

Takashi Hashimoto
Department of Dermatology, National Defense Medical College, Tokorozawa, Japan

Itch, also known as pruritus, is defined as an unpleasant sensation that evokes an urge to scratch. Itch has a significant effect on the patient's well-being, especially when it becomes severe or chronic (lasting more than 6 weeks). Itch is divided into two subtypes based on associated-pruritogens: histaminergic itch and non-histaminergic itch. Histaminergic itch mainly accounts for acute itch (lasting less than 6 weeks), while non-histaminergic itch contributes mainly to chronic itch. Non-histaminergic itch involves a variety of pruritogens other than histamine, such as IL-31, substance P, and platelet activating factor (PAF). This indicates that chronic itch can hardly be treated with antihistamines only. A variety of skin diseases feature chronic itch, and chronic spontaneous urticaria (CSU) is one of them. CSU features recurrent wheals with itch, and its itch has often been described to be stinging, tickling, and burning, but rarely as crawling, pinching, or stabbing. Itch of CSU is most troublesome at night and strongly affects the quality of life. Almost all patients with CSU desire for being free of itching as well as the absence of visible skin lesions as the most important therapeutic goals. However, treating itch of CSU is challenging. Itch of acute urticaria (lasting less than 6 weeks) can be controlled with antihistamines, as histamine from mast cells and basophils plays a key role in it. On the other hand, when urticaria becomes chronic (i.e. CSU), antihistamines do not necessarily and completely improve itch, indicating that other factors besides histamine may also participate in its pathogenesis. Recent studies have suggested the involvement of not only mast cells but also basophils and eosinophils in the pathogenesis of CSU. Basophils and eosinophils are capable of eliciting itch by activating peripheral nerve fibers and secreting non-histaminergic pruritogens including IL-31, substance P, and PAF. These cells and pruritogens can be good therapeutic targets for treating itch of CSU.

Biography

Education

2004 M.D.,	Tokyo Medical and Dental University, Tokyo, Japan
2015 Ph.D,	Tokyo Medical and Dental University, Tokyo, Japan

Experience

2004-2007	Junior and Senior Resident, Tokyo Medical and Dental University Hospital
2007-2008	Staff Dermatologist, Toride Kyodo General Hospital
2008-2010	Staff Dermatologist, Tsuchiura Kyodo General Hospital
2010-2012	Staff Dermatologist, Department of Dermatology, Tokyo Medical and Dental University Hospital
2012-2015	Assistant Professor, Department of Dermatology, National Defense Medical College
2015-2016	Staff Dermatologist, Yokohama City Minato Red Cross Hospital
2016-2017	Assistant Professor, Department of Dermatology, Tokyo Medical and Dental University Hospital
2017-2019	Research Fellow, Miami Itch Center, Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami, FL, USA
2020-Present	Junior Associate Professor, Department of Dermatology, National Defense Medical College

Morning Seminar 1

Mitsubishi Tanabe Pharma Corporation/Teikoku Seiyaku Co., Ltd.

December 4 (Sat) 8:00-9:00
Chair: Shinichi Imafuku

Tips for the treatment of chronic spontaneous urticaria

Naotomo Kambe
Department of Dermatology, Kyoto University Graduate School of Medicine

Chronic spontaneous urticaria (CSU) is characterized by recurrent hives for at least 6 weeks, with an estimated overall prevalence of 0.23%by a recent study. Symptoms of itching and wheals result from skin mast cell degranulation of histamine and other mediators, leading to vasodilation and infiltration by inflammatory cells. First-line therapy of CSU is non-sedating, second-generation H1 antihistamines, which actually relieves symptoms in many patients. This regimen is, however, insufficient to control symptoms in some patients. Omalizumab, a monoclonal IgG anti-human IgE antibody, is approved for antihistamine-refractory patients. We reported a patient whose basophil count decrease in peripheral blood had improved when urticaria was relieved by omalizumab (Kishimoto I, et al. Allergol Int 2019). The same phenomenon has been confirmed not only with omalizumab treatment but also with antihistamine treatment. A decrease in the number of peripheral basophils has been attracting attention as a useful tool for understanding the disease status of chronic urticaria. Furthermore, immunostaining has revealed that infiltration of basophils can be observed in skin affected by urticaria. Based on these observations, we hypothesize that the infiltration of basophils into the skin during the active phase of urticaria may lead to a decrease in the number of basophils in the peripheral blood.

Biography

EDUCATION

1988 - 1994	MD. Gunma University School of Medicine, *Maebashi, Gunma, Japan*
1996 - 1999	PhD. Department of Dermatology, Gunma University Graduate School of Medicine, *Maebashi, Gunma, Japan*
1998 - 1999	Department of Veterinary Clinic, Faculty of Agriculture, Tokyo University of Agriculture and Technology, *Fuchu, Tokyo, Japan*
1999 - 2001	Post Doctoral Associate. Division of Rheumatology, Allergy & Clinical Immunology, Medical College of Virginia, Virginia Commonwealth University, *Richmond, VA, USA*

POSITION OR ACADEMIC RANK

1994 - 1995	Resident. Department of Dermatology, Gunma University Hospital, *Maebashi, Gunma, Japan*
2001 - 2007	Assistant Professor. Department of Dermatology, Kyoto University School of Medicine, *Kyoto, Kyoto, Japan*
2007 - 2015	Associate Professor. Department of Dermatology, Chiba University Graduate School of Medicine, *Chiba, Chiba, Japan*
2015 - 2020	Associate Professor. Department of Dermatology, Kansai Medical University, *Hirakata, Osaka, Japan*
2020 - Present	Associate Professor. Department of Dermatology, Kyoto University School of Medicine, *Kyoto, Kyoto, Japan*

Morning Seminar 2

Japan Blood Products Organization

December 4 (Sat) 8:00-9:00
Chair: Masayuki Amagai

Elucidating pathomechanism and finding treatment of bullous pemphigoid, our target for research

Daisuke Tsuruta
Department of Dermatology, Osaka City University Graduate School of Medicine

Bullous pemphigoid (BP) is the most common autoimmune bullous disease. BP is triggered by autoantibodies against the basement membrane components BP180 (type XVII collagen) and BP230. The pathophysiology of blister formation is thought to comprise a mechanism involving cellular immunity associated with complement activation, and a mechanism of decreased cell adhesion caused by autoantibody (BP-IgG)-BP180 binding without complement involvement. The former mechanism is well-known. The latter mechanism is supported by two crucial findings: that keratinocyte adhesion is decreased by the administration of BP-IgG to cultured keratinocytes, which lack both complement and neutrophils; and that abrasion blisters form following the administration of F(ab) 2 BP-IgG to humanized mice, in which mouse BP180 is replaced by human BP180.

In the first part of this lecture, I will introduce our previous research on the mechanism of BP induction without complement involvement. We first performed live-cell imaging to demonstrate that keratinocyte migration was induced by BP-IgG administration to cultured keratinocytes without complement or neutrophils, confirming that the complement system is not necessarily required (Ozawa et al. 2010). Next, after gene transfer of GFP-BP180 into cultured keratinocytes and administration of BP-IgG, we demonstrated the internalization of BP180 into keratinocytes, and found that the mechanism of internalization is endocytosis by macropinocytosis (Hiroyasu et al. 2013). Furthermore, we showed that patient-derived IgG also causes endocytosis in the anti-BP180 mucous membrane pemphigoid (Naruse et al. 2016).

In the second half of this talk, I will introduce two recent studies that we have been conducting. The first is an investigation of the relationship between proteases and the pathogenesis of pemphigoid. This is a collaborative study with Professor David Granville of the University of British Columbia. Granzyme B is known to be abundant around pemphigoid lesions; however, its role has only now been clarified. Using three animal models, we have demonstrated that the pathogenesis of pemphigoid diseases involves the secretion of granzyme B from basophils and mast cells, which promotes the degradation of hemidesmosomal molecules and recruitment of neutrophils. These findings support that topical granzyme B inhibitor may be a treatment option in pemphigoid diseases (Hiroyasu et al. 2021). In a subsequent study, we are examining the pathological role of granzyme K. Our preliminary data suggest that granzyme K is likely to trigger itching via PAR2 activation in neuron cells.

As described above, there remain many unresolved issues surrounding BP, with no shortage of interesting topics to discuss.

Biography

1986-1992	Medical School; Osaka City University Medical School
1992-1994	Residency; Osaka City University Hospital
1994-1999	Graduate School; Osaka City University Graduate School of Medicine
Board Certification; Japanese Dermatological Association	
Positions;	
1998-2000	Teramoto Memorial Hospital
Northwestern University the Feinberg School of Medicine (post doctoral research fellow 2000-2003 under Professor Jonathan Jones)	
2003-2005	Clinical Assistant Professor, Osaka City University Hospital
2005-2011	Assistant Professor, Osaka City University Graduate School of Medicine
2011	Associate Professor, Kurume University
2011-2013	Assistant Professor, Osaka City University Graduate School of Medicine
2013-present	Professor and Chairman, Osaka City University Graduate School of Medicine
2019-present	Specially appointed Vice President, Osaka City University

Morning Seminar 3

ONO PHARMACEUTICAL CO., LTD.

December 4 (Sat) 8:00-9:00
Chair: Atsushi Otsuka

Significance of tumor-associated macrophages to predict the efficacy and immune-related adverse events by anti-PD1 antibodies

Taku Fujimura
Department of Dermatology, Tohoku University Graduate School of Medicine, Sendai, Japan

Although anti-programmed cell death 1 antibodies (PD1 Abs) (e.g., nivolumab, pembrolizumab) have been widely used for treating advanced melanoma as an anchor drug, its efficacy appears limited especially in Asian population. Ipilimumab, cytotoxic T-lymphocyte antigen (CTLA-4) Abs, is another immune checkpoint inhibitor that activates and increases T cells, and therefore, ipilimumab is one of the promising drugs especially in combination with nivolumab for advanced melanoma. Indeed, as we previously reported, administration of this combination could be the optimal therapy for unresectable advanced melanoma with multiple organ metastasis, although severe immune-related adverse events (irAEs) could be main concern. In addition, the efficacy of ipilimumab in patients with nivolumab-resistant melanoma is extremely low after objective tumor progression. Therefore, biomarkers to predict or evaluate the efficacy of anti-PD1 Abs are needed to avoid subjecting patients to potentially severe AEs. Since tumor-associated macrophages (TAMs) could produce various proinflammatory chemokines that are correlated with the development of melanoma, this seminar focuses on the recent development of biomarkers for assessing the efficacy and irAE of anti-PD1 Abs, especially focusing on TAMs-related factors, such as soluble (s)CD163 and chemokines. Among chemokines, we especially focused on CXCL5, CXCL10, CCL19, CCL22 and CCL26. For example, CCL22 recruits CCR4+ Tregs at the tumor site, leading to the induction of peripheral immune tolerance to develop melanoma, which could be a biomarker for liver metastasis of melanomas. CXCL5 increases PD-L1 expression on cancer fibroblasts to suppress the anti-tumor immune response against melanoma, which could be a biomarker for the prediction of efficacy of anti-PD1 Abs as well as irAEs. The present study suggested that these TAMs-related factors may be a useful biomarker for the selection of those cutaneous melanoma patients most likely to benefit from anti-melanoma immunotherapy.

Biography

Education and professional experience

1992-1998	Tohoku University Graduate School of Medicine, M.D. degree
1998-1999	Internship in Department of Dermatology, Tohoku University Graduate School of Medicine
1999-2000	Internship in Department of Dermatology, Iwaki Kyoritsu General Hospital
2000-2002	Division of Immunoregulation, Institute for Genetic Medicine, Hokkaido University, Doctor's course
2002-2004	Department of Dermatology, Tohoku University Graduate School of Medicine, Doctor's course
	Department of Immunology, Tohoku University Graduate School of Medicine, Doctor's course
2004-2007	Assistant Professor of Department of Dermatology, Tohoku University, Graduate School of Medicine
2007-2010.1	Department of Dermatology, University of Heidelberg, Research fellow
2008-2010	Postdoctoral research fellows of Alexander von Humboldt Foundation
2010-	Assistant Professor of Department of Dermatology, Tohoku University, Graduate School of Medicine
2017-	Lecturer of Department of Dermatology, Tohoku University, Graduate School of Medicine

Monitoring of genetic biomarkers for *BRAF*-mutated melanoma

Yukiko Kiniwa
The Department of Dermatology, Shinshu University, Nagano

Liquid biopsy is low-invasive examination using liquid samples, including blood, fluid, and urine. In liquid biopsy, circulating tumor cells (CTC), cell-free DNA, and cell-free RNA are identified and measured. They usually represent tumor burden, mutation of tumor cells, and protein overexpression. Therefore, they are useful biomarker for both diagnosis and prediction of prognosis. CTCs flow out from primary or metastatic tumor sites. CTCs contain died cell, which are apoptotic or eliminated by anti-tumor immune response. However, some CTCs have potential to be source of metastasis. Thus, investigating nature of CTC is useful for clarifying the mechanism of metastasis and drug resistance as well as for the development of targeting therapies. In melanoma patients, CTCs are present even in the early stage. This is a potential mechanism of relapse in the patients who are completely resected in the early stage. Investigation of *BRAF*-mutated melanoma, number of CTCs reflects drug response during treatment with BRAF/MEK inhibitors. Furthermore, genetic heterogeneity of *BRAF* may contribute to drug resistance of BRAF/MEK inhibitors. These findings demonstrate the usefulness of CTC analysis in melanoma for monitoring targeted therapies as well as understanding mechanism of drug resistance.

Biography

Education

1987-1993	Shinshu University School of Medicine (M.D.)
2002	Shinshu University School of Medicine (Ph.D.)

Occupation

1993-1995	Intern, Department of Dermatology, Shinshu University Hospital, Nagano
1995-1996	Nagano Red Cross Hospital, Nagano
1996-1998	Resident, Department of Dermatology, Shinshu University Hospital, Nagano
1998-2000	Research Fellow, Institute for Advanced Medical Research, Keio University, Tokyo
2000-2003	Clinical Fellow, Department of Dermatology, Shinshu University Hospital, Nagano
2003-2006	Postdoctoral Associate, Center for Cell and Gene Therapy, Baylor College of Medicine, U.S.A.
2006-2011	Assistant Professor, Department of Dermatology, Shinshu University, Nagano
2011-2018	Senior Assistant Professor, Department of Dermatology, Shinshu University Hospital, Nagano
2018-present	Associate Professor, Department of Dermatology, Shinshu University, Nagano

Morning Seminar 4

Maruho Co., Ltd.

December 5 (Sun) 7:50-8:50
Chairs: Masashi Akiyama
Manabu Fujimoto

Itching mechanism in Atopic Dermatitis -from basic to clinical

Gyohei Egawa
Department of Dermatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Itching/pruritus is a skin-specific sensation that sometimes significantly reduces quality of life in patients. Atopic dermatitis is one of the diseases that can suffer from severe itching. The mechanism of itching is complex; not only nerves but also epidermal keratinocytes, skin barrier function, and immune cells are involved in the etiology, and various molecules such as histamine, neuropeptides, opioids, and inflammatory cytokines mediate itch in the lesional skin and central nervous systems. Understanding the mechanisms of itch is essential to better management of atopic dermatitis since the itch-scratch cycle is a central pathogenesis of the patients.

In this seminar, I will summarize the current understanding of the itching mechanism in atopic dermatitis in an easy-to-understand manner. As well known, itching in atopic dermatitis is resistant to antihistamine drugs, suggesting the involvement of other itch-inducing mediators. In particular, essential role of type 2 inflammatory cytokines such as interleukin (IL)-4, 13, and IL-31, are now focused. In the clinical setting, an anti-IL-4 receptor-alpha antibody, dupilumab, is used and sometimes brings about a rapid improvement of itching as well as improvement of other skin manifestations. In addition, an anti-IL-31 receptor A antibody, nemolizumab, is awaiting approval. (At the time of this abstract's submission). With the advent of these drugs, the management of itching in atopic dermatitis patients has entered a new era, and dermatologists need to know how to use them and how they work.

Biography

Occupation:

2001- Resident, Department of Dermatology, Kyoto University
2008- Research fellow (Center for Innovation in Immuno-regulative Technology and Therapeutics)
2010- Assistant professor, Department of Dermatology, Kyoto University
2014- Postdoctoral fellow, Centenary institute, Sydney
2016- Assistant professor, Department of Dermatology, Kyoto University
2020- Lecturer, Department of Dermatology, Kyoto University

Morning Seminar 4

Maruho Co., Ltd.

December 5 (Sun) 7:50-8:50
Chairs: Masashi Akiyama
Manabu Fujimoto

Itch of urticaria

Michihiro Hide
Hiroshima City Hiroshima Citizens Hospital, Hiroshima, Japan

Itch and wheal are the major symptoms of urticaria; both abruptly appear and disappear within 24 hours. The intensity of these symptoms in urticaria is independent, but well correlated parameters for evaluating chronic urticaria. The way of itch sensation in urticaria may vary among individuals, but is partially characterized by the subtypes of urticaria. The itch of chronic spontaneous urticaria (CSU) tends to appear in the evening towards morning. Cholinergic urticaria (CholU) and delayed pressure urticaria may develop pain rather than itch. Most cases of angioedema do not accompany itch.

Atopic dermatitis (AD) is another common pruritic skin disorder and shares many pathogenetic backgrounds with urticaria. Those include the involvement of IgE, mast cells, histamine, and skin infiltrations of lymphocytes and granulocytes, such as eosinophils and basophils. Of note, several studies have revealed that IL-31, a cytokine which transduces acute itch to the sensory nerve, was elevated in not only the sera of patients with AD, but also the sera of patients with urticaria, and was identified in basophils in skin lesions of CSU. Moreover, the increased serum level of IL-31 in CSU was decreased after treatment with omalizumab. However, the level of serum IL-31 was not correlated with disease severities. Thus, IL-31 appears to be associated with a step in the pathogenesis of urticaria, but needs to be further investigated in terms of the role in itch and wheal formation.

Among subtypes of urticaria, CholU is unique, not only because of painful sensations but also triggers that induce sweating, such as exercise and hot-bath. It shares many characteristics with AD. Approximately half of patients with CholU currently suffer or have suffered from AD. Up to two thirds of patients with CholU show type I allergy to human sweat components, represented by MGL_1304, a soluble protein produced by *Malassezia globosa.* Moreover, leakage of a sweat component has been demonstrated in dermis of both AD and CholU patients, including patients who are not sensitized to the sweat antigen. Since human sweat contains substantially higher concentrations of histamine, either sweat antigens or histamine may induce itch and/or pain by directly activating nerves or via mast cell degranulation when sweat components are leaked into the skin. Further investigations and precise classification of the pathogenesis of urticaria are expected for better treatment of itch of such refractory disorders.

Biography

Education:

1984	Graduated Hiroshima University School of Medicine (MD), Hiroshima, Japan
1988	Graduated Graduate School of Medical Science, Hiroshima University (PhD)

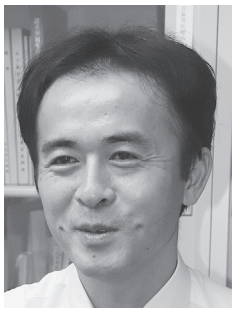
Occupations:

1988	Clinical fellow, University Hospital, Hiroshima University School of Medicine
1988-1990	Special Volunteer/Visiting associate, NIH, Bethesda, USA
1990-1993	Research fellow, St. Thomas's Hospital, London, UK
1993-1996	Dermatologist, Onomichi General Hospital
1996-1999	Research associate, Hiroshima University School of Medicine, Department of Dermatology
1999-2001	Assistant professor, Hiroshima University School of Medicine, Department of Dermatology
2001-2021	Chairman and Professor, Hiroshima University, Department of Dermatology
2016-2020	Dean, Hiroshima University School of Medicine
2020-2021	Vice president, Hiroshima University
2021-Now	Director, Hiroshima City Hiroshima Citizens Hospital
	Special Advisor and Visiting Professor, Hiroshima University

Morning Seminar 5

Sanofi K.K.

December 5 (Sun) 7:50-8:50
Chair: Kenji Kabashima



The role of basophils and IL-4Rα in itch in Atopic Dermatitis

Atsushi Fukunaga
Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, Japan

Atopic dermatitis (AD) is a pruritic inflammatory skin disease with a chronic but relapsing course. Itch in AD involves complex mechanisms including chemical mediators such as histamine and Type 2 inflammatory cytokines such as IL-4, IL-13 and IL-31. Antihistamines have demonstrated poor efficacy in AD, contrast to its effectiveness in urticaria. Although acute itch is protective mechanism to rapidly expel noxious environmental stimuli, chronic itch exacerbates chronic inflammatory skin diseases such AD via repeated scratch exacerbating skin barrier and inflammation. It has been proved that the IL-4Rα signal is strongly involved in itching in AD, and many clinical trials on the itching-improving effect of the IL-4Rα antibody dupilumab in AD have been reported. Based on these backgrounds, our facility has focused on basophils in AD patients as an important source of IL-4 and histamine. Our study showed that activated steady status and distinctive FcεRI-mediated responsiveness in basophils of AD were characteristics. Further, recent study demonstrates that allergen-stimulated basophils promote acute itch flare via leukotriene C4-neuronal axis. In addition, it has been reported that human basophils are a source of IL-31 involved in chronic itch. This lecture will focus on the importance of Type 2 inflammatory cytokines and basophils, the source of type 2 inflammatory cytokines, in itch in AD.

Biography

Education and Positions

1997	M.D., Kobe University School of Medicine, Kobe, Japan
1997-1998	Residency, Dermatology, Kobe University Hospital of Medicine, Kobe, Japan
1998-2000	Residency, Dermatology, Shinnittetsu Hirohata Hospital, Himeji, Japan
2000-2004	Ph.D.; Kobe University Graduate School of Medicine, Kobe, Japan
2004-2005	Staff Dermatologist, Kobe University Hospital of Medicine, Kobe, Japan
2005-2006	The Head Physician, Dermatology, Miki City Hospital, Miki, Japan
2006-2008	Postdoctoral Fellow, Department of Immunology, University of Texas, MD Anderson Cancer Center, Houston, USA
2008-2012	Assistant Professor, Department of Dermatology, Kobe University Graduate School of Medicine, Kobe, Japan
2013-	Senior Lecturer, Kobe University Hospital of Medicine, Kobe, Japan
2020-	Associate Professor, Department of Dermatology, Kobe University Graduate School of Medicine, Kobe, Japan

Morning Seminar 5

Sanofi K.K.

December 5 (Sun) 7:50-8:50
Chair: Kenji Kabashima

New Mechanisms of Itch in Atopic Dermatitis

Brian S. Kim[1,2,3,4]
[1]Department of Medicine, Division of Dermatology,
[2]Center for the Study of Itch and Sensory Disorders,
[3]Department of Anesthesiology,
[4]Department of Pathology and Immunology, Division of Biology and Biomedical Sciences, Washington University School of Medicine, St. Louis, MO, USA

The type 2 immune response has evolved to arm the mammalian host with the capacity to expel parasites and noxious environmental substances from barrier surfaces. One critical aspect of this defense mechanism is stimulating protective behavioral responses such as scratching. Increasingly, it is appreciated that a number of cytokines associated with type 2 immunity such as IL-4, IL-13, and IL-31 play critical roles in triggering itch via direct interactions with sensory neurons. However, the cellular mechanisms that activate such itch-sensory circuits remain unclear. Further, the key molecular events that initiate and regulate such highly conserved type 2 immune-neuronal interactions is a major field of inquiry in barrier immunology. Herein, we highlight how basophils are dominant sources of IL-4 and critically promote atopic dermatitis (AD)-associated skin inflammation in mice. However, in contrast to their role in chronic inflammation, we show that basophils are uniquely activated in human AD and play a previously unrecognized role in promoting acute itch flares via a novel leukotriene C4-neuronal axis. Collectively, these findings support an emerging paradigm in which itch is an evolutionarily conserved behavioral extension of the highly diverse type 2 immune response. Further, we propose that the itch-scratch reflex represents a model paradigm by which a variety of neuroimmune physiologies can be probed across multiple barrier surfaces.

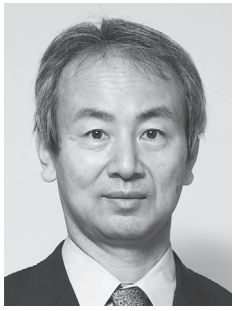
Biography

Dr. Kim's laboratory focuses on the regulatory mechanisms that underlie skin inflammation and the sensation of itch as a model paradigm of neuroimmunology. He has >80 peer-reviewed publications, multiple NIH grants, designed pivotal clinical trials, and is an inventor of multiple itch-centered technologies. His research in neuroimmune regulation of itch and atopic dermatitis has led to awards and funding from the NIH, Doris Duke Charitable Foundation, American Skin Association, American Academy of Dermatology, American Society for Clinical Investigation, American Dermatological Association, and International League of Dermatological Societies. He holds a patent for the use of JAK inhibitors for chronic itch. He is on the scientific advisory board for Abrax Japan, Granular Therapeutics, Recens Medical, National Eczema Association, and Cell Reports Medicine.

Luncheon Seminar 1

NOV division, TOKIWA Pharmaceutical Co., Ltd

December 3 (Fri) 11:50-12:50
Chairs: Shinichi Sato
Yayoi Tada



Beta7 integrin and cutaneous disorders

Takafumi Kadono
Department of Dermatology, St. Marianna University School of Medicine

β7 integrin, a cell adhesion molecule, is present in the form of α4β7 integrin or αEβ7 integrin. α4β7 integrin is expressed on most leucocytes and interacts with its primary ligand, mucosal addressin cell adhesion molecule-1, which is preferentially expressed in gut-associated lymphoid tissues. β7 integrin regulates leukocyte migration to secondary lymphoid organs together with L-selectin. Leukocyte migration to Peyer's patches is mainly regulated byβ7 integrin, whereas leukocyte migration to peripheral lymph node is mostly L-selectin-dependent. As for leukocyte migration to mesenteric lymph node, cooperation between β7 integrin and L-selectin is important. When we immunized mice with various routes, immune responses following subcutaneous were severely diminished by L-selectin deficiency. Interestingly, the additional β7 integrin deficiency further decreased subcutaneous immune responses. After oral immunization, β7 integrin deficiency affected only antigen-specific IgA responses, whereas all antigen-specific Ig titers were severely reduced by β7 integrin/L-selectin double deficiency.

In this seminar, we would like to introduce the role of β7 integrin in cutaneous disorders. For that purpose, we examined the role of β7 integrin in contact hypersensitivity model, Arthus reaction model, and systemic sclerosis model. In contact hypersensitivity model, β7 integrin-deficient mice, not αE integrin-deficient mice, were defective in contact hypersensitivity responses. β7 integrin-deficient lymphocytes had difficulty in reaching the skin under inflammatory conditions. Thus, α4β7 integrin contributes to contact hypersensitivity responses by regulating T cell migration to inflammatory skin.

In Arthus reaction model, αE integrin-deficient mice as well as β7 integrin-deficient mice revealed diminished reverse Arthus reaction. Part of the reason was the decreased recruitment of mast cells that expressed β7 integrin, and the other reason was the reduced numbers of CD8 T cells that expressed αE integrin. Lastly we would like to mention systemic sclerosis model using bleomycin. The loss of αE integrin decreased bleomycin-induced dermal thickness and collagen contents. αE integrin deficiency increased the number of CD11b- αE integrin- dermal dendritic cells that produced RALDH1, which is important for the induction of regulatory T cells.

Biography

1992	M.D. Degree, University of Tokyo
1993	Department of Dermatology, Mitsui Memorial Hospital
1995	Department of Dermatology, Toranomon Hospital
1997	Assistant, Department of Dermatology, University of Tokyo
2000	Research Associate, Department of Immunology, Duke University Medical Center
2005	Assistant Professor, Department of Dermatology, University of Tokyo
2011	Associate Professor, Department of Dermatology, University of Tokyo
2015	Associate Professor, Department of Dermatology, St. Marianna University School of Medicine
2018	Professor, Department of Dermatology, St. Marianna University School of Medicine

Luncheon Seminar 1

NOV division, TOKIWA Pharmaceutical Co., Ltd

December 3 (Fri) 11:50-12:50
Chairs: Shinichi Sato
Yayoi Tada

Extracellular vesicles in skin aging

Masatoshi Jinnin
Department of Dermatology, Wakayama Medical University Graduate School of Medicine, Wakayama, Japan

Extracellular vesicles are small, capsule-like structures that are secreted by many cell types. Their roles have been unknown for a long time, but recent studies have shown that exosomes, for example, contain various proteins, lipids, and microRNAs that can be taken up by other recipient cells and induce functional and physiological changes. In the field of anti-aging, there is a possibility that extracellular vesicles play a central role in tissue repair process during the transfer of adipose tissue-derived mesenchymal stem cells and platelet-rich plasma therapy. We have been studying microRNAs and exosomes in the pathogenesis of skin aging and intractable skin ulcers, and this talk will discuss recent advances in the study of extracellular vesicles in skin aging.

Biography

Educational Background & Professional Experience

1993-1999	Tokyo University (MD)
1999-2000	Resident, Department of Dermatology, Tokyo University Hospital
1999-2001	Resident, Department of Dermatology, Tokyo Teishin Hospital
2001-2005	Department of Dermatology, Graduate School of Medicine, University of Tokyo (PhD)
2005-2006	Assistant Professor, Department of Dermatology, Tokyo University Hospital
2006-2008	Research associate, Department of Developmental Biology, Harvard School of Dental Medicine
2008-2014	Lecturer, Kumamoto University
2014-	Associate Professor, Kumamoto University
2017-	Professor, Department of Dermatology, Wakayama Medical University

Luncheon Seminar 2

Eisai Co., Ltd./AbbVie GK

December 3 (Fri) 11:50-12:50
Chair: Keiichi Yamanaka

Recent advances in the pathogenesis and therapy of pyoderma gangrenosum and hidradenitis suppurativa

Toshiyuki Yamamoto
The Department of Dermatology, Fukushima Medical University, Fukushima, Japan

Pyoderma gangrenosum (PG) is a representative neutrophilic dermatosis, and presents with refractory, sterile, deep ulcers most often on the lower legs. Clinically, PG is classified into several types, i.e. ulcerative, bullous, pustular, superficial (vegetative), and peri-stomal type. PG can be triggered by surgery or cesarean section, which is termed post-operative PG. In addition, even minor trauma, i.e. needle prick or catheter insertion, can become a causative factor. Such a phenomenon induced by both major and minor triggering events is well-known as pathergy. Because PG is occasionally associated with systemic diseases including rheumatoid arthritis, inflammatory bowel disease, hematologic malignancy, and Takayasu arteritis, it is important especially for rheumatologists, gastroenterologists, and hematologists, to recognize this disease. Additionally, PG rarely occurs in children and pregnant women, with or without systemic diseases. A recent Japanese survey have revealed that the age of Japanese patients tends to be higher compared with foreign studies, ulcerative colitis is the most common co-morbidity, and the rate of pathergy is similar. On the other hand, hidradenitis suppurativa (HS) is primarily caused by follicular occlusion due to infundibular hyperkeratinization and dilatation, occasionally associated with inflammatory bowel diseases and autoinflammatory syndrome. Both innate and acquired immunity is involved in the etiology of PG and HS, and tumor necrosis factor (TNF) plays an important role in both disorders. Recently, adalimumab, a TNF inhibitor, has become available for refractory cases of both disorders. In the present review, current topics of the pathogenesis and therapeutic approach of PG and HS are discussed.

Biography

Positions

1988 Resident, Department of Dermatology, Tokyo Medical and Dental University
1992 Assistant, Department of Dermatology, Tokyo Medical and Dental University
2000 Lecturer, Department of Dermatology, Tokyo Medical and Dental University
2005 Associate Professor, Department of Dermatology, Tokyo Medical University
2007 Professor and Chairman, Department of Dermatology, Fukushima Medical University

Luncheon Seminar 3

TAIHO PHARMACEUTICAL CO., LTD./Janssen Pharmaceutical K.K.

December 3 (Fri) 11:50-12:50
Chair: Eiko Toichi

Diets and psoriasis

Tetsuya Honda
Department of Dermatology, Hamamatsu University School of Medicine, Hamamatsu, Japan

Psoriasis is a chronic inflammatory skin disease, in which cytokines, especially IL-23, TNF-a, and IL-17A play central roles in its development. Various biologics targeting those cytokines are now in clinical use for the treatment of psoriasis, and have shown significant therapeutic effects. Other than biologics, manipulation of dairy diets might be a therapeutic option for psoriasis, because epidemiological studies as well as basic researches using animal psoriasis model have suggested that some components of diets, such as dietary lipids, can be either good or bad for the development of psoriasis. We have been investigating the role of dietary lipids in the pathogenesis of psoriasis. For example, we have shown that high-fat diets containing abundant saturated fatty acids exacerbate, while lipid mediators derived from omega-3 poly-unsaturated fatty acids ameliorate psoriatic inflammation in mice, suggesting that regulation of dietary lipids can improve psoriasis symptoms. Direct actions of dietary lipids on cytokine production or indirect effects such as alternation of gut microbiota by diets have been proposed as potential mechanisms by which diets influence psoriasis development. In this seminar, we will review the mechanisms how diets regulate psoriatic inflammation, and discuss potential of diet intervention as a novel therapeutic strategy for psoriasis.

Biography

2000-2001	Intern, Department of Dermatology, Kyoto University Hospital, Kyoto, Japan
2001-2002	Resident, Department of Dermatology, Shimane Prefectural Hospital, Izumo, Japan
2002-2003	Resident, Department of Dermatology, Osaka Red Cross Hospital, Osaka, Japan
2003-2007	Ph.D. in Medicine, Kyoto University, Kyoto, Japan
2007-2010	Assistant Professor, Department of Dermatology, Kyoto University, Kyoto, Japan
2010-2012	Visiting Fellow, Lymphocyte Biology Section, Laboratory of Immunology National Institute of Allergy and Infectious Diseases, National Institute of Health
2012-2015	Associate professor, Department of Innovation Center for Immunoregulation Technologies and Drugs, and Department of Dermatology, Kyoto University Graduate School of Medicine
2015-2020	Assistant professor, Department of Dermatology, Kyoto University Graduate School of Medicine
2020-present	Professor, Department of Dermatology, Hamamatsu University School of Medicine

Luncheon Seminar 4

Sun Pharma Japan Ltd.

December 4 (Sat) 11:25-12:25
Chairs: Kenzo Takahashi
Norito Kato

A Novel Ultra-Low Level Cytokine Assay as a Potential Tool for Selecting Biologics for Psoriasis

Ayumi Yoshizaki
Department of Dermatology, Graduate School of Medicine, The University of Tokyo

Psoriasis presents with characteristic skin rashes and is a relatively common disease encountered in daily clinical practice. Although it is often thought of as a solely cutaneous disease, psoriasis has a background of systemic inflammation, which can lead to complications such as arthritis, metabolic, cardiovascular, and ocular diseases, which sometimes have a significant impact on the patient's prognosis. Hence, treatment that suppresses systemic inflammation is important in psoriasis treatment, and in fact, the advent of biologics has brought remarkable efficacy. The development of biologics has been actively pursued, and in Japan there are now more than 10 types of biologics. This means that there is now a wealth of treatment options available for psoriasis. While this is undoubtedly a great advantage for patients, in practice, there is often confusion about which formulation to use. The essence of biologics is that they are cytokine-targeted, cytokine-depleting drugs. Therefore, drug selection based on serum cytokine levels is considered to be one of the most appropriate methods. However, only a very small amount of cytokines exist in the sera, and to date, drug selection based on measurement of cytokine levels has not been done. In this session, I will introduce the ultra-low level cytokine measurement device which we have developed recently, and discuss new drug selection.

Biography

2006	M.D. degree, Nagasaki University, Japan
2006-2008	Residency, Department of Dermatology, Nagasaki University Hospital, Japan
2008-2011	Ph.D. degree, Nagasaki University Graduate School of Medicine, Japan (early graduation)
2011-2014	Postdoctoral associate, Department of Immunology, Duke University Medical Center, USA
2014-2015	Assistant professor, Department of Dermatology, Tokyo University, Japan
2015-	Lecturer, Department of Dermatology, Tokyo University, Japan
2018-	Chief, The Psoriasis Center, Tokyo University Hospital, Japan
2019-	Board member, Collaborative Research Organization for Micro and Nano Multifunctional Device, Tokyo University, Japan

Luncheon Seminar 4

Sun Pharma Japan Ltd.

December 4 (Sat) 11:25-12:25
Chairs: Kenzo Takahashi
Norito Kato

Pathophysiology of Psoriasis and the effect of IL-23 inhibition

Mayumi Komine
Department of Dermatology, Jichi Medical University

Psoriasis is one of major chronic inflammatory cutaneous diseases, and its treatment has recently been evolved tremendously. IL-23 is one of essential cytokines involved in the pathogenesis of psoriasis, and its inhibition has enormous effects in treatment of this disease. Nowadays, we have many choices to treat psoriasis patients, including inhibitors for TNF, IL-17, PDE4, JAKs, and the conventional therapeutics, such as etretinate and cyclosporine, and sometimes have difficulties in deciding which treatment measure to choose on the particular patient. There have been several guidelines and manuals for diagnosis and treatment of psoriasis from each country, and these guidelines help us choosing treatment mainly form medical point of view, but not really in the aspects of patients' preferences. In this seminar, I will try to show the efficacy and safety of IL-23 inhibitors, present some of my representative cases who gained benefit from IL-23 inhibitors, and try to draw some critical points for decision making on the choice of treatment in the real world setting.

Biography

Education:

1998	M.D., Ph. D. University of Tokyo, Faculty of Medicine
1988	M.D. University of Tokyo, Faculty of Medicine
1988	Graduated from University of Tokyo, Faculty of Medicine

Professional Background:

2018-present	Professor, Departments of Dermatology, and Biochemistry, Jichi Medical University
2016-present	Director, Center for Physician and Researcher Career Support, Jichi Medical University
2014-2016	Vice Director, Center for Physician and Researcher Career Support, Jichi Medical University
2008-2018	Associate Professor, Department of Biochemistry, Jichi Medical University
2007-2018	Associate Professor, Department of Dermatology, Jichi Medical University
2001-2007	Lecturer, Department of Dermatology, University of Tokyo
1999-2001	Lecturer and the ward chief, Department of Dermatology, Tokyo University Branch Hospital
1993-1996	Research Scientist, Department of Dermatology, New York University
1992-1999	Clinical Staff Doctor, Department of Dermatology, University of Tokyo
1990-1992	Clinical Staff Doctor, Department of Dermatology, Kanto Teishin Hospital
1988-1990	Clinical assistant, Department of Dermatology, University of Tokyo

Luncheon Seminar 5

ELC JAPAN K.K.

December 4 (Sat) 11:25-12:25
Chair: Chikako Nishigori

Melanogenesis connection with toll-like receptor signals

Kenshi Yamasaki
Tohoku University Hospital

The epidermis is in the outermost layer of the living body and is a place where external stimuli such as ultraviolet rays and microorganisms come into the first contact. Among cells constituting epidermis, melanocytes and melanin play a wide range of roles such as adsorption of metals, uptake of drugs, thermoregulation, and protection from foreign enemies by camouflage. In addition to pigment production, melanocytes possess function as antigen-presenting cells to modulate the immune response. Pigmentary disorders are observed in diseases associated with immunodeficiency such as Hermansky-Pudlak syndrome, indicating the molecular sharing between immune systems and machineries of pigment formation.

We have investigated how skin pigmentation was affected by genetic background as well as skin microenvironment. For the genetic approaches, we performed genome-wide association study (GWAS) for Japanese skin types using Tohoku Medical Megabank Cohort study. We identified OCA2 and others as associated genes. To investigate effects of the skin microenvironment on skin pigmentation, we examined if the innate immune stimulation via toll-like receptors (TLRs) affects melanin synthesis and melanosome transport. Melanocytes express functional TLRs. TLR2 enhances expression of melanogenetic genes, TYR, DCT, and MITF, to augment melanogenesis. In contrast, TLR3 suppresses expression of melanogenetic genes TYRP1 and DCT. Interestingly, despite of the melanogenetic gene suppression, TLR3 stimuli enhances melanin release from human melanocytes by inducing RAB27 and by facilitating melanosome transportation. TLR3 also enhances the melanin uptake by activating keratinocyte phagocytosis. TLR3 agonist Poly(I:C) upregulates keratinocyte melanosome uptake by controlling the expression and activity of protease-activated receptor 2 (PAR2) and RHO family members RHOA and CDC42. Thus, the sensing of the microenvironment by TLRs modulates melanogenesis and skin pigmentation. The innate immunity effects on melanogenesis suggest the significance of skin pigmentation in the biological defense of epidermis.

Biography

Education:

1992 M.D. Osaka University School of Medicine, Osaka, Japan
2003 Ph.D. Osaka University School of Medicine, Osaka, Japan

Postdoctoral Training:

2003-2008 Postdoctoral Fellowship, Division of Dermatology, University of California San Diego & VA Medical Center

Academic Appointments:

1996-1997 Clinical and Research Fellow, Department of Dermatology, Chiba University School of Medicine, Chiba, Japan (Chair: Prof. Hiroshi Shinkai)
1997-1998 Visiting Researcher, Department of Molecular Biology, Keio University, Tokyo, Japan (Chair: Prof. Nobuyoshi Shimizu)
1997-2006 Assistant professor, Department of Dermatology, Ehime University School of Medicine, Ehime, Japan (Chair: Prof. Koji Hashimoto)
2003-2008 Postdoctoral Fellow, Division of Dermatology, University of California San Diego & VA Medical Center San Diego (Chair: Prof. Richard L. Gallo)
2008-2010 Assistant Project Scientist, Division of Dermatology, University of California San Diego & VA Medical Research Foundation San Diego (Chair: Prof. Richard L. Gallo)
2010-present Associate Professor, Department of Dermatology, Tohoku University Graduate School of Medicine (Chair: Prof. Setsuya Aiba)

Luncheon Seminar 5

ELC JAPAN K.K.

December 4 (Sat) 11:25-12:25
Chair: Chikako Nishigori

A multi-prong understanding of hyperpigmentation

Tom Mammone
Estee Lauder Companies

Human skin color is determined by the amount and type of melanin, a light-absorbing molecule produced by a specialized cell called a melanocyte, that is present in the skin. Melanin is created within specialized structures called melanosomes within melanocytes. Excess melanin production, rapid melanosome transfer to keratinocytes, formation of melanin clusters, and accumulation of pigment at the skin's surface all contribute to the formation of hyperpigmentation, such as uneven skin tone and dark spots. In this presentation, Dr. Tom Mammone describes research into multiple ways at understanding uneven looking skin tone and dark spots.

A key step in the synthesis of melanin is the conversion of tyrosine to DOPAquinone by the enzyme tyrosinase. As such, tyrosinase is the rate limiting enzyme in the reactions leading to the production of the two melanin pigments, eumelanin and pheomelanin. Activation of this enzyme increases the production of melanin, resulting in an increase in pigmentation. Conversely, tyrosinase inhibition results in a decrease in melanin production and diminishes pigment. UP302 (1-(2,4-dihydroxyphenyl)-3-(2,4-dimethoxy-3-methylphenyl)propane), a synthetic derivative of the plant extract *Dianella ensifolia*, has been shown in vitro to help inhibit tyrosinase.

Melanin degrading enzymes have been shown to reduce pigment induced by ultraviolet light. Extracts from fungus and yeast species including *Trametes versicolor*, *Aspergillus fumigatus*, and *Saccharomyces cerevisiae* are known to have this activity. This can be relevant to melanin clusters that accumulate in the upper layers of the stratum corneum.

Corneocytes are naturally sloughed from the surface by the active process of desquamation. Aging and exposure to environmental aggressors reduce the speed of cell turnover and desquamation, leading to an accumulation of corneocytes and melanin clusters at the skin surface. Exfoliation removes dead skin cells, including those with accumulated excess pigmentation, that are not released by desquamation. Removal of the outermost layer(s) of corneocytes can smooth the surface of the skin and can also help to maintain an intact and healthy barrier to protect the skin from external elements. This can ultimately help prevent the development of irritation that may contribute to future hyperpigmentation.

Exploring multiple steps in the pathway that leads to the appearance of hyperpigmentation will help elucidate important approaches to addressing uneven looking skin tone and the appearance of dark spots.

Biography

Educational Background

1985	B.Sc. Biology, State University of New York at Stony Brook, New York
1996	Ph.D. Biology, St. John's University, New York
2008	Master in Business Administration, Dowling College, New York

Professional Experience

1984-1986	Research Assistant, Inouyo Laboratory, Department of Biochemistry - State University of New York at Stony Brook
1986-1988	Laboratory Manager, Biological Research and Development (BRD) Laboratory, R&D - The Estée Lauder Companies
1988-1990	Associate Scientist, Biological Research and Development (BRD) Laboratory, R&D - The Estée Lauder Companies
1990-1993	Research Scientist and Senior Scientist, Biological Research and Development (BRD) Laboratory, R&D - The Estée Lauder Companies
1993-1995	Group Leader, Biological Research and Development (BRD) Laboratory, R&D - The Estée Lauder Companies
1996-1998	Manager, Biological Research and Development (BRD) Laboratory, R&D - The Estée Lauder Companies
1998-2003	Director, Biological Research and Development (BRD) Laboratory, R&D - The Estée Lauder Companies
2003-Present	Laboratory Director, Clinique Brand Skincare Laboratory, R&D - The Estée Lauder Companies
2007-2009	Executive Director, NewVenture
2009-2014	Executive Director, Skin Physiology and Pharmacology, R&D - The Estée Lauder Companies
2014-Present	Vice President, Skin Physiology and Pharmacology, R&D - The Estée Lauder Companies

Luncheon Seminar 6

Kyowa Kirin Co., Ltd

December 4 (Sat) 11:25-12:25
Chairs: Sei-Ichiro Motegi
Masatoshi Jinnin

More than skin deep in psoriasis —IL17 and obesity/atherosclerosis—

Yukie Yamaguchi
Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

It has become well known that obesity and atherosclerotic inflammation are closely associated with a variety of immune disorders. In psoriasis in particular, the coexistence of obesity and cardiovascular disease has become an important perspective in clinical practice, and the mutual pathological mechanisms linking the two are being elucidated. Monocytes/macrophages play important roles both in cytokine production at the site of inflammation and in the foam cell formation leading to atherosclerosis. We recently evaluated the phenotype of circulating monocytes and monocytes-derived macrophages (MDMs) in psoriasis patients. M1/M2 markers were already detectable even in circulating monocytes and M2 levels were significantly decreased in psoriasis compared to that in controls, indicating M1 shift is already present in circulating monocytes of psoriasis patients even if who have no metabolic syndrome yet. CD36 level, a receptor for oxLDL its signal promotes atherosclerosis, was also upregulated in psoriasis-MDMs. Furthermore, a level of caveolin-1 (Cav-1), a membrane protein important for the signal transduction and that is downregulated in psoriatic monocytes, seems to be associated with M1/M2 differentiation of monocytes. Thus, the inflammatory phenotype of monocytes and MDMs may contribute to both psoriatic inflammation and atherosclerosis. In this seminar, we will discuss how pre-atherosclerotic inflammation is closely linked to psoriatic inflammation even in patients with psoriasis who are not yet obese based on our data, and present recent progress on associations of obesity and psoriasis or IL-17 and atherosclerosis.

Biography

2000	MD, Hamamatsu University School of Medicine, Shizuoka, Japan.
2001	Resident, Yokohama City University Hospital, Yokohama, Japan
2003	Fellow, Dermatology, Fujisawa City Hospital, Fujisawa, Japan
2004	Graduate student, Yokohama City University, Graduate School of Medicine, Yokohama, Japan
2005	Research Associate, Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan
2008	Postdoctoral associate in the division of Pulmonary, Allergy, and Critical Care of Medicine, University of Pittsburgh, USA
2010	Assistant professor, Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan
2013	Lecturer, Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan.
2018	Associate professor, Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan
2021.5-present	Professor, Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

Luncheon Seminar 6

Kyowa Kirin Co., Ltd

December 4 (Sat) 11:25-12:25
Chairs: Sei-Ichiro Motegi
Masatoshi Jinnin

Understanding of the pathogenesis of psoriasis from the perspective of female hormones

Tetsuya Honda
Department of Dermatology, Hamamatsu University School of Medicine, Hamamatsu, Japan

Psoriasis is a common inflammatory skin disease resulting from dysregulation of the interleukin (IL)-23/Th17 immune axis. Various genetic and environmental factors influence the development of psoriasis, including sex. Recent epidemiological studies from various countries have indicated that men are more prone to developing psoriasis than women. The severity of psoriasis is also reported to be higher in males than in females. Although the reasons for this sex deviation in the clinical phenotypes of psoriasis have remained unclear, sex hormones have been suggested to underlie the differential severity of psoriasis in the sexes. However, whether and how sex hormones influence psoriatic inflammation has remained unclear. In this seminar, we will overview the current understanding of the possible roles of sex hormones in the development of psoriasis. We will also share our recent findings about the role of estradiol, a female hormone in psoriasis pathogenesis. Using an imiquimod-induced psoriasis model in combination with ovariectomy, we found a possibility that estradiol plays protective roles in psoriatic inflammation. Mice without endogenous ovarian hormones by ovariectomy exhibited exacerbated psoriatic inflammation including increased production of IL-17A and IL-1beta, which was reversed by exogenously added estradiol. The suppressive effect of estradiol on the production of IL-1beta and IL-17A was abolished in mice lacking estrogen receptors in neutrophils and macrophages. IL-1beta, which is required for production of IL-17A in the psoriasis model, was mainly produced by neutrophils and inflammatory macrophages. Estradiol suppressed IL-1beta production from neutrophils and macrophages in mice both in vivo and in vitro and from human neutrophils in vitro. Our results suggest a novel mechanism for sex-dependent differences in psoriasis clinical phenotypes, and may shed new light on the pathology of psoriasis.

Biography

2000-2001	Intern, Department of Dermatology, Kyoto University Hospital, Kyoto, Japan
2001-2002	Resident, Department of Dermatology, Shimane Prefectural Hospital, Izumo, Japan
2002-2003	Resident, Department of Dermatology, Osaka Red Cross Hospital, Osaka, Japan
2003-2007	Ph.D. in Medicine, Kyoto University, Kyoto, Japan
2007-2010	Assistant Professor, Department of Dermatology, Kyoto University, Kyoto, Japan
2010-2012	Visiting Fellow, Lymphocyte Biology Section, Laboratory of Immunology National Institute of Allergy and Infectious Diseases, National Institute of Health
2012-2015	Associate professor, Department of Innovation Center for Immunoregulation Technologies and Drugs, and Department of Dermatology, Kyoto University Graduate School of Medicine
2015-2020	Assistant professor, Department of Dermatology, Kyoto University Graduate School of Medicine
2020-present	Professor, Department of Dermatology, Hamamatsu University School of Medicine

Luncheon Seminar 7

Eli Lilly Japan K. K.

December 5 (Sun) 12:45-13:45
Chairs: Makoto Sugaya
Hideyuki Ujiie

Novel pathogenesis and therapeutics on atopic dermatitis

Kenji Kabashima
Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan

Atopic dermatitis (AD) is a common skin condition, characterized by a complex, heterogeneous pathogenesis, including skin barrier dysfunctions, allergy/immunology, and pruritus. When the skin barrier is disrupted by, for example, the filaggrin gene mutation and/or environmental factors, the skin is predisposed to being penetrated by external stimuli. Exposure to protein antigens induces Th2-dominant conditions via mediators, such as thymic stromal lymphopoietin (TSLP). Th2 cytokines, IL-4 and IL-13, induces IgE class switch. In addition, it has recently been revealed that Th2 cells produce IL-31, which provokes pruritus, and that Th2 cytokines decrease filaggrin expressions by keratinocytes. These findings suggest that Th2 conditions lead to IgE induction, pruritus, and barrier dysfunctions. These findings suggest that Th2 environment is involved in skin barrier dysfunction, allergy/immunity, and barrier disruption. Herein, we will overview the highly complex interplay among skin barrier abnormality, allergy/immunology, and pruritus as a trinity in the development of AD. This integrated knowledge will lead to the advancement of precision medicine in atopic dermatitis.

Biography

Education:

1996 Kyoto University, Faculty of Medicine (MD)
2003 Kyoto University, Faculty of Medicine (PhD)

Occupation:

1996- Intern, United States Naval Hospital, Yokosuka
1997- Resident, University of Washington, Department of Internal Medicine
1998- Visiting Clinical Fellow, University of Washington, Department of Dermatology
1998- Clinical Fellow, Department of Dermatology, Kyoto University
2003- Assistant Professor, Department of Dermatology, Kyoto University
2003- Research Associate, Department of Microbiology and Immunology, University of California, San Francisco
2005- Associate Professor, Department of Dermatology, University of Occupational and Environmental Health
2008- Associate Professor, Department of Dermatology, Kyoto University Graduate School of Medicine
2010- Associate Professor, Department of Dermatology, Kyoto University Graduate School of Medicine
2015- Professor and Chairman, Department of Dermatology, Kyoto University Graduate School of Medicine
2015- Adjunct Principal Investigator, Singapore Immunology Network (SIgN)/Skin Research Institute of Singapore (SRIS), A*Star, Singapore
2017- Visiting Senior Consultant, National Skin Centre, Singapore

Luncheon Seminar 7

Eli Lilly Japan K. K.

December 5 (Sun) 12:45-13:45
Chairs: Makoto Sugaya
Hideyuki Ujiie

Neural mechanisms of itch and the role of JAK in atopic dermatitis

Yozo Ishiuji
Department of Dermatology, Jikei University School of Medicine, Tokyo, Japan

Recently, considerable progress has been made in dissecting the circuit mechanisms of itch at both the spinal and supraspinal levels. Upon stimulation, the itch signal is mediated via pruriceptive nerve fibers and the dorsal root ganglia extending to the dorsal horn of the spinal cord. Spinal projection neurons, which target multiple brain regions, serve as a key relay for sending various somatosensory information to the brain. Among different pathways, both spinothalamic and spinoparabrachial pathways are involved in the transmission of itch signals. Despite some differences in the brain regions revealed by different studies, most studies have found activation of the thalamus, primary and secondary somatosensory cortex (S1 and S2), prefrontal cortex (PFC), anterior cingulate cortex (ACC), insular cortex, premotor and motor cortex, ventral tegmental area (VTA), the nucleus accumbens (NAc), and parietal cortex. These distinct brain areas are thought to be involved in different aspects of itch signal processing. It was shown that the activity of dopaminergic neurons from VTA to NAc are important for driving itch-induced scratching behavior.

Several of the mediators either directly stimulate pruritus or sensitize sensory nerves to other pruritogenic stimuli. Once these mediators have bound to their specific receptors, they transmit their signals via the Janus kinase (JAK)/ Signal transducer and activator of transcription (STAT) pathway. The JAK family has four members: JAK1, JAK2, JAK3, and TYK2. Cytokines that are important for pruritus in atopic dermatitis (AD) (e.g., IL-31, IL-4, IL-13, and TSLP) transmit their signals via JAK-1 and JAK-2 into the cells. The deletion or inhibition of JAK-1/2 in animal models significantly reduced itch signaling induced by these mediators. In humans, JAKs were shown to play a critical role in pruritus when baricitinib, an oral JAK 1/2 inhibitor, significantly reduced pruritus in atopic dermatitis patients. IL-31, IL-4, IL-13, TSLP, and IL-5, as well as other cytokines influence inflammation and pruritus in AD. The potential to inhibit JAK-1 and JAK-2 with selective JAK-inhibitors opens a new treatment avenue, indicating that it may be possible to block several important itch mediators simultaneously. This avenue should enable us to treat chronic pruritus in AD and other chronically pruritic diseases more effectively. This seminar will provide the recent topics of neural mechanisms of itch and the role of JAK in AD.

Biography

Education

1995-2001	Jikei University School of Medicine

Occupation

2001-2004	Resident in General Medicine in Jikei University
2004-2005	Resident of Department of Dermatology in National Hospital Organization Nishisaitama-Chuo National Hospital
2005-2007	Research Fellow of Department of Dermatology in Wake Forest University, Winston-Salem, North Carolina, USA
2007-2009	Research associate of Department of Dermatology in NTT Medical Center Hospital
2009-2016	Research associate of Department of Dermatology in Jikei University
2016-Present	Assistant Professor of Department of Dermatology in Jikei University

Luncheon Seminar 8

Sanofi K.K.

December 5 (Sun) 12:45-13:45
Chair: Norito Katoh

Mechanism and future prospects of IL-4/13 in the treatment of atopic dermatitis

Gaku Tsuji[1,2]
[1]Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan,
[2]Research and Clinical Center for Yusho and Dioxin, Kyushu University Hospital, Fukuoka, Japan

Atopic dermatitis (AD) is an eczematous skin disease characterized by Th2-deviated skin barrier dysfunction, immune abnormalities, and pruritus. IL-4 and IL-13 are potent Th2 cytokines and Dupilumab, a fully human monoclonal antibody that binds IL-4Rα and inhibits signaling of both IL-4 and IL-13, has provided strong evidence for a highly significant efficacy in the treatment of AD. Furthermore, Dupilumab with concomitant topical corticosteroids improved signs and symptoms of AD. Although efficacious, topical corticosteroids have restrictions regarding duration, location, and extent of use. Considering the importance of topical agents in AD, the need for more effective and well-tolerated topical therapies remains. Aryl hydrocarbon receptor (AHR) is a chemical sensor that is expressed abundantly in epidermal keratinocytes. Oxidative AHR ligands such as dioxins and the environmental pollutant benzo(a)pyrene induce the production of reactive oxygen species contributing to exacerbation of skin inflammation. However, antioxidant AHR ligands such as phytochemicals, tryptophan photoproducts, and bioproducts of microbiomes inhibit reactive oxygen species generation via activation of nuclear factor-erythroid 2-related factor-2. In addition, antioxidative AHR ligands induce 1) the epidermal differentiation, including upregulation of Filaggrin and 2) downregulation of IL-33 that contributes to Th2-mediated skin inflammation and directly activates primary sensory neurons to evoke pruritus in AD. Therefore, topical application of antioxidant AHR ligands on the skin may counteract skin barrier dysfunction, Th2-shifted skin inflammation and pruritus in AD, leading to the enhanced therapeutic effect of Dupilumab on AD.

Biography

Education and professional experience

2021-present	Director, Research and Clinical Center for Yusho and Dioxin, Kyushu University Hospital
2019-present	Associate Professor, Research and Clinical Center for Yusho and Dioxin, Kyushu University Hospital
2017-2018	Assistant professor (Lecturer), Department of Dermatology, Graduate School of Medical Sciences, Kyushu University
2014-2016	Assistant professor, Research and Clinical Center for Yusho and Dioxin, Kyushu University Hospital
2012-2014	Visiting Fellow, Dermatology Branch in NIH (Mentor: Prof. Stephen I. Katz)
2011-2012	Assistant professor, Department of Dermatology, Graduate School of Medical Sciences, Kyushu University
2007-2011	Graduate school student, Ph.D. program, Department of Dermatology, Graduate School of Medical Sciences, Kyushu University
2006-2007	Medical director, Dermatology, Kitakyushu Municipal Wakamatsu Hospital
2005-2006	Senior resident, Department of Dermatology, Kyushu University Hospital
2004-2005	Medical staff, Dermatology, Saga Prefectural Hospital Koseikan
2002-2004	Resident, Department of Dermatology, Kyushu University Faculty of Medicine
2002	Graduated Tottori University Faculty of Medicine, Japan

Luncheon Seminar 9

Novartis Pharma K.K. Medical Division/Maruho Co., Ltd. Medical Affairs Dept.

December 5 (Sun) 12:45-13:45
Chairs: Ken Igawa
Toshiyuki Yamamoto

Molecular and cellular dynamics after anti-IL-17 mAb treatment for psoriasis

Toshiharu Fujiyama
Department of Dermatology, Hamamatsu University School of Medicine

Recently, the pathogenesis of psoriasis has become clearer and the treatment has developed dramatically. In the pathogenesis cascade, inflammatory DCs, activated by TNF-α in an autocrine manner, produce IL-23, which plays a crucial role for the maintenance of IL-17 producing T cells. IL-17 and IL-22 secreted by T cells accelerate the cell cycle of epidermal keratinocytes and induce hyperkeratotic epidermis. Since IL-23 locates upstream of the cascade, the blockade of IL-23 can suppress IL-17 producing T cells. However, the effect of IL-17 blockade on its producing T cells is complicated. To clarify this issue, we performed a clinical study focusing on the dynamics of T cells during anti-IL-17A mAb, Secukinumab treatment. It revealed that IL-17A blockade suppressed the skin infiltration of T cells, including Th17 cells. Notably, IL-17A producing CD8+ T cells were decreased not only in the lesional skin, but also in non-lesional skin after the treatment. Skin resident memory T cells (TRM), which reside in the skin for a long time are also considered to play important roles in the pathogenesis of psoriasis. Though the definition of TRM in the skin with active inflammation is not clear, the number of TRM marker-expressing (CD8+CD103+) T cells is increased in the active lesion, and it decrease even by topical treatments. After Secukinumab treatment, these cells were decreased in number but not in frequency in psoriasis lesion. We have detected IL-17A-producing PD-1+CD8+CD103+ T cells with skewed TCR Vb usage in psoriasis lesion. They are possibly the pathogenic T cells in psoriasis. Because these cells expressed IL-23 receptor, IL-23 blockade might suppress these cells while IL-17A blockade might cancel the function of these cells. The decrease of IL-17 producing T cells after the Secukinumab treatment can be explained by the indirect mechanisms. Secukinumab abrogates the vicious cycle in psoriasis pathogenesis. The suppression of IL-17 makes epidermal keratinocytes produce less chemokines or cytokines which enhance the inflammation. In addition, IL-17 blockade will also upregulate the immunomodulatory molecules, such as cholecystokinin (CCK) and its receptor CCKAR. CCK can inhibit differentiation of Th17 cells and enhance regulatory T cell differentiation. We have demonstrated that CCK is expressed by epidermal keratinocytes, and it plays suppressive role in psoriasis development in mouse model. CCK8 can suppress IL-6 production by keratinocytes via CCKAR. CCK8 and CCKAR are expressed in the epidermal keratinocytes in healthy subjects, although the expression is reduced in psoriatic skin. After the Secukinumab treatment, the expression of CCKAR and partially CCK8 was upregulated. CCK and CCKAR related downregulation of skin inflammation can also contribute the decreased infiltration of IL-17A producing T cells after IL-17A mAb treatment. In conclusion, IL-17A blockade normalize inflammation and indirectly reduces IL-17 A producing T cell infiltration.

Biography

1997-2003	Hamamatsu University School of Medicine
2003-2005	Resident, Hamamatsu University School of Medicine
2005-2008	Department of Dermatology, Fuji city general hospital
2009-present	Assistant Professor, Department of dermatology, Hamamatsu University School of Medicine

Luncheon Seminar 9

Novartis Pharma K.K. Medical Division/Maruho Co., Ltd. Medical Affairs Dept.

December 5 (Sun) 12:45-13:45
Chairs: Ken Igawa
Toshiyuki Yamamoto

Psoriasis as a systemic inflammation disease and an impact of IL-17A inhibition on it

Masahiro Kamata
Department of Dermatology, Teikyo University School of Medicine

Psoriasis is a chronic inflammatory skin disease characterized by scaly indurated erythema. It impairs patients' quality of life enormously. It has been recognized not only as a skin disease but as a systemic inflammatory disease since it also causes arthritis (psoriatic arthritis) and its association with cardiovascular events is indicated. The possible involvement of IL-17A in the pathogenesis of arthritis and the development of vascular dysfunction is suggested. In this lecture, we discuss a possible role of IL-17A in those comorbidities and an impact of IL-17A inhibition.

Biography

2004 - 2006	Residency, International Medical Center of Japan
2006 - 2006	Residency, The University of Tokyo Hospital
2006 - 2008	Residency, Mitsui Memorial Hospital
2008 - 2012	Graduate Student, Department of Dermatology, The University of Tokyo Graduate School of Medicine
2012 - 2013.3	Assistant, Department of Dermatology, The University of Tokyo, Graduate School of Medicine
2013.4 - 2015.9	Research Associate, Department of Immunology, Duke University Medical Center, Durham, USA
2015.10 - 2017.6	Lecturer, Department of Dermatology, The University of Tokyo
2017.7 - 2019.3	Lecturer, Department of Dermatology, Teikyo University School of Medicine
2019.4 -	Associate Professor, Department of Dermatology, Teikyo University School of Medicine

Evening Seminar 1

Medical Affairs, AMGEN K.K.

December 3 (Fri) 16:50-17:50
Chair: Mamitaro Ohtsuki

An update on the evidence of apremilast for psoriasis from research to practice

Masahiro Kamata
Department of Dermatology, Teikyo University School of Medicine, Tokyo, Japan

Since apremilast, an oral phosphodiesterase 4 inhibitor, was approved for the treatment of psoriasis in 2017, it has been widely used due to its efficacy and good tolerability with few limiting safety risks. However, data on the in vivo effects of apremilast on the expression of key cytokines involved in psoriasis such as IL-17 and IL-10 are limited. In the first half of my lecture, I will discuss the in vivo effect of apremilast on psoriasis, including the results of our study. In the second half, I focus on the characteristics of apremilast in a clinical view based on its current evidence, and then consider its optimal use.

Biography

2004 - 2006	Residency, International Medical Center of Japan
2006 - 2006	Residency, The University of Tokyo Hospital
2006 - 2008	Residency, Mitsui Memorial Hospital
2008 - 2012	Graduate Student, Department of Dermatology, The University of Tokyo Graduate School of Medicine
2012 - 2013.3	Assistant, Department of Dermatology, The University of Tokyo, Graduate School of Medicine
2013.4 - 2015.9	Research Associate, Department of Immunology, Duke University Medical Center, Durham, USA
2015.10 - 2017.6	Lecturer, Department of Dermatology, The University of Tokyo
2017.7 - 2019.3	Lecturer, Department of Dermatology, Teikyo University School of Medicine
2019.4 -	Associate Professor, Department of Dermatology, Teikyo University School of Medicine

Evening Seminar 2

Nippon Boehringer Ingelheim Co., Ltd.

December 3 (Fri) 16:50-17:50
Chair: Shigaku Ikeda

Disease burden of neutrophilic dermatoses: Patients' quality of life in generalized pustular psoriasis and hidradenitis suppurativa

Koremasa Hayama, Hideki Fujita
Department of Dermatolgy, Nihon University School of Medicine

Generalized pustular psoriasis (GPP) and hidradenitis suppurativa (HS) are classified as neutrophilic dermatoses, in which neutrophils play a central role in the pathogenesis. Both diseases are debilitating and long-lasting, severely impairing the patients' quality of life (QoL). The Short Form-36 health survey version 2 (SF-36v2) is a comprehensive QoL scoring tool used globally. Unlike dermatology quality of life index (DLQI), it can be used to make comparisons between skin diseases and ailments outside the field of dermatology. In addition, data from the general populations are determined, which allow for comparisons with the data from back ground population having a variety of health conditions. We investigated the QoL of patients with GPP and HS using SF-36v2. The QoL data of 83 GPP patients obtained from 2016 to 2019 (present group) was analyzed and compared with that of 105 patients collected in a previous survey conducted between 2003 and 2007 (past group). Although the QoL of the present patients was still largely impaired in comparison with the standard Japanese population, substantial improvement was found in some SF-36v2 subscales including "general health", "vitality", "social functioning" and "mental health" as compared with those of the past group. The prevalence of guidelines as well as comprehension of pathophysiology may have contributed to this improvement. We also examined the QoL of 63 HS patients using both DLQI and SF-36v2. The mean modified Sartorius score was 90.11 ± 95.81. DLQI of the patients averaged 9.78 ± 8.74, which was significantly correlated with Hurley stage and modified Sartorius score. Importantly, all eight elements of SF-36v2 were significantly impaired in HS patients as compared to Japanese national standard data. In conclusion, GPP and HS patients have lower QoL than the background general population. In addition to further understanding of pathophysiology, social support for the patients is also needed.

Biography

Education

2008-2012	Ph.D.
	Division of Cutaneous Science, Department of Dermatology, Nihon University Graduate School of Medical Science
1998-2004	M.D.
	Nihon university school of medicine

Professional Training and Employment

2014-present	Nihon university Itabashi Hospital department of dermatology
	Assistant professor/Senior Head of Dermatologic Ward
2012-2014	Nihon university Itabashi Hospital department of dermatology
	Assistant
2006-2008	Nihon university Itabashi Hospital department of dermatology
	Senior resident
2004-2006	Nihon university Itabashi Hospital resident

Evening Seminar 2

Nippon Boehringer Ingelheim Co., Ltd.

December 3 (Fri) 16:50-17:50
Chair: Shigaku Ikeda

Dynamics of inflammatory cytokines in generalized pustular psoriasis

Kazumitsu Sugiura
Department of Dermatology, Fujita Health University School of Medicine

With generalized pustular psoriasis (GPP), the skin of the whole body becomes flushed with sudden fever, and aseptic pustules occur frequently. Histopathologically, it forms Kogoj's spongiform pustules (neutrophil subcorneal pustules). This disease is characterized by repeated recurrences induced by upper respiratory tract infections, drugs such as antibacterial agents, pregnancy, and systemic steroid administration. Laboratory abnormalities associated with systemic inflammation are often associated with mucosal symptoms and arthritis during the course, and sometimes neutrophil cholangitis, cardiovascular failure, respiratory failure, ocular symptoms, and secondary amyloidosis. GPP is often pathogenic to autoinflammation due to abnormalities in genes associated with innate immunity. The etiology of GPP in Japan as autoinflammation is deficiency of interleukin 36 receptor antagonist (DITRA) and caspase recruitment domain-containing protein 14 (CARD14) mediated psoriasis (CAMPS) is common. The pathogenic gene for DITRA is the *IL36RN* gene and the pathogenic gene for CAMPS is the *CARD14* gene. In the *IL36RN* gene mutation, the functional deficiency of the gene product IL-36Ra is the pathogen, and in the *CARD14* gene mutation, the gain of function mutant of the gene product CARD14 is the pathogen of GPP. DITRA and CAMPS are included in the group of autoinflammatory diseases called autoinflammatory keratinization diseases (AiKD). For each of DITRA and CAMPS, analysis using a mouse model has progressed, and more detailed pathological conditions have been clarified. Genes that cause new pathogenesis *AP1S3* gene, *SERPINA3* gene, and *MPO* gene have also been reported overseas. In this talk, I will introduce the dynamics of inflammatory cytokines in GPP, focusing on IL-36.

Biography

Education

1988-1994	M.D. Nagoya University School of Medicine
1995-1999	Ph.D. Department of Dermatology, Nagoya University Graduate School of Medicine

Employment

1994-1995	Resident, Anjo Kosei Hospital
1998-2001	Research Associate, Autoimmune Disease Center, Molecular Experimental Medicine, The Scripps Research Institute
2001-2002	Research Associate, Department of Biochemistry II, Nagoya University Graduate School of Medicine
2008-2016	Associate Professor, Department of Dermatology, Nagoya University Graduate School of Medicine
2016-present	Professor and Chairman, Department of Dermatology, Fujita Health University School of Medicine

Evening Seminar 3

Minophagen Pharmaceutical Co., Ltd.

December 3 (Fri) 16:50-17:50
Chair: Makoto Sugaya

Therapeutic approaches for the treatment of cutaneous T-cell lymphoma: an update 2021

Toshihisa Hamada
Department of Dermatology, Takamatsu Red Cross Hospital, Takamatsu, Japan

Mycosis fungoides is a major type of cutaneous T-cell lymphoma, characterized by an indolent clinical course, especially in the early (or limited) stage disease. Skin-directed therapies such as photo(-chemo)therapy and topical corticosteroids are generally recommended as an initial therapeutic strategy for patients with the early-stage disease. In 2020, the Japanese clinical guideline for cutaneous lymphoma has been updated. For each type of cutaneous lymphoma, recommended treatments are listed in this guideline, depending on clinical stage or extent of the disease. Some of the listed therapeutic modalities have not been approved by the Japanese National Health Insurance system. In this guideline, interferon-γ and retinoids are recommended as an add-on therapeutic option for patients with early-stage mycosis fungoides that proves resistant to skin-directed therapy. Interferon-γ and retinoids can also be selected as initial treatment for patients with advanced-stage mycosis fungoides and Sézary syndrome, in combination with skin-directed therapy. Because cutaneous lymphoma is a radiosensitive neoplasm, radiotherapy can be selected as first-line treatment for tumorous lesion of cutaneous T-cell lymphoma. Recently, a low-dose regimen (8-12 Gy) of radiotherapy has emerged as a promising option for skin lesions resistant to skin-directed therapy. Patients with refractory clinical course may require systemic, targeted therapy such as histone deacetylase inhibitors, therapeutic monoclonal antibodies, and antibody-drug conjugates, or monochemotherapy (e.g. methotrexate, etoposide). Recent advances in understanding key molecular mechanisms involved in the development and progression of cutaneous T-cell lymphoma, have provided novel strategy for molecular targeted therapeutic modalities. However, combination therapy, maintenance therapy or quality of life therapy remains to be fully established. In 2021, denileukin diftitox, a recombinant fusion protein targeting interleukin-2 receptor, has been approved for relapsed/refractory cutaneous T-cell lymphoma. In this presentation, I will introduce a current outline of therapeutic strategy for patients with mycosis fungoides/Sézary syndrome, based on the updated Japanese clinical guideline for cutaneous lymphoma. I will also address the current topics in bexarotene treatment from the results of a nation-wide cohort study using data from post-marketing surveillance in Japan. Based on the results of this study, starting bexarotene at 300mg/m^2 and combination of photo(-chemo) therapy offer a promising efficacy for the treatment of patients with mycosis fungoides. In contrast, treatment-related adverse events occurred more frequently in patients who started with bexarotene at 300mg/m^2 than patients who started with bexarotene <300mg/m^2.

Biography

WORK EXPERIENCE:

2018 to date	Director of Dermatology, Takamatsu Red Cross Hospital
2015 – 2017	Lecturer, Department of Dermatology, Okayama University School of Medicine
2005 – 2015	Assistant Professor, Department of Dermatology, Okayama University School of Medicine
2003 – 2005	Resident, Department of Dermatology, Kawasaki Hospital

EDUCATION:

1998 – 2003	Postgraduate training, Department of Dermatology, Okayama University School of Medicine and Department of Dermatology, Okayama Rosai Hospital
1992 – 1998	Graduate Career, Tokyo Medical and Dental University School of Medicine

Evening Seminar 3

Minophagen Pharmaceutical Co., Ltd.

December 3 (Fri) 16:50-17:50
Chair: Makoto Sugaya

Photo(chemo)therapy for cutaneous T-cell lymphoma in combination with bexarotene

Akimichi Morita
Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

The 2020 Clinical Practice Guidelines for Cutaneous Lymphoma by the Japanese Dermatological Association recommend topical steroid therapy, phototherapy, or local radiation therapy as a local treatment for treating early-stage disease. The photo(chemo)therapy currently used for cutaneous T-cell lymphoma (CTCL) includes 311-nm narrowband UVB; 308-nm excimer light/laser; and topical, oral, or bath psoralen+UVA (PUVA). In a retrospective analysis of 62 patients with mycosis fungoides (J Dermatol, in press), bath-PUVA therapy was extremely effective for patients in stages IA and IB (complete response rates [CR] of 100% and 70%, respectively), but insufficient for those in stage IIB (partial response [PR] 40%, stable disease 20%, progressive disease 40%). Patients in stage IIIA showed favorable responses (CR, 44%; PR, 39%). Bath-PUVA therapy facilitates percutaneous penetration of psoralen and allows for more UVA irradiation. A UVA1 (340-400nm)-LED device was developed (J Dermatol Sci, 2019). In an open pilot study, 3 of 3 patients with early-stage mycosis fungoides (stages IA, IB) were effectively treated with a high/medium-dose UVA1 regimen (J Am Acad Dermatol, 1999). Compared with PUVA, UVA1 phototherapy avoids long-lasting skin photosensitivity and the requirement for eye protection, but the evidence remains limited. Bexarotene was approved as an oral therapeutic agent for CTCL in 2016 in Japan. In early-stage CTCL patients (L1069-23 study), 300 mg/m2 bexarotene provided an objective CR+PR rate of 54.0% (15/28 patients) on the basis of the Primary Endpoint Classification (PEC). A clinical Phase I/II study (B-1101 study) in 13 patients with CTCL in Japan reported a CR+PR of 61.5% on the basis of the modified Severity-Weighted Assessment Tool (mSWAT). A clinical phase III study (NCT00056056 published in 2012) of the CR+PR to the combination of PUVA therapy and the study drug compared with PUVA therapy alone in 93 patients with early CTCL confirmed no difference in the response rates between combination therapy and PUVA monotherapy, but combination therapy tended to decrease the required dose of UV irradiation. The efficacy and safety of combination therapy for Japanese CTCL patients are not yet established. We evaluated the efficacy and safety of photo(chemo)therapy and bexarotene combination therapy in 25 Japanese CTCL patients (J Dermatol, 2020) given daily oral bexarotene (300 mg/m2 body surface) followed by PUVA or narrowband UVB on the basis of mSWAT and PGA scores for up to 24 weeks. Twenty-four weeks after initiating treatment, the total response rate was 80.0% (mSWAT) and 84.0% (PGA). All patients experienced adverse events and drug reactions, including sepsis, anemia, and congestive cardiac insufficiency (n=1, each). Other adverse drug reactions were of mild to moderate severity. We are now conducting a randomized controlled study to compare bexarotene monotherapy and in combination with phototherapy.

Biography

Vice Director, Nagoya City University Hospital/Professor and Chairman, Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences.

Professor Akimichi Morita graduated from Nagoya City University and received his M.D degree in 1989, he later received his Ph.D in basic immunology at Aichi Cancer Center. As a Humboldt Foundation fellow, he studied photobiology and photoimmunology at Duesseldorf University and underwent further training at the University of Texas Southwestern Medical Center. He was appointed Professor and Chairman of the Department of Geriatric and Environmental Dermatology at Nagoya City University Graduate School of Medical Sciences in 2003 and currently holds the position of Vice Director of Nagoya City University Hospital.

He was the President of the Japanese Society of Investigative Dermatology (2018-2020) and has been involved in many other societies, such as the Japanese Society for Psoriasis Research. He has been a key member in many medicals publications, especially the Journal of Dermatological Sciences (JDS) as Editor in Chief from 2008-2013. Currently, He serves as a chief-in-editor for Photodermatology, Photomedicine, Photoimmunology. He has authored more than 200 publications in peer-reviewed journals (Total Impact Factor: 1200.3, h-index: 43).

Evening Seminar 4

AbbVie GK

December 4 (Sat) 17:25-18:25
Chair: Takashi Matsushita

The roles of Interferon Regulatory Factor-8 in psoriasis pathogenesis

Tomoya Watanabe
Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

Psoriasis is a systemic, chronic, immunologically mediated skin disease, in which IL-23/IL-17 axis is critical in the immunopathogenesis. Especially, it has been considered that dendritic cells, such as plasmacytoid dendritic cells (pDCs) and TNF-a and iNOS producing dendritic cells (Tip-DCs) play a key role in the pathogenesis of psoriasis. Interferon Regulatory Factors (IRFs) are the transcription factor family that is important for immunity and tumor suppression. IRFs are classified into 9 families in mammals. Among them, IRF8 is a 50 kDa transcription factor that was originally identified as a negative regulator of IFN-1, but is now recognized as an essential regulator for the development of multiple immune cell types. IRF8 is required for the development of DCs, monocytes, macrophages, basophils, and eosinophils while it inhibits the generation of neutrophils. IRF8 is also indispensable for the differentiation of cytotoxic T lymphocytes. Thus, Irf8 knock out mice develop immunodeficiency and a chronic myeloid leukemia (CML)-like syndrome and IRF8 expression is downregulated in CML patients. Importantly, mutations in the human IRF8 gene are associated with DC deficiency. The role of its function regarding DCs has been widely studied in mouse, yet association of IRF8 and psoriasis has not been reported. Recent studies demonstrated that IRF8 is associated with various dermatological diseases, such as systemic sclerosis, systemic lupus erythematosus, and Behcet's disease. Furthermore, microarray data analysis revealed that IRF8 is the common pathogenesis of psoriasis and atherosclerosis. In this session, recent findings of IRF8 in psoriasis will be reviewed from research.

Biography

Education

2007	M.D. St. Marianna University School of Medicine, Kanagawa, Japan
2010-2014	Ph.D. Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine

Professional experiences

2007-2009	Resident, Yokohama City University Hospital, Kanagawa, Japan
2009-2010	Fellow, Department of Environmental Immuno-Dermatology, Yokohama City University Hospital, Kanagawa, Japan
2014-2016	Assistant professor, Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Kanagawa, Japan
2016-2018	Postdoctoral Research Fellow, Division of Rheumatology & Immunology, Medical University of South Carolina, South Carolina, USA
2018-	Assistant professor, Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Kanagawa, Japan

Evening Seminar 4

AbbVie GK

December 4 (Sat) 17:25-18:25
Chair: Takashi Matsushita

Personalized nutrition for disease management in psoriasis patients

Yuki Hashimoto
Department of Dermatology, faculty of Medicine, Toho University, Tokyo, Japan

Psoriasis is a chronic inflammatory skin disease, and its characteristic symptoms, such as rash and arthritis, reduce the patient's QOL. Treatment is based on topical therapy. However, for patients with difficult-to-treat sites, joint symptoms, or severe diseases (such as Erythrodermic psoriasis/Generalized pustular psoriasis), oral medication, phototherapy, and, in recent years, biologics, have been available and enabled control of symptoms in many cases. Patients with psoriasis often have comorbidities such as hypertension, diabetes, and dyslipidemia, suggesting a relationship between lifestyle and exacerbation of symptoms or the onset of cardiovascular events. These patients also require intervention with medical treatment. In addition to PASI, BSA, and DLQI assessments, body weight and blood pressure should be measured. For patients with metabolic syndromes (MetS), it is also important to initiate aggressive diet and exercise therapies. Anti-MetS measures for psoriasis patients to be performed by dermatologists include: 1) making patients aware that they have MetS, 2) making them understand the risks associated with MetS, and 3) providing specific nutritional guidance for MetS control. Although it is often difficult to ensure the patient's adherence to nutritional guidance, involvement of a person responsible for meal preparation and a registered dietitian will facilitate the modification of the patient's dietary life to a proper one. It is beneficial to make patients understand that a satisfactory psoriasis treatment cannot be achieved without modification of their own behavior in addition to the correct diagnosis and appropriate treatment. Additionally, it is advisable to provide an environment that helps patients gain self-esteem by setting goals for individual patients, including lifestyle goals.

Biography

2000.3	Graduation of School of Medicine & became M.D., Toho University, Tokyo, Japan
2000.4-2002.3	Internship in Toho University Omori Hospital, Tokyo, Japan
2006	Degree of Ph.D., Graduate School, Toho University, Tokyo, Japan
2006.4-2017.3	Assistant, Department of Dermatology, faculty of Medicine, Toho University, Tokyo, Japan
2008.9-2009.8	Research fellow, School of Medicine, Harvard University, Boston, USA
2009.9-2010.8	Research fellow, School of Medicine, Cincinnati University, Cincinnati, USA
2013	Dermatology Special Board Certified
2017.4-present	Assistant professor, Department of Dermatology, faculty of Medicine, Toho University, Tokyo, Japan

Evening Seminar 5

UCB Japan Co. Ltd.

December 4 (Sat) 17:25-18:25
Chairs: Yoshihide Asano
Hideki Fujita

Psoriasis and the metabolic syndrome

Rei Watanabe
Department of Integrative Medicine for Allergic and Immunological Diseases, Graduate School of Medicine/Faculty of Medicine, Osaka University, Osaka, Japan

Psoriasis is an immune-mediated inflammatory skin disorder that is associated with systemic conditions such as obesity, hypertension, dyslipidemia, and insulin resistance. These systemic disorders are integrated as the metabolic syndrome. The patients with psoriasis tend to have higher body mass index, and they show approximately doubled prevalence of metabolic syndrome compared to nonpsoriatic subjects. The recent mendelian randomization approach suggests that obesity can be an independent causative factor for psoriasis. Metabolic syndrome is also regarded as a risk factor for psoriasis, and is related to more severe psoriatic manifestation. Psoriasis and metabolic syndrome share the same inflammatory disease pathways. TNFα and interleukin-17, which are the established key cytokines in the pathogenesis of psoriasis, take parts in the development of hypertension, adipogenesis, and insulin resistance. The cytokines released from both immune cells and adipocytes accelerate the progression of systemic inflammatory cascade called “psoriatic march”, leading to the higher cardiovascular risk in psoriasis. Then, the systemic inflammation in turn causes the exacerbation of skin disease.
In this session, the overlapped disease pathways of psoriasis and metabolic syndrome will be overviewed. I would like to emphasize the importance of targeting both skin condition and systemic condition in the treatment strategy of psoriasis.

Biography

1995.4-2001.3	Faculty of Medicine, The University of Tokyo
2001.6-2003.3	Trainee, Department of Dermatology, The University of Tokyo Hospital and Tokyo Kosei-Nenkin Hospital
2003.4-2007.3	Graduate School of Medicine, The University of Tokyo
2007.4-2009.8	Instructor, Department of Dermatology, The University of Tokyo Hospital and International Medical Center of Japan
2009.9-2014.3	Post-doctoral fellow, Department of Dermatology, Brigham and Women’s Hospital
2014.4-2014.7	Instructor, Department of Dermatology, The University of Tokyo Hospital
2014.7-2015.9	Lecturer, Department of Dermatology, The University of Tokyo
2015.10-2020.3	Assistant professor, Department of Dermatology, University of Tsukuba
2020.4-present	Specially appointed associate professor, Department of Integrative Medicine for Allergic and Immunological Disease, Faculty of Medicine, Osaka University

Evening Seminar 5

UCB Japan Co. Ltd.

December 4 (Sat) 17:25-18:25
Chairs: Yoshihide Asano
Hideki Fujita

Immunological aspects of psoriasis and significance of TNF-α inhibition

Hideki Nakajima
Department of Dermatology, Kochi Medical School, Kochi University, Kochi, Japan

The role of inflammatory cytokines in the immunopathological condition of psoriasis has been clarified by anti-cytokine therapy. In our recent study, we found the details of the cytokine cascade in psoriasis model in which the order of cytokine activation and the organ site of cytokine production were elucidated.
In the imiquimod model, a rapid increase in serum IL-1β, TNF-α, and IL-6 occurred 1 hour after imiquimod application, and these cytokines were no longer detected after 3 hours. These inflammatory cytokines' gene expressions were also rising rapidly in the liver. On the other hand, in the skin, the increased expression of inflammatory cytokines was maintained from 3 hours to 96 hours after application. Considering the fact that serum IL-23 and IL-17A were elevated 3 hours and 96 hours after application respectively, as a cytokine cascade IL-1β, TNF-α, and IL-6 were first produced in the liver, and then IL-23 and finally IL-17 were activated in the skin, which suggested the presence of a skin-liver inflammatory axis.
Because TNF-α is produced in both liver and skin and spreads inflammation systemically in psoriasis, it is considered that inhibition of TNF-α suppresses not only skin symptoms but also organ inflammation due to metabolic syndrome and arthritis.

Biography

Positions

Since2013	Associate Professor, Department of Dermatology, Kochi Medical School, Kochi University
2008-2013	Assistant Professor, Department of Dermatology, Kochi Medical School, Kochi University
2007-2008	Director of Dermatology, Kochi Prefectural Aki Hospital
2004-2007	Assisstant Professor, Department of Dermatology, Kochi Medical School, Kochi University.
1999-2004	Assisstant Professor, Department of Dermatology, Kochi Medical School.
1996-1999	Clinical Fellow, Department of Dermatology, Kochi Medical School.
1994-1996	Resident in Kochi Medical School Hospital (Dermatology).

Evening Seminar 6

Pfizer Japan Inc.

December 4 (Sat) 17:25-18:25
Chair: Nobuo Kanazawa

The Proper Use of Methotrexate for PsA

Akihiko Asahina
Department of Dermatology, The Jikei University School of Medicine

Psoriatic arthritis (PsA) means a pathological condition that involves skin symptoms of psoriasis accompanied by joint symptoms. PsA is classified for the spondylarthritis disease group. The comorbidity rate of PsA had been low (6-8%) in psoriasis patients, and it was believed that symptoms of PsA were mild. Today, however, the comorbidity rate rose to as high as 10-15%. This concomitant disease is believed to be severe now. Inflammatory cytokines are known to be involved in the formation of the pathological conditions for PsA, such as TNF, IL-17, and IL-23. The treatment environment has been significantly improved and more treatment options are currently available for biological preparations targeting these molecules.

In Japan, methotrexate (MTX) was approved as a therapeutic drug for rheumatoid arthritis (RA) in 1999. It is an anchor drug in the treatment of RA today. MTX has been globally used to treat psoriasis since the 1950s. In Japan, it was hard for pharmaceutical companies to get an approval for the psoriasis indication for many years. Public knowledge-based applications have been permitted lately. The Japanese Society for Investigative Dermatology submitted a request to the Ministry of Health, Labour and Welfare, and the history of the use of MTX was investigated twice. MTX was approved in March 2019 for marketing for the following indications: Plaque psoriasis, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis which do not respond to local treatment very well. The positioning of MTX in PsA treatment needs to be considered because of the difference in the pathological conditions for rheumatoid arthritis and PsA. Due caution should be paid to safety when MTX is used since MTX is associated with serious side effects including blood disorders, lung disorders, and infections.

The lecture starts with the elucidation of the 2019 Japanese guideline for the management of psoriatic arthritis and other countries' guidelines for the consideration of the positioning of MTX in PsA treatment. Then, I explain points regarding patient selection, patient monitoring, regimens, side effect management, and patient education. The explanation will help you ensure the proper use of MTX when prescribing it to PsA patients. At the end of the lecture, I will share the results of the nationwide survey of cases using methotrexate for psoriasis performed in 2017. It will be helpful when you use MTX for PsA in your everyday practice of medicine, containing a large number of cases of people treated with MTX for joint symptoms.

Biography

1981-1987	The University of Tokyo School of Medicine, Tokyo
1987-1998	Assistant, Department of Dermatology, The University of Tokyo, Tokyo
1992-1994	Research Fellow, MGH-Harvard Cutaneous Biology Research Center, U.S.A.
1998-2001	Assistant Professor, Department of Dermatology, The University of Tokyo, Tokyo
2001-2005	Associate Professor, Department of Dermatology, The University of Tokyo, Tokyo
2005-2014	Director, Department of Dermatology, National Hospital Organization Sagamihara National Hospital, Kanagawa
2014-2016	Associate Professor, Department of Dermatology, The Jikei University School of Medicine, Tokyo
2016-2018	Professor, Department of Dermatology, The Jikei University School of Medicine, Tokyo
2018-present	Professor and Chairman, Department of Dermatology, The Jikei University School of Medicine, Tokyo

Evening Seminar 6

Pfizer Japan Inc.

December 4 (Sat) 17:25-18:25
Chair: Nobuo Kanazawa

Let's think about the appropriate use of methotrexate for psoriasis

Yayoi Tada
Department of Dermatology, Teikyo University School of Medicine

In patients with psoriasis, interleukin (IL)-17, IL-22, and TNF-alpha released from lymphocytes activate epidermal cells to induce the thickening of the skin and release pro-inflammatory molecules which attract neutrophils. Methotrexate (MTX) is an oral medication that inhibits antibody production and lymphocyte proliferation, inhibits neovascularization and synovial proliferation by blocking the growth of endothelial cells and synovial fibroblasts, and blocks the migration of neutrophils to the inflammation site, among other actions, and has long been used as the anchor drug for the treatment of rheumatoid arthritis (RA) in Japan. MTX has been indicated for the treatment of psoriasis in many countries and became available for the treatment of psoriasis (patients with psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis who do not respond well to topical treatments) in March 2019 in Japan on the basis of a new drug application based on public knowledge. Accordingly, MTX as a treatment for psoriasis should be positioned clearly through real-world clinical experience.

MTX is expected to alleviate both skin and joint symptoms but needs careful monitoring for safety. MTX may cause serious adverse drug reactions (ADRs) such as myelosuppression, interstitial pneumonia, and lymphoproliferative disorders. Administration in patients with impaired renal function is contraindicated. Patients at risk for impaired renal function should be started on a low dose, with folic acid as needed, and carefully monitored during administration. Physicians should understand what the risk factors are for each type of ADR, how to prevent ADRs, and how to manage ADRs if any.

This lecture will focus on the following topics that are necessary to ensure the appropriate use of MTX in dermatology.
1) Describe basic information on MTX such as the mechanism of action, dosage regimens and the position in psoriasis treatment, and how to use MTX appropriately in different regimens such as those including biologics.
2) Describe common ADRs and how to prevent and manage them on the basis of the findings of ADRs to MTX in RA, and list important points that should be kept in mind by dermatologists.

Biography

Education

1995	M.D. Faculty of Medicine, The University of Tokyo
2001	Ph.D. Graduate School of Medicine, The University of Tokyo

Professional Experience

1995-1997	Resident, Department of Dermatology, The University of Tokyo
2001-2002	Assistant Professor, Department of Dermatology, The University of Tokyo
2002-2005	Research fellow, Dermatology Branch, National Cancer Institute, USA
2005-2006	Assistant Professor, Department of Dermatology, Teikyo University School of Medicine
2006-2008	Assistant Professor, Department of Dermatology, The University of Tokyo
2008-2011	Lecturer, Department of Dermatology, The University of Tokyo
2011-2013	Chief, Department of Dermatology, Kosei General Hospital
2013-2017	Associate Professor, Department of Dermatology, Teikyo University School of Medicine
2017-present	Chief Professor, Department of Dermatology, Teikyo University School of Medicine

Oral & Poster Sessions

The 46th Annual Meeting of the Japanese Society for Investigative Dermatology

P01-01[II-1]

Lymphotoxin β from T cells mediates the formation of high endothelial venule-like vessels in atopic dermatitis-like skin lesions in mice

○ Shuto Kanameishi[1], Sachiko Ono[1], Yuki Honda-Keith[1], Ryota Asahina[1], Tetsuya Honda[2], Kenji Kabashima[1,3]
[1]Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan, [2]Department of Dermatology, Hamamatsu University School of Medicine, Japan, [3]Singapore Immunology Network (SIgN) and Skin Research Institute of Singapore, Agency for Science, Technology and Research, Biopolis, Singapore

High endothelial venules (HEVs) contribute to the trafficking of naïve T cells and central memory T cells (Tcms) into secondary lymphoid organs by expressing a group of L-selectin ligands called peripheral node addressins (PNAd). In lymph nodes, lymphotoxin β receptor (LTβR) signaling from dendritic cells (DCs) is essential for the formation of HEVs. PNAd+ HEV-like vessels are also observed in the skin under certain inflammatory conditions, such as atopic dermatitis (AD). We first found that PNAd+ HEV-like vessels are formed in MC903-induced murine AD-like skin lesions dependent on LTβR signaling. We next questioned which cell mediates LTβR signaling for the HEV-like vessel formation in AD-like skin. To this end, we sought to identify LTβ expressing cells in AD skin. Analysis of publicly available single cell RNA-seq data of human AD skin showed high expression of LTβ on T cells and DCs. To evaluate the importance of LTβ on DCs and T cells in HEV-like vessel formation in the skin, we generated conditional knockout mice lacking LTβ only in DCs (*LTb*$^{f/f}$*CD11c*-Cre mice) or T cells (*LTb*$^{f/f}$*CD4*-Cre mice) and applied them to the AD model. The formation of HEV-like vessels in AD-like skin was normal in *LTb*$^{f/f}$*CD11c*-Cre mice, but was impaired in *LTb*$^{f/f}$*CD4*-Cre mice, suggesting that LTβ from T cells mediates HEV-like vessel formation in the skin. We further investigated whether naïve T cells and Tcms are infiltrated to AD-like skin via HEV-like vessels. Two-photon microscopic analysis demonstrated the infiltration of these cells into the skin through HEV-like vessels in mice. Taken together, our results indicate that LTβ from T cells mediates the formation of HEV-like vessels, which may be involved in the migration of naïve T cells and Tcms into AD skin.

P01-02[I-3]

AIM2 regulates anti-tumor immunity and serves as a therapeutic target for melanoma immunotherapy

○ Keitaro Fukuda[1,2], Ken Okamura[2], Rebecca L. Riding[2], Xueli Fan[2], Sean M. McCauley[3], Jeremy Luban[3,4], Takeru Funakoshi[1], Tomonori Yaguchi[5], Yutaka Kawakami[5], Anastasia Khvorova[6,7], Katherine A. Fitzgerald[8], John E. Harris[2]
[1]Department of Dermatology, Keio University School of Medicine, Tokyo, Japan, [2]Department of Dermatology, University of Massachusetts Medical School, Worcester, MA, [3]Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, MA, [4]Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, MA, [5]Division of Cellular Signaling, Institute for Advanced Medical Research, Keio University School of Medicine, Tokyo, Japan, [6]RNA Therapeutics Institute, University of Massachusetts Medical School, Worcester, MA, [7]Department of Molecular Medicine, University of Massachusetts Medical School, Worcester, MA, [8]Department of Infectious Diseases and Immunology, University of Massachusetts Medical School, Worcester, MA.

Cancer immunotherapy has limited efficacy for patients who have insufficient CD8+ T cell infiltration of their tumor, a characteristic known as “cold tumor”. Converting “cold tumor” to “hot tumor” by inducing immune infiltration would provide a valuable adjunctive therapy to improve the efficacy of this treatment approach. The STING and AIM2 pathways are activated by the presence of cytosolic DNA and STING agonists are being tested in clinical trials as adjuvant immunotherapy for cancers. We postulated that dissecting AIM2 function within the melanoma microenvironment could provide insight into better immunotherapies for melanoma. Here, we report that AIM2 exerts an immunosuppressive effect within the melanoma microenvironment in mice and correlates with tumor progression in human melanoma. The intravenous administration of *Aim2*-deficient dendritic cells (DCs) through a vaccination strategy results in homing of the DCs to the spleen and tumor, and enhanced efficacy of adoptive cell therapy and anti-PD-1 immunotherapy, thereby achieving therapeutic responses to cold melanomas. This effect did not depend on prolonged survival of vaccinated DCs, but on tumor-derived DNA that activates STING-dependent type I interferon secretion, which lead to the promotion of priming CD8+ T cells in the spleen and subsequent production of CXCL10 to recruit CD8+ T cells to the tumor. Additionally, loss of AIM2-dependent IL-1β and IL-18 processing enhanced the treatment response further by limiting the recruitment of regulatory T cells to the tumor. Finally, AIM2 siRNA-treated human DCs *in vitro* enhanced similar antitumor immune responses. Thus, targeting AIM2 in tumor-infiltrating DCs is a novel therapeutic strategy to enhance melanoma immunotherapeutic responses, turning cold tumors hot.

P01-03[C10-01]

Skin immune memory can be compensated by circulating CD4 T cells when the resident memory CD8 T cells are unfunctional

○ Shuichi Nakai[1,2], Rei Watanabe[2], Kiyoshi Hirahara[3], Toshinori Nakayama[3], Manabu Fujimoto[2]
[1]Research Department, Maruho Co., Ltd., Kyoto, Japan, [2]Department of Dermatology, Graduate School of Medicine, Osaka University, Osaka, Japan, [3]Department of Immunology, Graduate School of Medicine, Chiba University, Chiba, Japan

Tissue resident memory T cells (T_{RM}) are a subset of memory T cells which reside in peripheral tissues including skin for long term. As cell surface molecules of T_{RM}, CD69 suppresses the exit of T cells from peripheral tissue via down-regulation of S1P1, and CD103 is thought to be related to adhesion with keratinocytes. However, the detailed relation of these molecules with kinetics/function of T_{RM} is unknown. Herein, we analyzed the role of CD69 and CD103 in the development and functional activities of skin T_{RM} by use of a murine contact hypersensitivity model.
Wild type (WT) mice were sensitized on the abdomen with 0.5% DNFB at day -7 and the right ear was challenged with 0.15% DNFB at day 0. By day 28, $CD69^+CD103^+$ T_{RM} developed in the right ear, not in the left ear. When the both ears were re-challenged with 0.15% DNFB at day 28, the right ear showed severer swelling than the left ear at day 29 (right: 0.16 ± 0.01 mm vs left: 0.08 ± 0.01 mm). The same model was developed in CD 103 knockout (CD103KO) mice and CD69KO mice. While the number of infiltrating CD8 T cells in both ears of CD69KO and CD103KO was comparable with that of WT at day 28, CD69KO mice showed strong infiltration of CD4 T cells in both ears. The swelling in the right ear of CD 103KO was comparable with that of WT at day 29 (0.15 ± 0.03 mm) while that of CD69KO was weak (0.11 ± 0.04 mm). The left ear swelling of CD69KO was comparable with the right ear swelling (left: 0.11 ± 0.02 mm), and was suppressed by administration of FTY720 (0.04 ± 0.01 mm). Our data suggest the importance of CD69 on the kinetics and function of T_{RM}. Although the functional activity of T_{RM} is diminished in CD69KO, our results also suggest that the circulating memory CD4 T cells can partially compensate the role of T_{RM}.

P01-04[C10-02]

Neutrophil extracellular traps are involved in enhanced contact hypersensitivity response in IL-36 receptor antagonist-deficient mice

○ Yurie Hasegawa[1], Yohei Iwata[1], Hidehiko Fukushima[1], Yoshihito Tanaka[1], Soichiro Watanabe[1], Kenta Saito[1], Hiroyuki Ito[1], Mizuki Sugiura[1], Masashi Akiyama[2], Kazumitsu Sugiura[1]
[1]Department of Dermatology, Fujita Health University School of Medicine, Aichi, Japan, [2]Department of Dermatology, Nagoya University Graduate School of Medicine

Background: Loss-of-function homozygous or compound heterozygous mutations in *IL36RN*, which encodes interleukin-36 receptor antagonist (IL-36Ra), has been implicated in the pathogenesis of skin disorders. We previously reported that *Il36rn*$^{-/-}$ mice revealed enhanced contact hypersensitivity (CHS) response through increased neutrophil recruitment. In addition, we also found that *Il36rn*$^{-/-}$ mice showed severe imiquimod-induced psoriatic skin lesions and enhanced neutrophil extracellular trap (NET) formation. We hypothesized that NETs may play important roles in CHS response. To clarify this possibility, we examined CHS response and NET formation in *Il36rn*$^{-/-}$ mice.
Methods: We evaluated the severity of CHS response in wild-type and *Il 36rn*$^{-/-}$ mice. Ear thickness, histopathological features, and numbers of infiltrated cells were examined. NET formation was also examined by immunofluorescence staining. The mRNA levels of cytokines, chemokines, and growth factors were measured by real-time reverse transcription polymerase chain reaction. The T cell subsets in cervical lymph nodes were analyzed by flowcytometry. In addition, inhibition of NET formation by Cl-amidine, a peptidyl arginine deiminase inhibitor, on CHS response in *Il36rn*$^{-/-}$ mice was evaluated.
Results and Conclusion: *Il36rn*$^{-/-}$ mice showed enhanced CHS response, and increased inflammatory cell infiltration and NET formation. *Il36rn*$^{-/-}$ mice had increased mRNA expression of cytokines and chemokines. Furthermore, blockade of NET formation improved CHS response. Thus, the current study indicated that IL-36Ra deficiency exacerbates CHS response due to excessive inflammatory cell recruitment, NET formation, and excessive cytokine and chemokine production, and NET formation may play important roles in CHS response.

P01-05[C10-03]

Tumor necrosis factor-alpha plays crucial role in both the induction and maintenance of cytotoxic T lymphocyte-induced dermatitis

○Toshiya Miyake, Satoshi Nakamizo, Gyohei Egawa, Kenji Kabashima
Department of Dermatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

The essential role of tumor necrosis factor-alpha (TNF-α) in cytotoxic T lymphocyte (CTL)-related skin diseases such as graft versus host disease (GVHD) and severe drug eruption is not fully elucidated. To clarify this, we administered TNF-α inhibitor, etanercept, to a murine GVHD model. Ivl-mOVA transgenic mice, in which membrane-bound ovalbumin (mOVA) is expressed under the control of involucrin (Ivl) promoter that is specifically activated in the epidermis were transferred with CD8+ T cells from ovalbumin-specific T cell receptor transgenic (OT-I) mice (day 0). These mice developed GVHD-like dermatitis by day 7 and half of them died by day 21. The administration of etanercept ameliorated the dermatitis and improved the survival rate. Using flow cytometry and two-photon microscopy, we revealed that etanercept administration attenuated OT-I CD8+ T cell proliferation in skin-draining lymph nodes and inhibited the infiltration of OT-I CD8+ T cells into skin. These results suggest that OT-I CD8+ T cells require TNF-α for developing inflammation. We then transferred OT-I CD8+ T cells into TNF-α-deficient Ivl-mOVA mice, and found that these mice developed dermatitis, but the skin inflammation resolved earlier than Ivl-mOVA mice and survival rate improved. Furthermore, we transferred OT-I CD8+ T cells into bone marrow chimeric mice and found that the survival rate of TNF-α-deficient Ivl-mOVA mice reconstructed by Ivl-mOVA mice was higher than the opposite chimeric mice. These results suggest that TNF-α production by radio-resistant cells is required to retain the inflammation developed by CTL. Our study demonstrates that TNF-α is essential for both the induction and maintenance of CTL-mediated dermatitis, and that TNF-α could be a new therapeutic target for these diseases.

P01-06[C10-04]

IL-31, a major pruritogen in a mouse model of atopic dermatitis, is generated through the macrophage/TSLP/periostin axis

○Takashi Hashimoto, Takahiro Satoh
Department of Dermatology, National Defense Medical College, Tokorozawa, Japan

Atopic dermatitis (AD) is a common skin disease that causes intractable itch. IL-31 has recently gained attention as a potential therapeutic target for AD itch. Although Th2 cells have been implicated as the main cellular sources of IL-31, IL-31 is also secreted by a variety of other immune cells. In this study, we aimed to assess the contribution of macrophages as IL-31-secreting cells and elucidate the mechanisms of IL-31 generation in a mouse model of AD. Remarkable scratching behaviors were observed in an MC903-induced mouse AD model, which was significantly ameliorated by local injection of an IL-31RA antagonist, implying dependency of the scratching behavior on IL-31. Massive dermal infiltrates of IL-31(+) cells were detected in the skin lesions, and more than 80% of IL-31(+) cells were MOMA-2(+) macrophages. MOMA-2(+)/IL-31(+) cells also expressed an M2 macrophage marker, arginase-1, indicating that they were of the M2 phenotype. Depletion of macrophages with clodronate resulted in improvement of the scratching behavior and a decrease in dermal IL-31(+) macrophages. Skin lesions in the MC903-induced mouse AD model also featured increased expression of epidermal TSLP and dermal periostin. An ex vivo study showed that TSLP/periostin stimulated IL-31 generation from murine peritoneal macrophages. Consistent with these, blockade of TSLP and/or periostin significantly reduced the number of IL-31(+) macrophages, with attenuation of scratching behaviors. Itch in the MC903-induced mouse AD model appears to largely depend on IL-31 generation through the macrophage/TSLP/periostin axis rather than Th2 cells.

P01-07[C10-05]

Attenuation of DTH by oral tolerance depends on regulatory T cells in the sensitization phase

○Arisa Akagi[1], Akihiko Kitoh[2], Sho Hanakawa[2], Kenji Kabashima[1,2]
*[1]Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan, [2]Singapore Immunology Network and Skin Research Institute of Singapore, Agency for Science, Technology and Research (A*STAR), Singapore*

Background: Delayed-type hypersensitivity (DTH) can be attenuated by prior oral administration of the same antigen, which is called oral tolerance. Oral tolerance is thought to stem mainly from the induction of $Foxp3^+$ regulatory T cells (Tregs) in the gut-draining lymph nodes (dLNs).
Aim: To provide direct evidence whether and when (in the sensitization or elicitation phase) Tregs suppress DTH in orally tolerized mice.
Methods: Mice were fed with or without ovalbumin (OVA) for 5 days. Two days later, mice were sensitized intradermally with OVA emulsified in alum. Five days after sensitization, DTH was elicited by subcutaneous injection of OVA into the ear. Ear thickness was measured 24 h after elicitation.
Results: DTH responses to OVA were significantly attenuated in mice with prior feeding of OVA. This attenuation of DTH in OVA-fed mice was abrogated by in vivo depletion of Tregs. Given that Tregs can suppress DTH, potentially both in the sensitization and elicitation phases, we next examined the effect of OVA feeding on immune responses in these two phases of DTH separately. We isolated cells from dLNs of OVA-immunized skin in OVA-fed or water-fed mice, adoptively transferred the cells into naive mice, and assessed DTH responses in those recipient mice after challenge with OVA. Ear swelling after challenge was significantly attenuated in mice transferred with OVA-fed mice-derived cells compared to those transferred with water-fed mice-derived cells. By contrast, ear swelling after challenge with OVA was comparable in OVA-fed and water-fed mice transferred with cells from dLNs of OVA-immunized skin in water-fed donor mice.
Conclusion: Attenuation of DTH by oral tolerance depends on Treg-mediated immuno-suppression during sensitization.

P01-08[C10-06]

IL-10 production potency in peripheral blood B cells predicts prognosis of alopecia areata

○Yutaka Matsumura[1,2], Rei Watanabe[1], Yuumi Nakamura[1], Manabu Fujimoto[1]
[1]Department of Dermatology, Course of Integrated Medicine, Graduate School of Medicine, Osaka University, Osaka, Japan, [2]Department of Dermatology, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan

Interleukin-10 (IL-10)-producing regulatory B cells (Breg) take part in the restoration of immune-mediated inflammation. Their abnormalities in number or function are recognized in some autoimmune and inflammatory skin disorders. However, the involvement of Breg in alopecia areata (AA) remains unexplained. We compared IL-10 production from different B-cell fractions in the peripheral blood of 30 AA patients and 16 healthy controls (HC) by flow cytometry analysis. Then, IL-10 production in B cells in response to LPS and CpG was higher in AA than in HC (4.71 vs 1.93% in average, p=0.5300). The ratio of $CD19^+CD24^{hi}CD38^{hi}$ cells (24hi38hi), which include the main Breg fraction, was comparable between AA and HC (12.20 vs 10.56%, p=0.36). While this fraction showed high IL-10 production (3.25%) compared to $CD19^+CD24^{low}CD38^{mid}$ (24lo38md) and $CD19^+CD24^{hi}CD38^{low}$ (24hi38lo) fractions (1.64 and 1.98%, respectively) in HC, IL-10 was upregulated in all the three fractions in AA (5.82% in 24hi38hi, 4.52% in 24lo38md, 4.32% in 24hi38lo). When the patients with 50% or greater area of hair regrowth in one year were defined as responders (R, n=14) and the others as non-responders (NR, n=16) regardless of treatments, IL-10 production in B cells was higher in R than in NR (6.50 vs 3.15%, p=0.0069). Though IL-10 production in 24hi38hi was comparable (7.39 vs 4.45%, p=0.1033), IL-10 in the other two fractions was higher in R than in NR (24lo38md: 6.25 vs 3.01%, p=0.0136; 24hi38lo: 6.43 vs 2.47%, p=0.0009). These results suggest the increased potency of IL-10 production not only in 24hi38hi, the unique Breg fraction, but in wide range of B-cell fractions of AA, and this broad IL-10-producing capacity may contribute to the restoration of chronic inflammation.

P01-09[C10-07]

New epicutaneous sensitization model to protease antigen: itch-associated skin inflammation, a variety of Th subsets and IgE

○Tomoko Yoshimura[1,2], Toshiro Takai[1], Seiji Kamijo[1], Toru Kimitsu[1,2], Yurie Masutani[1,2], Takasuke Ogawa[2], Ko Okumura[1], Hideoki Ogawa[2], Shigaku Ikeda[1,2]
[1]Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine, [2]Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine

Background: Environmental allergen sources such as mites or Staphylococci contain or produce proteases. Here we establish a new murine model of epicutaneous (e.c.) sensitization to protease antigen, which shows itch-associated skin inflammation. Methods: Mice were e.c. administered with a model protease antigen, papain, which belongs to the same cysteine protease family with mite major group 1 allergens and Staphylococcus proteases, via ear skin that was treated with a detergent, sodium dodecyl sulfate (SDS) consecutively throughout the experiment. Skin inflammation, barrier dysfunction, itch, IgE production, and Th differentiation were analyzed. Results: The e.c. administration of papain to SDS-treated skin induced the responses including skin inflammation associated with itch and Th2/Th9/Th17/Th22 cytokine producing antigen-specific T cell differentiation. Non-protease antigens, protease inhibitor-treated papain and ovalbumin (OVA), showed less or no promotion of the responses except that protease inhibitor-treated papain showed Th2 differentiation equivalently with papain. Conclusions: The results suggest that protease activity and detergent-treated skin conditions synergistically promote itch-associated skin inflammation and various types of antigen-specific adaptive immunity. In the present model, the capacities to induce adaptive immune responses differ between the architecture of papain even without protease activity and OVA. Interestingly, the protease activity of papain was critical for induction of Th17/Th22 but was dispensable for Th2 in the model. The model could be useful for elucidation of mechanisms for e.c. sensitization and itch-associated skin inflammation induced by penetration of allergen source- or Staphylococci-derived proteases.

P01-10[C10-08]

Revisiting the dogma of contact dermatitis; even single hapten application can induce allergic contact dermatitis in situ

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Contact dermatitis is one of the most common skin disorders caused by chemical antigens called hapten and largely divided into irritant (non-allergic) and allergic ones. It is generally considered that the antigen-specific allergic contact dermatitis (ACD) is T cell-mediated and only occurs in the pre-sensitized individuals; however, we wondered whether T cells have any role even during the 1st contact to the antigen, or just prepared for the 2nd antigen challenge. To study this issue, we used a "single application" model and found that a significant ear swelling occurred at the hapten application site 6 days later. This "delayed" skin inflammation did not develop when the mice were pre-treated with T cell-depletion antibodies, suggesting T cell-dependent. We further demonstrated that the systemic sensitization to the hapten lasted only for 10 days, except for the hapten-applied sites. Based on these observations, we classified contact dermatitis in the following 3 phases; when hapten contacts on the skin, an antigen-nonspecific, transient ear swelling is induced within several hours and lasted for a few days (irritation phase). Around 6 days later, when the antigen-specific T cells increase in the body, antigen-specific systemic sensitization to the hapten is established (effector phase). At this time, T cell-mediated skin inflammation occurs at the hapten-applied sites. After that period, the mice become incapable of responding to the hapten, except for the hapten-applicated site (memory phase). Our study proposes a novel concept that antigen-specific ACD can occur even in the hapten-unexperienced individuals and provides essential knowledge for the better management of ACD patients.

P01-11[O07-01]

Chronological classification of alopecia areata based on PD-1 expression revealed by scRNA-seq analysis-assisted immunohistochemistry

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Alopecia areata (AA) is a common autoimmune disease of hair follicles impacting patients' psychosocial aspects with disfigured appearance. Treatments of AA are limited to non-specific immunosuppression and thus the development of a rationale-based treatment for AA is a substantial clinical demand. It has been shown that programmed cell death 1 (PD-1) was up-regulated in early lesion of AA in mice, suggesting that PD-1 involved in the pathogenesis of AA. Indeed, breach of PD-1/PD-1 ligand 1 (PD-L1) axis by nivolumab can induce AA as an immune-related adverse event. Herein, we analyzed PD-1 expression pattern in AA by utilizing a published single-cell RNA sequence (scRNA-seq) data set of an AA patient and immunohistochemistry of AA skin lesions. First, analysis of scRNA-seq revealed that PD-1 was expressed mainly in INFγ+, CXCR6+ Th1/Tc1 cells. Next, we devised pathological classification criteria of AA into acute and chronic phase with two indexes, i.e., (1) anagen/telogen ratio, an established marker reflecting disease course of AA, and (2) number of inflamed hair follicles, an indicator of disease activity. Then, immunohistochemistry revealed distinct characteristics between the acute and chronic phase of AA, that is, PD-1 was expressed in 0-30% of CD8+ T cells around hair follicles in acute and chronic phase of AA lesion. Our results clearly demonstrated that PD-1 was involved in pathogenesis of AA. We are currently analyzing PD-1 expressions on other T cells and PD-L1 expression on dendritic cells. This study will provide a basis for disease-specific immunotherapy of AA.

P01-12[O07-02]

Treating pemphigus vulgaris (PV) and foliaceus (PF) by inhibiting the neonatal Fc receptor: phase 2 open-label trial with efgartigimod

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Efgartigimod, an engineered Fc fragment that inhibits the activity of the neonatal Fc receptor (FcRn), was evaluated in an open-label phase 2 adaptive trial (NCT03334058). 34 mild to moderate PV and PF patients were enrolled to evaluate the safety, pharmacodynamics, pharmacokinetics, and efficacy of efgartigimod. In four sequential cohorts, efgartigimod was dosed at 10 or 25 mg/kg intravenously with various dosing frequencies, as monotherapy or add-on therapy to low-dose oral prednisone. Patients treated with efgartigimod had mostly mild to moderate adverse events balanced between doses. A strong correlation between serum IgG level reduction, anti-desmoglein (Dsg) autoantibody level reduction and improvement of pemphigus disease area index scores and clinical outcomes was observed throughout the trial. The median pharmacodynamic effects at day 29 following 4 weekly infusions were 62% and 66% reductions in total IgG at 10 and 25 mg/kg, respectively. A rapid clearance of anti-Dsg antibodies was observed, which reached a median 61% reduction from baseline for anti-Dsg-1 and 49% reduction for anti-Dsg-3 antibodies at the end of the induction phase. Disease control (DC) was achieved in 28 of 31 patients (90%) after a median time of 17 days. Six of eight patients who started efgartigimod monotherapy at baseline achieved DC. Complete clinical remission was achieved with prolonged maintenance therapy in 64% of patients (14/22 total; 5/7, 10 mg/kg; 9/15, 25 mg/kg) after a median time of 92 days in combination with corticosteroids (median daily dose 0.26 mg/kg, range 0.06-0.48). 14 relapses were reported in 11 patients who achieved DC (39%), with a median time to first relapse of 211 days. A phase 3 trial of efgartigimod in PV and PF (NCT04598451) is ongoing.

P01-13[O07-03]

Elucidating the role of CARD14 signaling in Type 2 immune response

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Background: Caspase activation and recruitment domain (CARD) are signaling molecules that mediate innate and adaptive immune responses. CARD14 signaling was demonstrated to be crucial for IL23/IL-17 pathway in psoriasis. However, whether CARD14 signaling is involved in other inflammatory skin conditions has been unclear. The identification of two heterozygous missense mutations in CARD14 in three patients with atopic dermatitis (AD) raised the question whether CARD14 is involved in the pathogenesis of type 2 immune diseases. Methods: Female mice of both C57BL/6J and Balb/c background expressing non-functional CARD 14 by removing part of exon 2 and 3 were challenged with various murine AD models, Calcipotriol (MC903) model, contact hypersensitivity model with repeated oxazolone application and murine dry skin model with acetone/ether/water mixture. In each model, we measured ear thickness, trans epidermal water loss and scratching behavior. The number of inflammatory cells populations and cytokines production were measured by flow cytometry. We measured changes in gene expression using qPCR. Results: Compared to age and sex matched littermate controls, there was no statistically significant difference in CARD14-/- mice response in any of the above-mentioned models. Conclusion: Throughout different murine AD models we could not demonstrate an essential role of CARD14 in type 2 immune response. However, no single murine AD models fully recapitulate the human AD. CARD14 might be involved in immune response to skin pathogens being downstream of various pattern recognition receptors thus can contribute to AD pathogenesis by facilitating recurrent skin infections. To validate this hypothesis, we are currently challenging CARD14-/- mice with various skin infection models.

P01-14[O07-04]

The effect of topical 5-azacytidine in irritant and allergic contact dermatitis

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DNA methylation is one of major epigenetic mechanisms by which regulate a panel of gene expressions. An old but a revisiting compound, 5-azacytidine, is a pyrimidine nucleoside analog of cytidine that can inhibit DNA methyltransferase, induce cell differentiation, and has direct cytotoxicity on abnormal bone marrow hematopoietic cells. Thus, systemic administration of 5-azacytidine has been approved for the treatment of myelodysplastic syndrome and acute myeloid leukemia. However, the effect of topical 5-azacytidine on skin inflammation is largely unknown. To this end, we utilized croton oil (CrO)-induced irritant contact dermatitis (ICD) model and 2,4-dinitrofluorobenzene (DNFB)-induced allergic contact dermatitis (ACD) model. At day -1, vehicle or 1 mg of 5-azacytidine solution was applied to each ear. At day 0, 1% CrO was applied to both ear, and ear thickness was measured over time. Interestingly, the ear swelling response to CrO in 5-azacytidine-treated ear was significantly increased and prolonged compared with that of vehicle-treated ear. In DNFB-induced ACD model, topical application of 1 mg of 5-azacytidine solution to the abdomen one day before the sensitization with 0.5% DNFB did not alter following ear swelling. In sharp contrast, topical application of 1 mg of 5-azacytidine solution to the ear of 0.5% DNFB-sensitized mice one day before the elicitation with 0.2% DNFB significantly decreased ear swelling compared with that of vehicle applied ear. These data suggest that topical 5-azacytidine differently influences ICD and ACD as well as sensitization phase and elicitation phase of ACD. Topical 5-azacytidine must modify a bunch of gene and protein expressions. However, it could be a therapeutic option of ACD.

P01-15[O07-05]

Molecular mechanisms of mucosal mast cell differentiation

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Mast cells are classified into two groups: connective tissue type and mucosal tissue type. Whereas there are only a few mucosal mast cells (MMCs) in normal mucosal tissues, MMCs are abundant in inflamed mucosa. The MMC hyperplasia plays a key role in allergic inflammation in the mucosa. Thus, mucosal inflammation can be attenuated by inhibiting the expansion of MMC numbers. However, the mechanism of MMC differentiation is unclear. Here, we show that the differentiation of mouse MMCs is promoted by interdependent action of Notch and TGF-β signaling. First, we confirmed that Notch ligands or TGF-β differentiate mouse bone marrow-derived mast cells, which exhibit an immature phenotype of mast cells, into mature MMC-like cells, which express MMC markers mouse mast cell protease (mMCP)-1, mMCP-2, and αE integrin (CD103). We next found that the MMC marker expression was dramatically enhanced in the presence of both Notch ligands and TGF-β. Interestingly, Notch signaling-mediated MMC marker expression was suppressed by a TGF-β signaling inhibitor, and TGF-β signaling-mediated marker expression was suppressed by a Notch signaling inhibitor. These results indicate that Notch and TGF-β signaling act synergistically and interdependently to induce the differentiation of MMCs. Finally, we elucidated that Notch signaling upregulated the expression of MMC marker genes through epigenetic deregulation of the promoter regions of these genes and promotion of the nuclear localization of TGF-β signaling transducer Smad4. These mechanisms may contribute to the rapid expansion of MMC numbers during allergic mucosal inflammation.

P01-16[O07-06]

iSALT structures in B-cell type pseudolymphoma and their potential for local plasmacytoid differentiation in the skin

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Cutaneous pseudolymphoma (CPL) is a heterogeneous group of benign skin disorders that simulate cutaneous lymphomas clinically and histologically. Among them, cutaneous B cell pseudolymphoma (CBPL) represents reactive B cell proliferation in response to antigenic stimuli. In previous reports, the lymphoid follicles accompanied by B cell proliferation often include plasmacytoid differentiation. However, it remains unknown what the plasmacytoid differentiation of CBPL is based on. We conducted immunohistochemical analysis of the lesions which exhibited CBPL and CBPL-like follicles histologically considering the spatial distribution of lymphocytes. We detected inducible skin-associated lymphoid tissue (iSALT) structures that we reported previously. We also revealed that CD19+/IgD+/CD27-, IRF4+/CD38+, IRF4+/CD138+, BCL6+, CD21+, KI67+, or IgG-positive cells in the reactive follicles. Further analysis revealed that AID is positively stained in CD19+/CD27-/IgD- cells in the follicles. These spatial staining pattern mimicked those of lymph nodes. The spatial distribution of cells required to plasmacytoid differentiation existed in the reactive follicles in the lesion. These findings suggest the possibility of local B cell differentiation and possible plasmacytoid differentiation in the lesion of CBPL and CBPL-like follicles.

P01-17[O07-07]

Hyaluronan regulates murine irritant contact dermatitis model via Langerhans cell activation

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Although spongiosis is a hallmark of allergic contact dermatitis (ACD), it is known that irritant contact dermatitis (ICD) also induce spongiosis in the epidermis. We have shown that the expression of hyaluronan synthase 3 (HAS3) mRNA increases in the spongiotic dermatitis in association with decrease in E-cadherin, leading to spongiosis by accumulation of hyaluronan in the intercellular spaces in epidermis (Ohtani T, et al. J Invest Dermatol. 2009). To explore the role of hyaluronan in ICD, we examined the mRNA expression of HAS1, HAS2, and HAS3 in the epidermis of an ICD mouse model 24 hours after the application of 1-fluoro-2,4-dinitrobenzene (DNFB) once to the ear. In this ICD model, epidermal HAS3 and HAS2 mRNA expression were increased, while HAS1 mRNA expression was not detected. Histochemical staining with hyaluronan-binding protein (HABP) confirmed hyaluronan deposition in the epidermis. When ICD was induced in $Has3^{-/-}$ mice, the accumulation of hyaluronan in the epidermis was still detected. In contrast, when ICD was induced in $HAS3^{-/-}HAS2^{f/f}$K5 Cre mice, which lacks HAS3 in whole body and HAS2 in epidermis, there was no accumulation of hyaluronan in the epidermis. Moreover, ear swelling after DNFB painting was significantly reduced compared with that in wild type (WT) mice. We further revealed the induction of Ia antigen by Langerhans cells after DNFB painting was less pronounced in $HAS3^{-/-}HAS2^{f/f}$K5Cre mice. These results suggest that ICD induced epidermal hyaluronan deposition synthesized by HAS2 and HAS3, which causes Langerhans cell activation in ICD.

P01-18[O07-08]

A possible niche for B-cell development in the skin in primary cutaneous plasmacytosis suggesting the presence of a functional unit as iSALT

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Primary cutaneous plasmacytosis (PCP) is a rare skin disease, which is described by the infiltration of plasma cells in the dermis frequently accompanied with well-developed lymphoid follicles and compartmentalized T-cell zones. Such structures of PCP lesions resemble tertiary lymphoid structures (TLS) which we proposed as inducible skin-associated lymphoid tissue (iSALT) in humans. However, it is not fully addressed if B-cell differentiation towards plasma cells occurs within such skin lesions. We previously reported that lymphoid follicles in some human skin diseases harbored the cellular components corresponding to TLS. This study aimed to immunohistochemically assess if the lymphoid follicles of PCP harbor the characteristics of TLS, and if B-cell lineage cells at various developmental stage exist. Histopathological analyses were performed with three cases of PCP. Lymphoid follicles of PCP lesions comprised of demarcated B-cell zone encompassing follicular dendritic cells. The B-cell zone was lined with CXCL13 expressing fibroblast-like cells and surrounded by T-cell zones where peripheral node addressin-positive blood vessels, suggestive of high endothelial venules, were developed. The distribution pattern of resting B-cells, activated B-cells, plasmablasts and plasma cells were comparable with that of lymph nodes. Our data showed that these structures of lymphoid follicles in PCP were identical to those of TLS in the skin. The presence of various developmental B-cell stages indicated PCP lesion provided a niche for the locally differentiating B-cells towards IgG-expressing plasma cells.

P01-19[O07-09]

Optimal methods for human skin T-cell analysis

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Background: Tissue-resident memory T (T_{RM}) cells reside in peripheral tissues, including the skin. In humans, T_{RM} cells exist in both the epidermis and dermis, but their composition, phenotype, and function are not fully elucidated. To analyze T cells in both the epidermis and dermis, the skin needs to be incubated with Dispase II to separate the two layers. The next step varies among researchers; the subsequent enzymatic digestion of epidermis and dermis is popular, whereas the spontaneous migration method can also be done. **Objective:** This study aimed to determine the strengths and limitations of the enzymatic digestion method and spontaneous migration method. **Methods:** Healthy, non-inflamed human skin was incubated with Dispase II to separate the epidermal and dermal sheets, which were subject to either subsequent enzymatic digestion or floated on a medium to obtain emigrants. **Results:** An enzyme combination of Dispase II and collagenases, but not collagenase alone, cleaved CD4, CD8, and CD69 on skin T cells. The spontaneous migration method lost ～20% of T cells in the floating sheets. However, there was no significant bias with regard to CD103 expression between emigrants and remaining T cells in the sheets. Through the spontaneous migration method, it was determined that there were 10^4 and 10^5 $CD3^+$ T cells per 1 cm^2 of epidermis and dermis, respectively. **Conclusions:** The spontaneous migration method might be useful for skin T-cell analysis.

P01-20[O07-10]

Differentially expressed circulating exosomal microRNAs as biomarkers for disease severity in psoriasis patients

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Several kinds of literature have reported the association between the disease activity of systemic inflammatory diseases and circulating exosomal microRNA(miRNA)s. miRNA is previously known to be associated with hyperproliferation of keratinocytes and abnormal immune activation in psoriasis. Therefore, we aimed to reveal the possible relationship between circulating exosomal miRNAs and the disease severity of psoriasis. We classified psoriasis patients into groups based on psoriasis area and severity index (PASI) score. Plasma samples were collected from 10 patients in the discovery phase, and 15 patients in the validation phase based on Ajou University Hospital Psoriasis Cohort from May 2016 to March 2021. We performed next-generation RNA sequencing to identify 9 upregulated and 10 downregulated exosomal miRNAs that were differentially expressed between the groups. Also, we were able to identify specific circulating exosomal miRNAs in which the expression levels were disease activity-dependent. miR-4488 was upregulated, while miR-5698 and miR-1255b-p were downregulated in severe group patients. Especially, miR-4488 significantly correlated with other clinical disease activity assessment scores. Thus, we believe that the miRNAs may serve as an objective biomarker for psoriasis disease activity.

P01-21[O07-11]

Anti-inflammation effects of decanoic acid in a mouse of contact hypersensitivity: on a possible new drug for inflammatory skin disease

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Decanoic acid is used as an additive in injections to prolong the action of drugs because of its lipid solubility. In addition, decanoic acid has been speculated to have anti-inflammatory effects. In this study, we examined its anti-inflammatory effects on a mouse model of dinitrofluorobenzene (DNFB)-induced irritant contact dermatitis. Mice were divided into four treatment groups. In Groups 1, mice were challenged with a twice application of 50 µl of 0.5% DNFB on the abdomen for sensitization. Then, mice were challenged once on both ears with 20 µL of 0.5% DNFB to induce skin inflammation. In Group 2, mice were further treated with a single application of decanoic acid ointment in volume of 0.05 g surface of each ear 30 min later after challenge. In Group 3, mice were further treated with a single application of veseline ointment instead of decanoic acid ointment in Group 2. In Group 4, mice were served as a control and 50 µl of acetone was applied on the abdomen. Then 20 µl of acetone was applied single to each ear. Ear thickness was measured at 0, 4, 8, 24, 48, 72 and 96 hours after ear challenge. In group 2 mice showed less ear thickness than in groups 1 and 3 mice (after DNFB challenge 72h: Group 1, 515.00±30.68 µm, Group2, 395.67±11.26 µm, Group3, 435.14±11.26 µm, 96h: Group1, 607.67±73.23 µm, Group2, 426.50±26.67 µm, Group3, 568.71±7.70 µm.). These results suggest that decanoic acid ointment may have a therapeutic effect on inflammatory skin diseases.

P02-01[II-2]

Autoantigen-specific B cells targeted single-cell RNA-seq reveals the functional heterogeneity in pemphigus patients

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In contrast to other autoimmune diseases, identification of well-defined autoantigens, desmoglein (Dsg) 1 and 3, in pemphigus give us deeper understanding of B cell mediated autoimmunity with antigen specificity. Although only a few Dsg-specific B cells were obtained from patients, we analyzed the characteristics of these autoantigen-specific B cells using a single-cell technique. Fluorescent labeled Dsg protein enabled to detect Dsg-specific memory B cells in patient's peripheral blood. Detected proportion of Dsg-specific memory B cells were correlated with serum anti-Dsg antibody titer in pemphigus peripheral blood (Dsg1: R^2=0.39, P=0.012, Dsg3: R^2=0.27 P=0.049). Among 3 patients, total 92 Dsg-specific B cells and 115 non-Dsg-specific B cells were single cell sorted and performed single cell RNA-seq analysis. Of 10518 detected genes, 253 genes were identified as statistically differentially expressed genes (DEGs). These gene expressions were heterogeneity among Dsg-specific B cells, even if they shared the same antigen specificity. Detected DEGs included genes associated with inflammation (S100A8/A9, CCL3), differentiation (TIMP1, BATF), or T-cell interactions (TNFSF9). These genes did not overlap with the DEGs detected in influenza HA1 (foreign antigen) -specific B cells, suggesting the specific gene expression of autoantigen-specific B cells. Time-course analysis of Dsg1-specific B cells before and after treatment in a pemphigus foliaceus patient revealed suppression of several genes related with B cell activation pathways (MAP3K1, CD70) while those suppression were not seen in non-Dsg1-specific B cells. Our approach may clarify how each treatment affects pathogenic B cells, leading to discovery of novel therapeutic targets in autoimmune diseases.

P02-02[I-5]

Abnormally activated B cells with TLR9 up-regulation in Fli1-depleted mice: a possible predisposing condition for systemic sclerosis

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Systemic sclerosis (SSc) is an autoimmune disease characterized by vasculopathy and organ fibrosis, occurring subsequent to systemic inflammation. So far, we have revealed that the deficiency of transcription factor Fli1 in mice induces various SSc-like phenotypes. Nowadays, this finding is reinforced by a notable research showing the association among extended repeat alleles of *FLI1* $(GA)_n$ microsatellite, lower *FLI1* mRNA levels and susceptibility to human SSc. Besides, our facility demonstrated the efficacy of B cell depletion therapy using rituximab for dermal and pulmonary fibrosis of SSc. Thus, Fli1-deficient B cells may have a key role in SSc.
Splenic B cells of Fli1-depleted mice produced more interleukin-6 (IL-6) than those of wild-type mice under bleomycin treatment *in vivo* or CpG stimulation *in vitro*. Flow cytometry analysis revealed that $CD21^{neg\sim mid}CD23^-$ B cells were increased in Fli1-depleted splenocytes. Though this fraction generally consists mainly of $CD93^+$ immature cells, the increased cells in Fli1-depleted mice were $CD19^{high}CD93^-CD43^+$ activated B cells. Importantly, these aberrant cells expressed IgM^{low}, IgD^{high} and toll-like receptor (TLR) 9^{high}, suggesting an autoimmune inflammatory phenotype. Of note, they were also increased in bone marrow (BM). Additionally, TLR9 was upregulated in Fli1-depleted pre-B cells in BM prior to the upregulation of CD19, suggesting that excessive TLR9 upregulation occurred in the early stage of B cell differentiation. Taken together, these results indicate that Fli1 deficiency spontaneously induces early TLR9 upregulation and chronic activation in B cells through aberrant differentiation. Given the significance of TLR9 upregulation in SSc immune cells, Fli1 deficiency contributes to inducing an SSc-like property in B cells.

P02-03[C04-01]

Blockade of CD122 on skin resident memory T cells suppresses the development of mucocutaneous graft-versus-host disease

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The presence of antigens stimulates naïve T cells to differentiate into effector and memory T cells, and resident memory T (T_{RM}) cells reside permanently in organ tissues. The involvement of T_{RM} cells has been demonstrated in the pathological conditions of various skin diseases, such as psoriasis, fixed drug eruption and vitiligo. CD122, which is the ß chain subunit of interleukin (IL)-2 and IL-15 receptors, is expressed in immune cells including T_{RM}. Here we investigated whether CD122 signaling on skin $CD8^+T_{RM}$ mediates the development of mucocutaneous graft-versus-host disease (GVHD). In our murine model of mucocutaneous GVHD, a mouse expressing chicken ovalbumin (OVA) on the membrane of epidermal keratinocytes (K14-mOVA mouse) develops acute GVHD-like erosive mucocutaneous disease, and subsequently chronic GVHD-like sclerodermatous skin disease, after a transfer of OVA-specific T cell-receptor transgenic $CD8^+$T cells (OT-I cells). We found that the ratios of $CD103^+CD69^+$ epidermal and $CD103^-CD69^+$ dermal TRM-phenotypes OT-I cells, on which the expression of CD122 was upregulated, were increased along the time axis in the skin of OT-I cell-transferred K14-mOVA mice. K14-mOVA mice were administered with an anti-CD122 blocking antibody (ChMBC7), which blocks IL-2 and IL-15 to bind to memory T cells stronger than to effector T cells, 7 days after a transfer of OT-I cells. Blockade of CD122 reduced the total skin-infiltrating OT-I cells, especially epidermal T_{RM}-phenotype OT-I cells. Anti-CD122 antibody-treated mice developed milder acute/chronic GVHD-like mucocutaneous diseases than control antibody-treated mice. Collectively, skin T_{RM} mediated the development of mucocutaneous GVHD, and blockade of CD122 may be an effective treatment strategy for mucocutaneous GVHD.

P02-04[O12-07]

IFN-γ signaling has both pro-inflammatory and immunoregulatory roles depending on the cell types in interface dermatitis in mouse

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IFN-γ is an effector cytokine of cell-mediated immunity that plays pivotal roles in most immune responses. We have previously established Dsg3 specific-dermatitis model. Adoptive transfer of Dsg3-specific TCR transgenic (H1) $CD4^+$ T cells into *Rag2*$^{-/-}$ mice resulted in T cell infiltration into the epidermis and induced interface dermatitis. Furthermore, *Ifng*$^{-/-}$ H1 T cells do not cause interface dermatitis when transferred into *Rag2*$^{-/-}$ mice, indicating that IFN-γ produced by H1 T cells plays an important role. In this study, we used IFN-γ receptor (Ifngra)$^{-/-}$ mice to investigate the roles of IFN-γ signaling in the dermatitis. Naive *Ifngra*$^{-/-}$ $CD4^+$ T cells stimulated with anti-CD3 and anti-CD28 antibodies and IL-12 showed poor Th1 differentiation compared to WT T cells *in vitro* (6.7 ± 0.79% vs 1.2 ± 0.35%, P=0.002). In addition, adoptive transfer of *Ifngra*$^{-/-}$-H1 T cells to *Rag2*$^{-/-}$ did not cause dermatitis. In contrast, when H1 T cells were transferred into *Ifngra*$^{-/-}$-*Rag2*$^{-/-}$ mice (n=3), dermatitis appeared earlier with more severe phenotype than when *Rag2*$^{-/-}$ mice were used as recipients (n=3) (clinical score, 22 ± 2.9% vs. 4 ± 1.3%, P=0.01). Flow cytometry analysis showed higher proportion of IL-17a-producing H1 T cells in the skin-draining lymph nodes of *Ifngra*$^{-/-}$-*Rag2*$^{-/-}$ recipients than in *Rag2*$^{-/-}$ recipients (72 ± 0.65% vs 21 ± 0.56%, P=0.01), although there were no differences in Th1, Th2 or iTreg. These results indicate that IFN-γ signaling of H1 T cells is essential for the induction of interface dermatitis, while in non-T and B cell populations IFN-γ signaling functions as immunoregulatory, especially efficient to suppress Th17 responses. Thus, IFN-γ signaling can exert not only pro-inflammatory but also anti-inflammatory effects, depending on cell types that accept the signal.

P02-05[O12-08]

IL-9 promotes skin inflammation via Pyy in imiquimod-induced psoriasis-like dermatitis

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Several studies have demonstrated that IL-9 plays a role in the pathogenesis of psoriasis. However, IL-9-related mechanism is still unclear. The aim of this study is to elucidate the role of IL-9 in imiquimod (IMQ)-induced psoriasis-like dermatitis. The score of dermatitis and histopathological changes were assessed. First, we found that IL-9 expressed on mast cells and IL-9 receptor (IL-9R) expression increased in the IMQ-induced skin lesions of wild-type (WT) C57BL6 mice. IL-9 intradermal injection into IMQ-induced skin lesions significantly exacerbated the severity of dermatitis with increased epidermal thickness and mast cells infiltration compared to PBS injection. In contrast, the administration of neutralizing IL-9 antibody attenuated the severity of dermatitis and decreased mast cell infiltration. To further investigate the role of IL-9 in keratinocytes, we established the keratinocyte-specific IL-9 receptor α-chain knockout mice ($K14^{CRE/ERT}$ $IL\text{-}9R^{fl/fl}$ mice, IL-9R cKO mice when treated with tamoxifen). IL-9R cKO mice significantly attenuated the severity of IMQ-induced dermatitis with reduction of epidermal thickening and mast cell number compared to control mice. Interestingly, the results of transcriptome analyses showed that peptide tyrosine-tyrosine (Pyy), a member of the neuropeptide Y family, decreased in the epidermis of IL-9R cKO mice. Moreover, blockade of Pyy ameliorated the severity of IMQ-induced dermatitis and decreased mast cell infiltration in WT mice. In vitro, bone marrow-derived mast cells increased IL-9 production under Pyy stimulation. These results indicate that the interaction between keratinocytes and mast cells is involved in the exacerbation of psoriasis-like dermatitis via the IL-9/Pyy axis.

P02-06[C04-02]

Activation of TNF/NF-κB signaling by linear ubiquitination specifically exacerbates a murine imiquimod-induced psoriasis model

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Tumor necrosis factor (TNF) is important in inflammatory skin diseases, including contact dermatitis (Th1 inflammation), atopic dermatitis (Th2 inflammation), and psoriasis (Th17 inflammation). In fact, molecularly targeted drugs against TNF have been demonstrated to be effective in skin diseases such as psoriasis. TNF has two major molecular biological actions: activation of NF-κB and induction of cell death. Recently, the linear ubiquitination by linear ubiquitin chain assembly complex (LUBAC), which consists of HOIL-1L, HOIP and SHARPIN, is essential for TNF activation/NF-κB signaling. It has been demonstrated that HOIP activates TNF/NF-κB signaling, while HOIL-1L inhibits TNF/NF-κB signaling. In this study, to investigate the importance of TNF/NF-κB signaling in skin diseases, we used mice lacking the RING1 domain, the active site of HOIL-1 (HOIL1ΔRING1 mice). In these mice, HOIL-1 is suppressed and TNF/NF-κB signaling is enhanced. HOIL1ΔRING1 mice did not differ from wild-type mice in either a DNFB-induced contact dermatitis model or an MC903-induced atopic dermatitis model. On the other hand, in the imiquimod-induced psoriasis model, HOIL1ΔRING1 mice showed more severe clinical manifestations than wild-type mice. To examine whether TNF/NF-κB signaling is important in immune cells or in the radio-resistant cells, such as stromal cells of the skin, we generated HOIL1ΔRING1 bone barrow chimeric mice, and found that TNF/NF-κB signaling is important in skin stromal cells. These results indicate that TNF/NF-κB signaling in stromal cells is important for the pathogenesis in psoriasis and inhibitors of TNF/NF-κB signaling targeting stromal cells may be a new therapeutic target for drug discovery in psoriasis.

P02-07[C04-03]

Possible involvement of IL-22-producing $CD8^+CD103^+$ T cells in the epidermal hyperplasia of atopic dermatitis

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Epidermal hyperplasia is one of the histological hallmarks of atopic dermatitis (AD), a chronic inflammatory skin disease mainly caused by type 2 cytokines including (IL)-4/IL-13. Th17 cytokines such as IL-17A and IL-22 are also produced in AD lesions. Among these cytokines, IL-22 is suggested to be involved in epidermal hyperplasia in AD. It has been reported that $CD103^+$ T cells, which include resident memory T cells and activated effector T cells, are abundant in the AD lesions. However, it remains unknown how $CD103^+$ T cells are involved in epidermal hyperplasia. To investigate the involvement of $CD103^+$ T cells in epidermal hyperplasia in AD, we collected skin biopsy samples from 21 AD patients, and performed a histological analysis for the evaluation of epidermal hyperplasia and localization of $CD103^+$ T cells. We also performed a flow cytometric analysis of cytokine production (IL-4, IL-5, IL-13, IL-17A, IL-22) from $CD103^+$ T cell in the biopsy samples after expanding them in vitro using anti-CD3/CD28 mAb and IL-2. Then, we analyzed the relation between epidermal hyperplasia and the cytokine-producing ability of $CD103^+$ T cells or localization of them in the skin. We found a significant correlation between epidermal thickness and the percentage of $IL\text{-}22^+CD8^+CD103^+$ T cells, not $IL\text{-}22^+CD8^+CD103^-$ T cells, $IL\text{-}22^+CD4^+CD103^+$ T cells, and $IL\text{-}22^+CD4^+CD103^-$ T cells. Significant correlation was also observed between epidermal thickness and the percentage of $IL\text{-}13^+$ or $IL\text{-}17A^+$ $CD8^+CD103^+$ T cells. Histologically, $CD8^+$ $CD103^+$ T cells were observed in both epidermis and dermis, and epidermal thickness was correlated with the number of dermal $CD8^+CD103^+$ T cells. These results suggest the importance of $IL\text{-}22^+CD8^+CD103^+$ T cells in the epidermal hyperplasia in AD lesions.

P02-08[C04-04]

The role of FcγRIIB in a murine bleomycin-induced scleroderma model

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Background: Systemic sclerosis (SSc) is a systemic autoimmune disease that is characterized by excessive fibrosis. FcγRIIB is a low-affinity receptor for the Fc fragment of IgG. FcγRIIB is expressed on the surface of several leukocyte subsets and functions in negative feedback pathways to down-regulate B cell antigen receptor signaling. Objective: The aim of the present study was to investigate the role of FcγRIIB in the development of a murine bleomycin-induced scleroderma model. Methods: An experimental fibrosis model was generated by the subcutaneous injection of bleomycin into wild-type (WT) and FcγRIIB-deficient (FcγRIIB-/-) mice. Skin and lung fibrosis, and inflammatory cell infiltration were histologically assessed. Cytokine and chemokine expression levels were measured by real-time polymerase chain reaction. Results: The severity of fibrosis in the skin and lungs was significantly greater in bleomycin-treated FcγRIIB-/- mice than in bleomycin-treated WT mice. In the skin of bleomycin-treated mice, the numbers of CD8+ T cells, F4/80+ macrophages, MPO+ neutrophils, NK1.1+NK cells, and B 220+ B cells were significantly higher in FcγRIIB-/- mice than in WT mice. The expression levels of TNF-α, IL-1β, ICAM-1, CXCL2, and CCL3 in affected skin were significantly higher in FcγRIIB-/- mice than in WT mice. Adoptive transfer of splenic leukocytes from FcγRIIB-/- mice into WT mice resulted in exacerbated skin and lung fibrosis compared with WT mice without adoptive transfer. Conclusion: This study suggested that FcγRIIB plays an inhibitory role in skin and lung fibrosis. Moreover, signal regulation through FcγRIIB has potential as a therapeutic approach for SSc.

P02-09[C04-05]

Serine protease inhibitor A3n, an endogenous granzyme B inhibitor, alleviates graft-versus-host disease reaction in human skin

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[Background] Previous reports investigating skin biopsy samples of patients with cutaneous graft-versus-host disease (GVHD) suggested that granzyme B, one of cytotoxic factors produced in CD8 T cells, might mediate cutaneous GVHD reaction presenting interface dermatitis (IFD)/ lichenoid tissue reaction (LTR) histopathologically. Additionally, our previous report using a modified murine model of cutaneous GVHD-like dermatitis showed that granzyme B not only induces keratinocyte death in IFD/LTR, but also mediated infiltration of cytotoxic T cell into the epidermis. [Methods] We established a model of cutaneous GVHD reaction in a transplanted human skin tissue on a NSG mouse with an intravenous injection of allogenic human T cells, which were stimulated with anti-CD3/CD28 stimulating antibodies, interleukin (IL)-2, IL-7 and IL-15 beforehand. The mouse was intravenously administrated with a recombinant protein for serine protease inhibitor A3n (SERPINA3n), an endogenous factor inhibiting granzyme B activity. [Results] Flow cytometric analyses revealed that the stimulated human T cells were activated with production of granzyme B. In the human skin tissues on the NSG mice with a transfer of the activated allogenic T cells, IFD/LTR, which was characterized by dyskeratotic keratinocytes with dermal infiltrating of inflammatory cells, was observed constantly. The cutaneous GVHD reaction presenting IFD was milder on SERPINA3n-treated mice than controls, with reduced numbers of dyskeratotic cells in independent 2 experiments (0 and 0.25 cells/mm2, and 0.22 and 1 cells/mm2). [Conclusion] Granzyme B would be important for the development of cutaneous GVHD reaction in human skin.

P02-10[C04-06]

Occurrence of immune reconstitution inflammatory syndrome can be predicted by cytokine profiles in DPP-4i-associated bullous pemphigoid

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Immune reconstitution inflammatory syndrome (IRIS) is characterized by a paradoxical deterioration of clinical symptoms suggestive of infectious disease associated with recovery of immune responses after reduction or discontinuation of immunosuppressive agents. We have recently demonstrated that dipeptidyl peptidase-4 inhibitors-associated bullous pemphigoid (DPP-4i-BP) represents a manifestation of IRIS and that the outcome of DPP 4i-BP can be determined by the magnitude of rapid immune cell recovery after DPP-4i cessation. However, some patients spontaneously resolved while other patients developed two types of IRIS, either infectious or autoimmune (J Am Acad Dermatol, in press). Although the occurrence of IRIS has usually been evaluated by expansions of immune cells, we asked whether measurements of many serum cytokine/chemokines before and after DPP-4i cessation could predict disease progression to IRIS. In total, eleven patients with DPP-4i-BP were included. Here, we demonstrate that patients with DPP-4i-BP who achieved spontaneous resolution after DPP-4i cessation showed no significant increase in any cytokine/chemokine levels while those with IRIS showed a significant increase in IFN-α, IFN-γ, IL-10, IL-6 and IP-10 after DPP-4i cessation. These changes in cytokine/chemokine levels after DPP-4i cessation occurred before administration of immunosuppressive agents. The results of our small cohorts indicate that DPP-4i-BP patients can be managed depending on changes in cytokine/chemokine levels after DPP-4i cessation. In conclusion, we confirmed that the combined detection of an increase in IFN-α, IFN-γ, IL-6, IL-10 and IP-10 levels using serum cytokine/chemokine assay showed a good performance in immunologically confirming IRIS.

P02-11[C04-07]

Persistent dermatitis resulted in the gastro-intestinal amyloidosis, reduced absorption of nutrients, and hypoalbuminemia

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The detailed mechanism of emaciation in inflammatory skin condition has not been elucidated so far, nor the therapeutic efficacy to emaciation is also unknown. Using dermatitis model mouse, we investigated the pathophysiology of emaciation in inflammatory skin condition and the medication for emaciation. We employed spontaneous skin inflammatory model mice overexpressing human caspase-1 in the epidermal keratinocyte. Nutrition level was examined in the serum, and the gastrointestinal tract was histologically and functionally investigated. Feces were collected and α1-antitrypsin in concentration was measured. FITC-dextran in blood was also measured. Inflammatory skin model mice showed a marked decrease in serum albumin level. The amyloid deposition was detected in the gastrointestinal tract. The α1-antitrypsin in feces was abundantly detected in dermatitis model, and FITC-dextran was undetected in blood. The serum amyloid A1 was detected in the gastro-intestinal tract. We will also present the effect of IL-17A deletion, the administration of neutralizing antibodies against TNF-α and IL-α/β, and Janus kinase (JAK) inhibitors for amyloidosis. In the persistent dermatitis model, amyloidosis was detected probably due to the large amounts of inflammatory cytokines produced in the inflamed skin, inducing amyloid production in the liver and deposition in gastrointestinal tract, resulting in the nutritional deficiency. The active control of skin inflammation may be useful for preventing amyloidosis.

P02-12[O12-09]

Periostin may act on monocytes to be differentiated into macrophages with fibrotic phenotype in patients with systemic sclerosis

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Recent studies have implicated monocytes/macrophages play important roles in the pathogenesis of systemic sclerosis (SSc). We have previously reported levels of circulating periostin were increased in SSc, and it was positively correlated with modified Rodnan's total skin thickness score (mRSS). Therefore, we focused on the effect of periostin on monocytes to see whether it affects on differentiation of monocyte-derived macrophages (MDMs). Monocytes were purified from blood samples which were obtained from 9 dcSSc patients and 5 healthy controls, and were differentiated into macrophages. Flow cytometry analysis confirmed increased proportion of CD68+CD163+ and CD68+CD206+ cells from SSc patients compared with those from healthy controls. The mRSS was positively correlated with the proportion of CD80-CD206+ cells. Next, monocytes were differentiated under recombinant periostin (rPeri) stimulation and mRNA expression levels of SSc-related profibrotic factors were determined in MDMs. Expressions of TGFβ, TNFα, and IL-6 were increased in rPeri-stimulated MDM1 than those of controls. Higher αSMA, FN1, and EGR1 expressions were found in rPeri-stimulated MDM2, indicating that periostin may induce macrophages with fibrotic phenotype regardless M1/M2. Similar tendency on induction of profibrotic factors by rPeri was confirmed in SSc-derived MDMs. Interestingly, IRF8, a transcriptional factor which was known to be downregulated in SSc monocytes, was upregulated in rPeri-MDMs from healthy subjects, but tended to be downregulated in those from SSc patients, indicating that the response to periostin may be different in monocytes from healthy individuals and SSc patients. In conclusion, periostin may be involved in the pathogenesis of SSc by influencing on macrophage differentiation.

P02-13[O12-10]

Apremilast downregulates IL-17 production and induces splenic regulatory B and T cells in imiquimod-induced psoriasis

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Background: Apremilast, a selective inhibitor of the enzyme phosphodiesterase 4, is efficacious for psoriasis. However, detailed in vivo effects of apremilast on psoriasis remain to be elucidated.
Purpose: To examine the *in vivo* effects of apremilast on psoriasis.
Method: Psoriasiform dermatitis was induced by applying imiquimod (IMQ) on the murine shaved back skin for six days. Mice were treated with apremilast or vehicle intraperitoneally daily.
Results: Apremilast alleviated IMQ-induced psoriasiform dermatitis clinically and pathologically on days 3 to 6 by reducing infiltration of antigen-presenting cells and interleukin (IL)-17A-positive cells and increasing infiltration of Foxp3-postive cells into the skin on day 6. In addition, apremilast reduced mRNA expression of IL-17A, IL-17F, and IL-22 in the skin on day 2, and decreased IL-17A-producing γδ T cells in the dermis on day 6. Furthermore, apremilast induced regulatory T cells and regulatory B cells in the spleen but not in the draining lymph nodes.
Conclusion: In conclusion, apremilast downregulated IL-17 production and induced splenic regulatory B cells and regulatory T cells in an IMQ-induced psoriasiform dermatitis mouse model.

P02-14[O12-11]

Withdrawn

P02-15[O12-12]

Establishment of nail psoriasis mouse model by topical application of imiquimod

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The application of imiquimod (IMQ) on mouse skin can induce psoriasis-like skin inflammation, and it is now widely used as a psoriasis mouse model. We hypothesized that IMQ application on mouse nail induce inflamed nail lesions and can serve as a model of nail psoriasis. Male BALB/c mice were smeared IMQ for seven days after nail removal or without nail removal. Compared with the control group, pathological changes of nail lesions in the nail removal group, including neutrophils in the nail bed epithelium, hyperkeratosis with parakeratosis, serum-like proteinaceous exudates within the horny layer, focal change in the granular layer and psoriasiform hyperplasia of the nail bed epithelium, are similar to the typical phenotype of human nail psoriasis. Immunohistochemistry staining showed that NF-kB expression, which reportedly increases in a human psoriatic nail, upregulated in nail bed lesions of the nail removal IMQ-treated group is significantly higher than the nail removal petrolatum-treated group. Expression of CK6, an established marker of hyperproliferative and activated keratinocytes in psoriasis, also showed a significant difference between the IMQ-treated and the petrolatum-treated group. These results suggest the similarity between IMQ induced nail lesions and human nail psoriasis. The establishment of this rapid and convenient model will allow fast therapeutic screening and promote nail psoriasis research.

P02-16[O04-01]

Optimization of ELISAs for IgA antibodies in autoimmune bullous skin diseases

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Most autoimmune bullous skin diseases (AIBDs) are mediated essentially by IgG autoantibodies against structural proteins of the desmosomes at cell-cell junctions and of the hemidesmosomes at dermo-epidermal junctions. Enzyme-linked immunosorbent assays (ELISAs) are useful to detect IgG antibodies against Dsg1/Dsg3, BP180, BP230, and type VII collagen (COL7) in AIBDs, using commercial ELISA kits. Some AIBDs are mediated by IgA antibodies, which can also be detected by commercial IgG ELISA kits with some ingenuity regarding the secondary antibody. In this study, we aimed to optimize and standardize the detection of IgA antibodies using commercial IgG ELISA kits. We first compared 5 different secondary anti-IgA antibodies and found different results depending on the nature and dilution of the secondary antibody. For Dsg 1 and Dsg3 ELISAs, the results of whole secondary antibody with Fc portion gave much higher backgrounds than those of F(ab')2 fragment. We hypothesized that the presence of Fc portion may be responsible for the backgrounds. Then, using a selected labeled anti-IgA secondary antibody of F(ab')2 fragment, we successfully established sensitive and specific IgA ELISAs, in which the cut-off optical density (OD) values were defined as 0.146, 0.121, 0.291, 0.297, and 0.054 for Dsg1, Dsg3, BP180, BP230 and COL7, respectively by mean +3 SD of the results of 37 healthy control sera. For secondary anti-IgA antibody, we recommend using labeled F(ab')2 fragment, rather than whole antibody, at dilution of 1:6000. This study for the first time demonstrated optimized ELISA protocol for IgA antibodies to various skin autoantigens in AIBDs, which could avoid false negatives or positives.

P02-17[O04-02]

Relationship between treatment responsiveness and immune checkpoints in Halo nevus

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A nevus cell nevus surrounded by vitiligo is called a Halo nevus (HN) or Sutton's nevus and is said to be caused by a T-cell mediated immune response to nevus antigens. Sutton's phenomenon, which is the occurrence of vitiligo around malignant melanoma or blue nevus, etc, is also known. Especially, vitiligo in melanoma patients is called melanoma-associated vitiligo and recognized to associate with favorable outcomes. It's sometimes observed in patients who respond to immune checkpoint inhibitor (ICI) therapy as a preferable immune-related adverse event (irAE), the mechanism has attracted attention. However, there are few reports on analyses of immune checkpoint including PD-1/PD-L1 in HN. In the present study, to evaluate the relationship between immune checkpoint and HN, we performed immunohistochemical analysis using formalin-fixed paraffin-embedded (FFPE) samples collected from 38 HN patients (16 males and 22 females, mean age 20.47 years) whose nevus were resected in Nagoya City University Hospital. Of the 29 cases that we were able to follow after nevus excision, 12 cases showed improvement of the surrounding vitiligo and 17 cases showed no change or expansion of vitiligo. Immunohistochemical findings showed that PD-L 1 expression was positive in 25 of 36 cases, and cases with improved vitiligo after nevus excision were predominantly PD-L1 negative. PD-1 expression in infiltrating cells was positive in 19 of 38 patients, but there was no significant correlation between PD-1 expression and improvement of vitiligo. These results suggest that more than local immune responses are involved in vitiligo formation in PD-L1-positive HN, and the analysis of immune responses in PD-L1-positive HN may lead to elucidation of the mechanisms of tumor immunity and irAEs.

P02-18[O04-03]

The presence of multiple epitopes within BP180 molecule in a case of dipeptidyl peptidase-4 inhibitor-related bullous pemphigoid

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Dipeptidyl peptidase-4 inhibitors (DPP-4i) are commonly now used for patients with diabetes mellitus because of their relatively fewer side effects. However, it is well known that DPP-4i may cause bullous pemphigoid (BP). Herein, we present a rare case of DPP-4i-related BP, in which we detected IgG antibodies against multiple epitopes within BP 180. To our knowledge, only a few studies have reported similar cases. A 60-year-old man with type II diabetes mellitus had been undergoing hemodialysis for 4 years due to diabetic nephropathy and had been taking DPP-4i (teneligliptin) 20 mg daily for 41 months. Subsequently, blisters developed rapidly on the trunk and arms of the patient. The initiation of daily oral administration of prednisolone 40 mg daily with the discontinuation of DPP-4i improved his symptoms. Detailed immunoblotting analyses revealed that IgG antibodies in the patient sera reacted with multiple epitopes within BP180, i.e., full length BP180, recombinant proteins (RPs) of the noncollagenous 16a (NC16a) and C-terminal domains and LAD-1. Furthermore, the reactivities with the NC16 a domain RP and LAD-1, but not full length BP180 and C-terminal domain RP were positively correlated with the skin symptoms during the disease course, indicating that autoantibodies to NC16a domain and LAD-1 may be pathogenic in this case. Given the increased use of DPP-4i, the accumulation of similar cases is of significant importance.

P02-19[O04-04]

Cautions for the discrepancy between CLEIA and ELISA and the presence of non-pathogenic antibodies are needed in pemphigus management

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Pemphigus is an intractable autoimmune blistering disease caused by IgG autoantibodies against the extracellular domains of desmoglein (Dsg) 1 and Dsg3. Titers of anti-Dsg autoantibodies in chemiluminescent enzyme immunoassay (CLEIA) and enzyme-linked immunosorbent assay (ELISA) generally correlate with the disease severity. Herein, we investigated discrepancies between disease severity, the results in indirect immunofluorescence (IIF), and antibody titers in ELISA and CLEIA in a 70-year-old female patient with pemphigus vulgaris. The patient with erosive oral mucosal lesions and erythematous skin lesions initially showed negative results in Dsg1 and Dsg3 CLEIAs and IIF, which became positive in later stages. In contrast, all sera taken at several time points, including the CLEIA negative time, showed positive results in ELISAs for both anti-Dsg1 and anti-Dsg3 antibodies. This result indicated that ELISA is more sensitive than CLEIA in some pemphigus sera presumably due to insufficient antigen-antibody reaction time in CLEIA. However, the ELISA titers did not correlate with disease severity. Pathogenic antibodies, but not non-pathogenic antibodies, react with epitopes with Ca2+-dependent three-dimensional structures, which are disrupted in EDTA-treated ELISA. Therefore, we also performed ELISAs with or without EDTA treatment, and found the presence of both pathogenic and non-pathogenic antibodies in the sera, which might cause the discrepancy between ELISA titers and diseases severity. The results in our study suggested that we should be careful for the different sensitivity between CLEIA and ELISA and the possible presence of non-pathogenic auto antibodies for the better management for pemphigus patients.

P02-20[O04-05]

Effects of decanoic acid on imiquimod-induced psoriasis-like dermatitis in mice

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Decanoic acid, is used as an additive in injections to prolong the action of drug because of its liquid solubility. In this study, we examined its anti-inflammatory effects on a mouse model of imiquimod-induced psoriasis-like dermatitis. We used female BALB/c mice (age, 7-8 weeks). The mice were randomly divided into five groups and treated with reagent for six days. In Group A, mice were treated with a daily topical dose of 30mg of 5% IMQ on the shaved back. In Group B, mice were treated with a daily topical dose of 30mg of 5% IMQ and 50mg of 10% decanoic acid on the shaved back. In Group C, mice were treated with a daily topical dose of 30mg of 5% IMQ and 50mg baseline vehicle on the shaved back. In Group D, mice were treated with a daily topical dose of 50mg of 10% decanoic acid on the shaved back. In Group E, mice were treated with a daily topical dose of 50mg vaseline vehicle on the shaved back. The severity of dorsal skin lesions was evaluated according to Psoriasis Area and Severity Index score system, which consists of measures for skin erythema scaling and thickness. Each parameter was scored independently on a scale from 0 to 4. The mean epidermis thickness was 80.2 ± 22.7 μm in Group A, 54.7 ± 6.6 μm in Group B, 79.1 ± 11.1 μm in Group C, 21.1 ± 3.7 μm in Group D, 24.8 ± 5.4 μm in Group E. There was no significant difference between groups. The average number of CD 3, CD8 positive T cells in dermis of Group B was less than Group A and C. Our data suggests that decanoic acid has anti-inflammatory effects in imiquimod-induced psoriasis-like dermatitis in mice. We are currently evaluating the mRNA expression of inflammatory cytokines in the lesional skin.

P02-21[O04-06]

Severe skin inflammation leads to salivary gland atrophy and dysfunction

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Psoriasis is an inflammatory skin disease, and patients with psoriasis have an increased risk for cardiovascular events and other medical complications. Atopic dermatitis, a systemic inflammatory skin disease, is also considered to be associated with cardiovascular diseases. Additionally, dental caries tends to occur more frequently in patients with psoriasis and atopic dermatitis. Although it has been clarified that skin inflammation affects the internal organs, its effects on salivary glands and dry mouth have not been clarified. Thus, our study aims to investigate the effects of dermatitis on the salivary gland. An inflammation model mouse that overproduces interleukin-1β in epidermal keratinocytes was used. Mice were stimulated with pilocarpine, and saliva was collected. Salivary secretion was reduced in dermatitis mice than in normal littermate controls. Histologically, dermatitis mice showed amyloid deposition, glandular atrophy, and fibrosis in the salivary glands. Expression of inflammatory cytokines in the salivary glands was higher in mice with dermatitis. Secretion of cytokines in saliva was not significantly different. Mice with skin inflammation showed decreased salivary secretion and histological changes, which may cause periodontal disease and dental caries because the oral environment could not be maintained; therefore, appropriate control of skin inflammation is essential.

P02-22[O04-07]

A new murine model of human eosinophilic fasciitis: role of IL-5 and IL-17

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Eosinophilic fasciitis is a disease that causes diffuse inflammation in the subcutaneous fascia and skin sclerosis. In the previous study, we confirmed that subcutaneous injection of bleomycin induce inflammation and fibrosis of fascia in mice. Moreover, the number of eosinophils increased in the early stage of the experiment, and TGF-β gene expression was enhanced with the increase in the number of eosinophils according to real-time PCR analysis, which closely resembles in human eosinophilic fasciitis. IL-5 is the most potent activator of eosinophils and is produced by Th2 cells and ILC2s. IL-5 plays an important role in eosinophilic inflammatory diseases such as asthma, and treatment of asthmatic patients with IL-5 and IL-5 receptor antibodies has been established. It has also been reported that serum IL-5 production is increased in human eosinophilic fasciitis. On the other hand, IL-17 was reported to induce fibrosis and inflammatory cells in lesions of systemic scleroderma, but the association between human eosinophilic fasciitis and IL-17 remains unclear. In this study, we examined the role of IL-5 and IL-17 in our murine model. We are examining the collected fascial tissue by real-time PCR to evaluate the expression level of IL-5, IL-5R and IL-17 families.

P03-01[II-3]

Keratinocyte Regnase-1, a down-modulator of skin inflammation, contributes to protection from carcinogenesis through regulating COX2

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The relationship between chronic inflammation and carcinogenesis has been controversial, despite known clinical evidence such as squamous cell carcinoma (SCC) on chronic skin ulcers. We previously demonstrated that a ribonuclease Regnase-1 (Reg1) in keratinocytes, played a down-modulator of skin inflammation in a cross-regulatory fashion with proinflammatory signals. Here, we addressed a question as to whether Reg1 had a protective role in skin carcinogenesis. Repeated exposure of ultraviolet B resulted in marked epidermal hyperplasia in keratinocyte-specific Reg1 KO mice (K5.Reg1KO) compared with wild-type controls and final development of atypical epidermis, resembling solar keratosis at much earlier time point than controls. Next, we employed the two-stage carcinogenesis protocol using 7,12-dimethylbenz(a)anthracene (DMBA) and 12-O-tetradecanoylphorbol-13-acetate (TPA). Notably, K5.Reg1KO mice developed 10 papillomas per head at around 10 weeks of the initiation, while no tumor emerged in controls. At 20 weeks they were converted to SCC in K5.Reg1KO mice. These data indicated that keratinocyte Reg1 had protective roles from tumorigenesis. We focused on changes of Ptgs2 expression on K5.Reg1KO mice skin, since Reg1 is also known to downregulate cyclooxygenase-2 (COX2), which is encoded by the Ptgs2 gene. RT-qPCR revealed that Ptgs2 mRNA expression was upregulated in K5.Reg1KO keratinocytes when treated with TPA. Moreover, COX2 inhibition attenuated the epidermal thickening in K5.Reg1 KO mice by treatment with TPA, indicating epidermal Reg1 plays a regulatory role not only in skin inflammation but skin carcinogenesis through down-modulation of COX2. Therefore, enforced Reg1 expression under the inflammatory condition may be relevant for the prevention of skin cancer.

P03-02[C11-01]

Frequent driver mutations of *FOXA1* in extramammary Paget's disease

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Extramammary Paget's disease (EMPD) is a neoplastic skin disease of indeterminate origin with an unknown genetic cause. We performed comprehensive genetic analysis or targeted gene sequencing in 48 patients with EMPD. We identified *FOXA1* mutations (a *GAS6-FOXA1* fusion gene and ten somatic hotspot mutations in the *FOXA1* promoter region) in 11 of these 48 patients (23%). Additional mutations were identified in *PIK3CA* (6 patients) and in *HIST1H2BB*, *HIST1H2BC* and *SMARCB1* (1 patient each), but none were found in other frequently mutated genes associated with cancer. Global gene expression analysis using EMPD samples found the upregulation of PI3 kinase-AKT-mTOR signaling. *ABCC11*, which is specifically expressed in the apocrine secretory cells and is necessary for their sweat secretion, was upregulated in the EMPD samples. This upregulation suggests that Paget cells originate from apocrine secretory cells. Immunohistochemically, FOXA1 expression was prevalent in all EMPD samples analyzed and was associated with estrogen receptor expression. Our results indicate that EMPD frequently involves *FOXA1* mutations. This is the first report of a fusion gene in EMPD, and the combination of *GAS6* and *FOXA1* is a novel fusion pair. The hotspot mutation in the *FOXA1* promoter region, in addition to mutations within the coding sequence, has been reported in breast cancer and leads to the overexpression of *FOXA1* through increased E2F binding. The frequency of the promoter mutation is apparently higher in our EMPD cohort (21%) than in breast cancer (<1%), suggesting the importance of FOXA1 upregulation in EMPD. FOXA1 is a transcriptional pioneer factor for the estrogen receptor, and the present results suggest that certain treatments for hormone-dependent cancers could be effective for EMPD.

P03-03[C11-02]

Clonal expansion of somatically-mutated keratinocytes in KID syndrome

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Somatic mutations accumulate in normal-appearing tissues, and by tracking the somatic mutations, researchers have shown that clonal expansion frequently occurs in normal-appearing tissues. Clonal expansion does not occur in a stochastic manner; instead, clones harboring cancer driver mutations are positively-selected. One remaining question is whether clonal expansion in normal-appearing tissues represents an initiating event leading to carcinogenesis. We show that clonal expansion does not necessarily require cancer driver mutation by analyzing skin samples from a patient with KID syndrome.
A patient with KID syndrome harboring a germline mutation in *GJB2* (p.D 50N) developed numerous normal-appearing ("revertant") patches of skin in areas that had been affected by chronic Candidiasis. We intensively sampled the revertant skin (hereafter referred to as "rev/cand"), areas affected by Candidiasis but not reverted ("non-rev/cand"), and areas not affected by Candidiasis at all ("no-cand"). Epidermis was separated, and extracted DNA was analyzed by exome sequencing. Clonal expansion was detected in all rev/cand and non-rev/cand samples but not in no-cand samples. In all 5 rev/cand samples, single clones occupied the whole samples (1mm or 4mm in diameter). Strikingly, each rev/cand sample carried a different somatic mutation in *GJB2*, suggesting synchronous emergence of the mutant clones. Taken together, additional mutation in *GJB2* likely offers selective advantage to skin keratinocytes in a patient with KID syndrome if the skin is affected by chronic Candidiasis. In conclusion, our case exemplifies that clonal expansion per se does not necessarily represent events that predate carcinogenesis; rather, it is likely an appropriate response to persisting environmental insults.

P03-04[C11-03]

Next-generation sequencing revealed tumor immunity-related factors interacting with tertiary lymphoid structures in cutaneous angiosarcoma

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Recently some reports suggest that tertiary lymphoid structures (TLSs), defined as CD20-positive B cell follicles surrounded by CD3-positive T cells, are promising biomarkers that correlate with a better prognosis and predict response to immune checkpoint inhibitors (ICIs) in several cancers, but their implications in cutaneous angiosarcoma (CAS) is not yet established. To clarify the value of TLSs and tumor immunity-related factors interacting with TLSs in CAS, we investigated 61 specimens from 31 patients diagnosed with CAS. We performed immunofluorescence staining for PD-L1, PD-1, CD8, CD3 and CD20, and compared gene expression using Next-generation sequencer between TLS-rich 6 samples (TLS-R) and TLS-poor 9 samples (TLS-P). Patients with at least one TLS in the primary lesion had a significantly better prognosis than those without TLSs (log-rank, p=0.0032). In multivariate analysis, only TLSs correlated with prognosis among the choice of treatment and other immunological markers (HR=0.197, 95% CI, 0.046-0.838, p=0.028). The presence of TLS is negatively correlated with the tumor differentiation (Fisher's exact test, p=0.048). In RNA level, GADD45 gene expression was upregulated in TLS-R (p=0.0303), and gene expression of PD-1, PD-L1, STAT5a, and G6PD was upregulated in TLS-P (p=0.0394, 0.0002, 0.0291, 0.0293). Gene set enrichment analysis showed that genes relating to the cell matrix adhesion were highly expressed in TLS-R, while genes relating to B cell, IL-10, and STAT pathway were highly expressed in TLS-P. On the basis of these findings, the presence of TLSs was found to be a valuable prognostic biomarker for patients with CAS and was associated with active immune response.

P03-05[C11-04]

Loss of FAM83H plays a promoting role for cell migration and invasion in cutaneous squamous cell carcinoma via altered keratin distribution

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FAM83H is a member of the family with sequence similarity 83 (FAM83), and it has been implicated in dental enamel formation. Furthermore, previous studies suggest that FAM83H is involved in tumorigenesis. We previously clarified that TRIM29 binds to FAM83H to regulate keratin distribution and squamous cell migration. However, the role of FAM83H in normal/malignant skin keratinocytes has not been elucidated in detail. Here we investigate the expression of FAM83H in cutaneous squamous cell carcinoma (SCC) and its physiological function. An investigation of public databases revealed FAM83H to be highly expressed in the skin. Immunohistochemical analyses revealed FAM83H expression to be lower in malignant SCC lesions than in normal epidermis. The expression levels were even lower in advanced invasive tumors and were lower in poorly differentiated lesions compared to well-differentiated lesions. The mRNA expression levels of FAM83H in SCC tumors were also lower than in normal epidermis. The knockdown of FAM83H enhanced SCC cell migration and invasion, whereas the overexpression of FAM83H led to decreases in both. Furthermore, the knockdown of FAM83H enhanced cancer cell metastasis in vivo. Immunoprecipitation analysis showed that FAM83H forms a complex with TRIM29 and keratins. The knockdown of FAM83H induced a perinuclear distribution of keratins and decreased the expression levels of keratins in soluble fractions without altering keratin dimerization. Clinically, the loss of FAM83H correlates with an altered distribution of keratins. Our findings reveal a critical function for FAM83 H in regulating keratin distribution, as well as in the migration/invasion of cutaneous SCC, suggesting that FAM83H could be a crucial molecule in the tumorigenesis of cutaneous SCC.

P03-06[C11-05]

Blockade of glucose-6-phosphate dehydrogenase induces immunogenic cell death in malignant melanoma and Merkel cell carcinoma

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Glucose-6-phosphate dehydrogenase (G6PD) is one of the cytoplasmic enzymes involved in the pentose phosphate pathway, which is maintaining NADPH levels and protects the cell from oxidative damage. In a recent study in Merkel cell carcinoma (MCC), we found that the strength of G6PD expression was an indicator of tumor typing based on immune activity and inversely correlated with programmed death ligand-1 expression and prognosis. The purpose of this study is to investigate the mechanism of the relationship between G6PD and tumor immunity. We used melanoma cell lines (sk-mel-28, colo679) and MCC cell lines (MCC14/2, MCC26). Dehydroepiandrosterone (DHEA), 6-Aminonicotinamide (6-AN), and glucose-6-phosphate dehydrogenase inhibitor 1 (G6PDi-1) were used as G6PD inhibitors. We confirmed that inhibition of G6PD reduced tumor cell viability by XTT assay and increased high mobility group box 1 (HMGB1) by enzyme linked immunosorbent assay (ELISA). In immunocytochemistry, Calreticulin was observed to migrate to the cell surface and be released from the ruptured cell membrane. These results indicated that inhibition of G6PD induces immunogenic cell death (ICD). ICD is cell death that activates the immune response, which is consistent with our data showing that low G6 PD expression was associated with high tumor immune activity. G6PD is not only a promising biomarker, but also a new therapeutic target. Inhibition of G6PD in tumors makes tumors vulnerable to oxidative stress and induces a state in which ICD can occur. ICD may increase tumor antigen presentation, thereby increasing the therapeutic effect of ICD. As a drug that induces a phenomenon similar to the so-called abscopal effect, it may lead to clinical applications such as combined therapy with immune checkpoint inhibitors.

P03-07[C11-06]

DUSP4 positively controls the proliferation and infiltration ability of melanoma cells by activating ERK 1/2 via downregulation of DUSP6

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A subset of dual-specificity phosphatases (DUSPs) act as major negative regulators of mitogen-activated protein kinases (MAPKs), and their possible involvement in tumorigenesis has been suggested. Among them, DUSP4 preferentially dephosphorylates ERK1/2 and Jnk over p38. In the present study, we aimed to identify a possible role of DUSP4 in melanomagenesis. Examination of publicly available large-scale data on gene expression and dependency revealed a remarkably high DUSP4 expression and dependency of the melanoma cell lines compared with other tumor cell lines. No such high gene dependency specific to melanoma cells was observed for the other 24 DUSPs encoded in the human genome. Using melanoma cell lines, we confirmed that DUSP4 depletion impaired cell growth without notably inducing apoptosis for up to several days. In addition, DUSP4 depletion reduced the infiltration ability of melanoma cells. Interestingly, immunoblotting and kinase translocation reporter (KTR) data revealed that DUSP4 depletion induced a decrease in ERK1/2 phosphorylation but barely affected Jnk phosphorylation, suggesting that neither ERK nor Jnk was a direct target of DUSP4 in our experimental setting. Moreover, we found that DUSP4 depletion led to an increase in DUSP6 levels, possibly through a post-transcriptional process, and that high DUSP6 levels decreased the degree of ERK1/2 phosphorylation. Our data suggest that DUSP4 plays a role in maintaining high ERK1/2 activity by negatively regulating DUSP6, thus contributing to the survival and growth of melanoma cells.

P03-08[C11-07]

Tumor suppressive effect of anti-PD-1 antibody against angiosarcoma in a mouse model

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Angiosarcoma (AS) is known to have a high rate of lung metastasis and a poor prognosis, and effective treatment is required. In recent years, there have been several reports of cases in which anti-programmed cell death protein (PD)-1 antibodies (Abs) have been effective in treating patients with AS. However, no study has shown the effect of anti-PD-1 Ab on AS tumors using a mouse model. The objective was to investigate the effects of anti-PD-1 Ab on tumor growth of AS in mice. We used an AS mice model, in which mouse-derived AS cells were implanted subcutaneously. To investigate the effect of anti-PD-1 Ab on AS tumors in mice, anti-mouse PD-1 Ab was injected intraperitoneally. Tumor size, expression of programmed cell death-1 ligand-1 (PD-L1), and inflammatory cells infiltrating the AS tumor were examined. Immunofluorescence staining revealed that the AS tumor cells were positive for CD31 and PD-L1. We identified that the administration of anti-PD-1 Ab significantly inhibited the size of AS tumors in mice. In addition, tumor disappearance time was significantly shorter in the anti-PD-1 Ab group than in the control group. Immunohistochemical staining showed that the number of CD68+ macrophages and CD163+ M2-type tumor associated macrophages (TAMs) in AS tumors were significantly decreased by anti-PD-1 Ab administration. The number of CD8+ T cells in AS tumors in mice treated with anti-PD-1 Ab significantly increased than in control mice. In conclusion, anti-PD-1 Ab may inhibit TAMs infiltration in AS, increase CD8+ T cells, and suppress tumor growth of AS in vivo. We have shown using a mouse model that the administration of anti-PD-1 Abs could be an effective treatment for patients with AS.

P03-09[O10-01]

Combination treatment of topical imiquimod plus anti-programmed cell death 1 antibody exerts significantly potent antitumor effect

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The exact mechanisms of the imiquimod (IMQ)-induced antitumor effect have not been fully understood. Although both topical IMQ treatment and anti-programmed cell death 1 (PD-1) antibody may be used for primary skin lesions or skin cancers, the efficacy of each monotherapy for these lesions is insufficient. Using a murine tumor model, we aimed to elucidate the detailed mechanisms of the IMQ-induced antitumor effect and analyzed the antitumor effect of combination therapy of topical IMQ plus anti-PD-1 antibody.
IMQ inhibited the growth of MC38 tumor cells which were implanted in mice in parallel with the increase of $CD8^+$T cells and decrease of $FoxP3^+$ cells within tumors. IMQ up-regulated CD80, CD86, and MHC Class II in myeloid cells as well as CD69 in T cells in the LNs and tumors. We assessed the IMQ-induced antitumor effect in Rag1-deficient mice, which lack T and B cells, and homozygous CD19-Cre transgenic mice, which show significantly impaired B cell activation. Although IMQ failed to inhibit the tumor growth in Rag1-deficient mice, IMQ inhibited the tumor growth in homozygous CD19-Cre transgenic mice, suggesting that T cells may play a crucial role in the IMQ-induced antitumor effect. Furthermore, this antitumor effect was dependent on interferon γ.
We found that IMQ upregulated PD-1 expression in T cells and PD-L1/L2 expression in myeloid cells, indicating that IMQ induces not only T-cell activation but also T-cell exhaustion. Next, we assessed combination therapy of topical IMQ and anti-PD-1 antibody. We found that the combination therapy significantly suppressed the tumor growth as compared with each monotherapy. Collectively, our result suggests that the combination of IMQ and anti-PD-1 antibody is a promising therapy for skin cancer.

P03-10[O10-02]

Skin liquid biopsy method for assessing the lesional environment of cutaneous T-cell lymphoma

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Detailed analysis of cells infiltrating lesional skin cannot be performed in skin biopsy specimens by immunohistochemistry or cell separation techniques due to the potential destruction of minor cell populations by enzyme treatment in the isolation step. We hypothesized that cells could be identified in a small amount of blood obtained from the infiltrating lesional skin during diagnostic skin biopsies. We collected small amounts (～300 μl) of lesional blood and successfully isolated infiltrating cells using a cell sorter. We then applied this "skin liquid biopsy" technique to clarify the pathogenesis of cutaneous T-cell lymphoma (CTCL). Mass cytometry was used to compare the different cell populations between lesional and peripheral blood. The percentage of $CD4^+CD45RO^+$ and $CD8^+CD45RO^+$ T cells was increased in lesional blood. Next-generation RNA sequencing (RNA-seq) of the $CD4^+CD45RO^+$ T cells in the lesional blood showed increased expression of genes associated with cancer development and progression, such as *RYR2*, *DNAH9*, and *RGS1*. On the other hand, RNA-seq of $CD8^+CD45RO^+$ T cells in the lesional blood showed genes associated with tumor suppression and poorly cell division. In addition, the T cell receptor repertoire in lesional blood was skewed compared with that of peripheral blood. The serum chemokines also differed, with a characteristic chemokine pattern in lesional blood. In particular, high serum concentrations of the CCR4 ligands CCL17 and CCL22 were detected in lesional blood. Lesional blood was assumed to contain blood overflowing from capillary vessels in the lesion area. This liquid skin biopsy technique might provide new insight into the pathogenesis of CTCL and facilitate the evaluation of treatment efficacy for other skin inflammatory diseases.

P03-11[O10-03]

Global tyrosine kinome profiling revealed Src pathway as a novel therapeutic target in combination with HDAC inhibitors for CTCL

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Background: Histone deacetylase inhibitors (HDACis) are a novel therapeutic option against cutaneous T-cell lymphoma (CTCL) but with limited effects. Hence, combination therapies should be explored to enhance the effectiveness of HDACis. Objective: This study was conducted to identify novel therapeutic targets that can be combined with HDACis for treating CTCL. Methods: We assessed a global tyrosine kinase activity profiling of three CTCL cell lines (HH, MJ, and Hut78) with three HDACis (romidepsin, vorinostat, and belinostat) using the peptide microarrays. In addition, these cell lines were co-treated with romidepsin and an inhibitor against identified tyrosine kinase pathway. Results: Principal component analysis revealed that kinome expression patterns were mainly associated with the cell origin and were not affected by the drugs. Only some of the kinases were commonly activated by the HDACis. Most identified kinases were Src-associated molecules such as annexin A2, embryonal Fyn-associated substrate, and progesterone receptor. Phosphorylated Src was not observed in any untreated cell lines, whereas Src phosphorylation was detected in two of the three cell lines after HDACis treatment. Ponatinib, a Src inhibitor, significantly enhanced romidepsin-induced apoptosis not only in HH, MJ, and Hut78 cells, but also in Myla and SeAx CTCL cell lines. Conclusion: The Src pathway is a promising target for combination therapy with HDACis for CTCL.

P03-12[O10-04]

Matrin-3 is involved in cell cycle and apoptosis for survival in melanoma

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Background: A president study revealed that Matrin-3 is an essential component in maintaining fibroblast growth factor2 (FGF2)-mediated undifferentiation of neural stem cells (NSCs) using a proteomic approach. Melanoma arises from melanocytes that originate from neural crest stem cells, during development. Additionally, it has been reported that the expression of FGF2 is positively correlated with the progression of melanoma. Objective: We expected that matrin-3 as a downstream component of FGF2 might be associated with the aggressiveness or differentiation of melanoma. Methods: The matrin-3 expression was measured using human melanoma patients' tissues and human melanoma cell lines. We analyzed the effect of matrin-3 siRNA on the proliferation of human melanoma cell lines and focused on the cell cycle progression and apoptosis. We carried out in vivo xenograft tumor experiments by implanting A375 cells transfected with matrin-3 shRNA. Results: Matrin-3 was highly expressed in human melanoma, and matrin-3 knockdown inhibited the proliferation of murine melanoma cells in vivo and in vitro. Furthermore, we found that matrin-3 knockdown led to an accumulation of cells in the G1 phase and increase in apoptotic cell number. Conclusion: Our results suggest that matrin-3 could be a new therapeutic target for the treatment of melanoma.

P03-13[O10-05]

Frequent *FGFR3* and ras gene mutations in skin tags/acrochordons

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Seborrheic keratosis (SK) and skin tags/acrochordons (ST) are most common benign skin tumors that appear with age. SK is caused by the clonal expansion of mutant keratinocytes possessing somatic mutation in genes associated with the cell proliferation signaling pathway, i.e., *FGFR3* and ras genes. Such mutation has also been identified in dermatosis papulosa nigra, solar lentigines, benign lichenoid keratosis/lichen planus-like keratosis, and linear epidermal nevi. Despite being common, the pathogenesis of STs remains elusive. Here, we genetically analyzed a major subtype of STs characterized by developing multiple lesions on the neck and axilla and having a thin stalk and single spherical or disc-shaped head. We identified a single lesion-specific somatic mutation in *FGFR3*, *HRAS*, *KRAS*, *EGFR* or *PIK3CA* in 53 of 55 STs from 13 participants. All identified mutations were known causative mutations for SKs. 11 STs were separated enzymatically into the epidermis and dermis and the somatic mutations were identified from the epidermis but not from the dermis. These results indicate that the development of STs on the neck and axilla is induced by somatic driver mutation in *FGFR3* and associated genes in the overlying epidermis. Compared with reports of SK, the spectrum of driver mutation in STs showed no major differences in *FGFR3* dominance (36/55) or the spectrum of *FGFR3* mutation, suggesting that ST and SK are genetically identical. Supporting this idea, we found polypoid ST-like lesions on the neck and axilla but flat SK-like lesions on the body in two patients of linear epidermal nevi caused by a prenatal *FGFR3* mutation. Putative site-specific factors of the neck and axilla that may facilitate the development of skin protrusions should be investigated in future studies.

P03-14[O10-06]

Two opposite effects of desmoglein 3 on the growth of oral squamous cell carcinoma between anchorage-dependent and -independent conditions

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Previously, we evaluated the Desmoglein (Dsg) 3 expression in oral squamous cell carcinoma (OSCC) cell lines derived from the primary tumor (P cells) and the metastatic lymph nodes (LY cells) of 3 OSCC patients (No.7, 17, 58), and demonstrated that LY cells expressed more Dsg3 than P cells of the same patient. Here, we investigated the effect of Dsg3 expression on the growth of OSCC between anchorage-dependent (AD) and -independent (AID) conditions. Under AD conditions, WST-1 cell viability assays showed that P cells proliferated more than LY cells of the same patient (No.7: $P<0.01$; No.17, 58: $P<0.05$), suggesting the inverse effect of Dsg3 on the cell growth. After transferred into AID conditions, all the cell lines except for Dsg3-negative 7P cells, HSC3 and SAS showed increased Dsg3 expression by up to 50-fold, compared with AD conditions (7LY, 17LY, 58P, HSC3, SAS: $P<0.01$; 17P, 58LY: $P<0.05$). Under AID conditions, 17P cells somehow expressed more Dsg3 than 17 LY cells. In WST-1 assay under AID conditions, all the patients showed higher cell proliferation of Dsg3-high cells (7LY, 17P, 58LY) compared with Dsg3-low cells (7P, 17LY, 58P) (No.7, 17: $P<0.05$; No.58: $P<0.01$). When we comparatively analyzed Dsg3-negative 7P cells and Dsg3-expressing 7LY cells, 7P cells had a higher migration ability than 7LY cells under AD conditions, whereas 7LY cells had a higher colony forming ability than 7P cells under AID conditions. When we knockdown Dsg3 under AD conditions, WST-1 assay showed increased cell growth ability of 7LY, 17P, 17LY, HSC3 and SAS ($P<0.01$). These data suggested that Dsg3 may have two opposite effects on the growth of OSCC cells between AD and AID conditions. Dsg3 may play an important role in OSCC to gain an advantage for the growth in two different conditions.

P03-15[O10-07]

AID expression of B cells in the tertiary lymphoid structures implies an immunoglobulin class switching in tumor immunity

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Tertiary lymphoid structures (TLSs) can be formed in the border of numerous tumors. TLS displayed the same organization and functionality as canonical secondary lymphoid organs and contained B cell follicles for the differentiation of B cells. We reviewed 97 cases of basal cell carcinoma (BCC) digitized at Kyoto University from 2007 to 2018, in which we identified 68 lymphoid aggregates among them 6 had germinal centers. To clarify B cell maturation in TLSs in skin tumors, we evaluated CD19 and activation induced cytidine deaminase (AID) expression, the marker of class-switch recombination, with multiplex immunohistochemistry. As a result, double-positive cells of CD19 and AID were observed in B cell follicles with germinal centers in BCCs, indicating that some B cells of TLSs in BCCs perform immunoglobulin class switching at the local sites. These structures correspond to inducible skin-associated lymphoid tissue (iSALT), which is the concept of cutaneous local immunological network system. The iSALT has been found in murine contact dermatitis and human benign skin diseases, such as secondary syphilis infections and lupus erythematosus profundus (LEP). Our findings may suggest that cutaneous TLSs have a pivotal role in anti-tumor B cell immunity as the local immunological network of the skin.

P03-16[O10-08]

Serum Cytokeratin 18 as a Potential Prognostic, Diagnostic and Therapeutic Marker for Extramammary Paget's Disease

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Extramammary Paget's disease (EMPD) is a rare cutaneous adenocarcinoma with a generally good prognosis because of its slow-growing nature. However, the prognosis is unfavorable once it becomes invasive. No consensus has been achieved on the standard chemotherapy to treat metastatic EMPD. Therefore, a tumor marker that reflects disease progression and response to chemotherapy is required for adequate management of this disease. Cytokeratin 18 (CK18), an intermediate filament protein, is highly expressed in many types of cancer and is released into the blood by both necrosis and apoptosis of cells. Soluble forms of CK18 can be detected by relatively new enzyme-linked immunosorbent assays, M30 (for caspase-cleaved form) and M65 (for both caspase-cleaved and intact forms) assays. Serum CK18 has been reported to be a tumor marker for various types of carcinoma including breast cancer, which resembles EMPD in immunohistochemical and molecular profiles. In this study, we retrospectively measure the serum levels of CK18 (M30 and M65) and assess the significance of this protein as a tumor marker in EMPD. Immunohistochemical staining demonstrated that tumor cells of EMPD in both lesional skin and lymph node metastasis are positive for CK18. The baseline serum M30 and M65 levels in metastatic EMPD patients were significantly higher than those in non-metastatic patients. Serum M30 and M65 levels were correlated with serum carcinoembryonic antigen levels, which has previously been shown to be useful in the management of EMPD. We also illustrated that serial serum M30 and M65 levels might reflect and predict response to chemotherapy in EMPD. These results suggest that serum CK18 levels may be a useful tumor marker to monitor or predict tumor progression in EMPD.

P03-17[O10-09]

The MIF-CD74 interaction regulates the expression of PD-L1 in melanoma cells

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Interferon gamma (IFN-γ) has been reported as a key extrinsic stimulator of programmed cell death ligand 1 (PD-L1) expression on tumor cells, yet its mechanism is poorly understood. This study analyzed the role of CD74 and its ligand macrophage migration inhibitory factor (MIF) on PD-L1 expression, by immunohistochemical (IHC) analysis of melanoma tissue samples and in vitro analyses of melanoma cell lines treated with IFN-γ and inhibitors of the MIF-CD74 interaction. IHC analyses showed significant correlations between CD74 and PD-L1 ($p<0.01$). In vitro analysis of melanoma cell lines, which are known to secrete MIF constitutively and express cell surface CD74 upon IFN-γ stimulation, showed upregulation of PD-L1 levels by IFN-γ stimulation. This was suppressed by further treatment with the MIF-CD74 interaction inhibitor, 4-iodo-6-phenylpyrimidine (4-IPP). In the analysis of melanoma cell line WM1361A, which constitutively expresses PD-L1, CD74, and MIF in its non-treated state, 4-IPP treatment and transfecting siRNA targeting CD74 significantly suppressed the PD-L1 expression. These results indicated that MIF-CD74 interaction directly regulates the expression of PD-L1.

P03-18[O10-10]

Functional analysis of Rap2 in tumor microenvironment

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Rap2 (Rap2A, Rap2B and Rap2C) are Ras-like small G proteins. The function of Rap2 in cancer is not fully elucidated. Rap2B is expressed in Pam212, a mouse keratinocyte cell line. Pam212 cells form squamous cell carcinoma (SCC) in mice, but the cells are non-metastatic. In contrast, metastatic derivatives of Pam212 cells (LY and LU cells, named after lymph node and lung metastases) expressed extremely low levels of Rap2. We have found that Rap2 is expressed in tumor invasive monocytes (CD68 positive) in SCC tissue specimens. There are two types of macrophages, inflammatory phenotype (M1) and regenerative phenotype (M2). Tumor associated macrophage (TAM) promote cancer metastasis by enhancing angiogenesis as well as tumor cell growth, migration and invasion. Rap2B expression in murine bone marrow-derived cells was up-regulated by macrophage colony stimulation factor (MCSF). No difference in growth and morphology was found when bone marrow-derived cells from wild-type and Rap2B KO mice were stimulated by MCSF. Rap2 function in TAM is under investigation using Rap2B knockout mice.

P03-19[O10-11]

Clinicopathological parameters to predict prognosis in cutaneous angiosarcoma -a retrospective analysis

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Introduction: Cutaneous angiosarcoma (AS) is a rare aggressive sarcoma of vascular origin with a poor prognosis. Due to the paucity of the disease, the roles of clinicopathological parameters on prognosis have not been fully understood.
Materials and methods: We retrospectively reviewed clinicopathological data of 53 patients from 2009 January to 2021 May in the department of Dermatology at Kyoto University.
Results: Included patients had a median age of 72 years and 58.5% were male patients. The median body mass index (BMI) was 22.86. Current/former alcohol consumption and smoking were observed in 39.6% and 39.6% respectively. During the follow-up, 77.4% of the patients died with a median survival period of 13 months. Surgical treatment, chemotherapy, and radiotherapy were performed in 60.4%, 64.2%, and 50.9%, respectively. Seventy-eight percent of AS were found in the head/neck. Forty-two percent of the patients had nodular and patchy tumors whereas 44.2% and 13.5% showed nodular and patchy lesions, respectively. In univariate analysis, higher BMI, primary site of AS (head/neck vs others), clinical manifestation of AS (nodule vs nodule + patchy), surgical treatment were significantly associated with better overall survival (OS) whereas male gender and current/former alcohol consumption had a trend to have worse OS. The multivariate analysis showed that BMI, a primary site of AS, and clinical manifestation are independent prognostic factors on OS.
Conclusions: Clinicopathological features such as sex, BMI, alcohol consumption, primary site of AS, clinical manifestation, and surgical treatment could help to predict a prognosis in patients with AS. Further studies are warranted to confirm the prognostic factors in AS.

P03-20[C11-08]

Investigating Proteome Changes Between Primary and Metastatic Cutaneous Squamous Cell Carcinoma Using Mass Spectrometry

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Cutaneous squamous cell carcinoma (cSCC) is a common malignancy worldwide and the first as the cause of death from keratinocytic carcinomas. Around 5% of primary cSCCs metastasize, leading to a 5-year survival rate of only 11%. This paper aims to investigate the proteome profile of primary and metastatic cSCC lesions for the identification of potential diagnostic biomarkers and molecular alterations. Liquid chromatography coupled with mass spectrometry workflow was used to analyse the proteome profile of formalin-fixed and paraffin-embedded samples of primary and metastatic cSCC lesions. Statistical and bioinformatics analysis was performed to identify differentially abundant proteins and molecular alterations between the lesions. A total of 5037 proteins were identified across the samples of which 19 proteins including ISG15, APOA1 and MARCKS with roles in metastasis were increased and 11 proteins including DMKN, APCS and CST6 decreased in metastatic cSCC lesions relative to the primary phenotypes. The proteomic data separated the lesions based on their histopathological diagnosis. Bioinformatics analysis revealed that cell migration, cell survival and immune response are likely activated, and apoptosis is inhibited in metastatic cSCC lesions. Two samples were reclassified after PCA analysis. Also, a supervised machine learning algorithm using the proteomic data predicted with 89% accuracy if a primary lesion would eventually metastasise to a regional body site. Exploring these findings further will allow their translation into the clinic for improved tumour diagnosis, staging and therapeutic intervention.

P03-21[O10-12]

Evaluating the efficacy of cetuximab, avelumab and cetuximab plus avelumab in treating perineural invasion of cutaneous SCC

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Perineural invasion (PNI), defined as the invasion of tumour cells into the perineural space of a peripheral nerve, is one of the high-risk features of cutaneous squamous cell carcinoma (cSCC) and prognosticates poor outcomes. SCC spread to sensory and/or motor nerves leads to deficits such as paraesthesia and results in high morbidity and mortality. Treatment includes surgery and/or radiotherapy. There is no specific targeted therapy to treat these patients. Our lab previously detected EGFR overexpression in 90% cases of perineural spread (PNS) of cSCCHN and ~70% of primary tumors of later PNS. Also, high frequencies of PD-1$^+$ CD8$^+$ T cells have been found in the PNS of SCC patients. Our previous data suggest that anti-EGFR and checkpoint inhibitor therapies could be effective in treating PNI/PNS of cSCC. The aim of this study was to test efficacy of cetuximab, avelumab and cetuximab plus avelumab in the humanised sciatic nerve model PNI of cSCC.

P04-01[C06-01]

Antibodies to desmocollin (Dsc) 3, but not Dsc1, in pemphigus sera directly block heterophilic transinteraction between desmoglein and Dsc

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Anti-desmocollin (Dsc) antibodies are detected in some cases of classical or non-classical types of pemphigus, particularly paraneoplastic pemphigus, pemphigus herpetiformis and pemphigus vegetans. The pathogenic significance of anti-Dsc antibodies in pemphigus is largely unknown, while that of anti-desmoglein (Dsg) antibodies is well established. In this study, we aimed to analyze whether anti-Dsc autoantibodies in pemphigus sera block the heterophilic interaction of Dsgs and Dscs by bead aggregation assays using various combination of recombinant Dsg/Dsc, which can detect aggregation inhibitory effects of both IgG and IgA antibodies. We selected 17 sera with IgG or IgA antibodies with Dscs but not with Dsgs by ELISA; i.e, 8 sera reactive exclusively with Dsc1, 8 sera reactive exclusively with Dsc3 and one serum reactive with both Dsc1 and Dsc3. Six of the 9 anti-Dsc3 antibody positive sera inhibited heterophilic interaction between Dsg3 and Dsc3. Assays with various Dsg/Dsc combinations indicated that the inhibition was specifically induced by anti-Dsc3 antibodies in the sera, except for the serum reactive with both Dsc1 and Dsc3. In contrast, only one of the 9 anti-Dsc1 antibody positive sera inhibited Dsg1/Dsc1 adhesion. The serum also blocked the aggregation of Dsg1/Dsc3 beads, indicating the concurrence of anti-Dsg1 antibodies, which were too low to be detected by ELISA. Therefore, none of anti-Dsc1 antibody positive sera seemed to block the transinteraction of Dsc1 with Dsgs. These findings suggest that anti-Dsc3 antibodies may cause blisters by direct inhibition of Dsg/Dsc heterophilic transinteraction, the same mechanism for anti-Dsg antibodies. In contrast, anti-Dsc1 antibodies may induce blisters by different mechanisms such as intercellular signaling.

P04-02[O02-10]

Antifibrogenic effects of sunitinib in a bleomycin-induced scleroderma model

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Sunitinib blocks the tyrosine kinase activity of platelet-derived growth factor (PDGF) and PDGF receptors, as well as the vascular endothelial growth factor (VEGF)/VEGF receptor pathway, which plays an important role in the development of systemic sclerosis. We examined the efficacy of sunitinib in a mouse model of scleroderma induced by bleomycin. Sunitinib was administered orally. Histopathological examination showed that sunitinib treatment suppressed dermal fibrosis and decreased dermal thickness. The numbers of mast cells in the skin of sunitinib-treated mice were significantly lower compared with those in PBS-treated mice. Moreover, the amount of collagen in the skin of sunitinib-treated mice was significantly lower compared with that in the PBS-treated mice. Semiquantitative histopathological scoring of the lungs did not show a significant inhibition of fibrosis in sunitinib-treated mice. These data suggest that sunitinib may be a therapeutic agent for human scleroderma.

P04-03[O02-11]

Anti-glycation properties of Carnosine in 3D skin equivalent models and its implications in prevention of premature skin aging

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Glycation is a non-enzymatic reaction involving free reducing sugars and macromolecules leading to the formation of advanced glycation end products (AGEs). Such modifications are one of the major causes of skin aging, linked to oxidative stress, and ultimately result in impaired elasticity due to cross-linking of the elastic fibres thereby playing a significant role in visible skin aging. Using full thickness skin equivalent models, we evaluated the capacities of the natural dipeptide molecule Carnosine (beta-alanyl-L-histidine) to inhibit the formation of AGEs. Topical application of 0.5% aqueous solution of Carnosine resulted in significant and reproducible reduction of collagen-linked fluorescence (CLF, Ex370nm/Em440nm, $p<0.001$) induced by methylglyoxal and indicative of the protective effect on the elastic fibres. Skin aging is thought to be associated with accumulation of senescent fibroblasts in dermis and expression of the senescence associated secretory pathway (SASP) factors. Pre-treatment of cultured dermal fibroblasts with Carnosine ameliorated the senescent phenotypes induced by methylglyoxal, including ECM alterations, reduced cell densities and proliferative potential as well as intracellular ROS production measured by DCFDA probe. The effects of glycation and Carnosine treatment are presently validated in more detail in skin models, with focus on ECM, fibroblast densities and epidermal morphology alongside localised expression of glycation markers such as Carboxymethyl-lysine (CML). Carnosine is a naturally synthesised compound with effect on cellular energy metabolism. Understanding the anti-glycation properties of Carnosine in organotypic skin models can inform further applications as an effective ingredient in anti-aging skincare formulations.

P05-01[III-1]

An important role of Syntaxin-4 in nuclear degradation in corneoptosis, a unique cell death of keratinocytes

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The stratum corneum (SC), the outermost layer of the epidermis, consists of nonviable anuclear keratinocytes and functions as an air-liquid interface barrier. The unique cell death, corneoptosis, of the uppermost stratum granulosum keratinocytes (SG1 cells) initiates the formation of functional SC, although the exact mechanism of nuclear degradation remains unclear. Here, we performed *in vivo* live imaging of lysosomes in SG1 cells, whose proteases are considered to degrade organelles, and attempted to identify a key factor for lysosome recruitment. We found that among syntaxin (STX) family, proteins that involve intracellular organelle trafficking, the levels of mRNA for STX4 and STX12 were high in the mouse SG cells. Mouse SG1 cells that exogenously expressed GFP-STX4 revealed that GFP-STX4 localized around the nucleus and colocalized with lysosomes. Neither C-terminal transmembrane domain-deleted GFP-STX4 nor GFP-STX12 localized to perinucleus. Additionally, the electron microscopic analysis of SG1 cells in upper epidermis-specific STX4 conditional knock out ($^{uepi}STX4^{-/-}$) mice revealed that lysosomes did not localize to the nucleus at postnatal day 9. This $^{uepi}STX4^{-/-}$-epidermis exhibited acanthosis, hyperkeratosis, and hypergranulosis accompanied by increased number of SG1 cells compared to those of wild type mice. Finally, $^{uepi}STX4^{-/-}$ mice had a lower weight gain and die at around postnatal day 10. These results suggested that nuclear degradation of $^{uepi}STX4^{-/-}$-SG1 cells were dysregulated due to the impaired recruitment of lysosomes and STX4 is a key localizing factor of lysosomes in SG1 cells for their nuclear degradation in corneoptosis.

P05-02[III-4]

Type XVII collagen contributes to epidermal patterning

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Mammals exhibit epidermal patterning, as seen in mouse tail scales and human skin microtopography. The mechanisms behind the development of such patterning have not been elucidated. Here, we show that type XVII collagen (COL17), a niche for epidermal stem cells, modulates epidermal patterning. In mouse tail epidermis, the scales were found to be more slender in Col17-null mice than in Col17-intact mice. The transgenic rescue of Col17-null skin by the expression of human COL17 under the keratin 14 promoter reversed the slender-scale phenotype. Although COL17 interacts with the cell polarity factor aPKC-PAR complex, mice with dysfunctional aPKC did not show slender scales, suggesting that this phenotype is not related to cell polarity. As Col17-null skin shows skin fragility, we investigated wound-related factors that might account for the slender scales. The expression of wound-induced keratins was pronounced in Col17-null tail epidermis. Skin regeneration after wounding in C57BL/6 mice led to the slender scales, as seen in Col17-null skin. The slender-scale phenotype of the regenerated skin was alleviated by human COL17 overexpression in the epidermis. In a human junctional epidermolysis bullosa patient, COL17-negative, but not COL 17-positive, areas showed coarse epidermal patterns. These results demonstrate that COL17 is involved in regulating mouse tail scale morphology and human skin microtopography. Our study illuminates the role of the stem cell niche in tissue pattern formation.

P05-03[C06-02]

A skin-derived antimicrobial peptide human beta defensin-3-induced autophagy activation improves the skin barrier in atopic dermatitis

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The skin barrier dysfunction is one of the major pathogenic factors of atopic dermatitis (AD). We recently observed that the skin-derived antimicrobial peptide human beta-defensin (hBD)-3 improved the tight junction (TJ) barrier function in human primary keratinocytes through autophagy activation; however, the in vivo role of hBD-3 in AD development remains unclear. To evaluate the effect of hBD-3 on skin inflammation and TJ barrier function in AD mice, we established a skin-specific autophagy knockout AD mouse model (K14CreAtg7F/F AD mice). Following treatment with mouse beta-defensin (mBD)-14, a mouse homolog of hBD-3, we evaluated the dermatitis score, ear thickness, scratching behaviour and transepidermal water loss (TEWL) in autophagy-deficient AD mice. The expression of autophagy markers such as LC3 and p62 and TJ-related proteins in the skin samples was evaluated by Western blot and immunofluorescence, while the autophagic structure was assessed using electron microscopy. We observed downregulation of LC3, enhancement of p62, deterioration of autophagic structure and decrease of TJ-related proteins in the lesional skin of wild-type AD mice. Interestingly, mBD-14 treatment resulted in repairment of autophagy status and TJ barrier in AD mice. Moreover, K14CreAtg7F/F AD mice displayed increased ear thickness, severe dermatitis and scratching behaviour compared to the wild-type AD mice. Most importantly, mBD-14 failed to improve dermatitis in K14CreAtg7F/F AD mice, suggesting that activation of autophagy is required for the mBD-14-mediated improvement of AD symptoms. Collectively, our findings provide evidence that hBD-3 might be a therapeutic target for the treatment of AD, a skin disorder characterized by dysfunctional autophagy and skin barrier.

P05-04[C06-03]

Wnt/β-catenin signaling stabilizes hemidesmosomes in keratinocytes

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Keratinocytes are attached to the underlying basement membrane through hemidesmosomes (HDs) in the skin. HDs undergo assembly and disassembly to promote the differentiation and migration of keratinocytes. Wnt/β-catenin signaling is a crucial pathway that controls skin morphogenesis and homeostasis. Our group previously reported that type XVII collagen (COL17), an HD component, stabilizes Wnt/β-catenin signaling and proper stem cell maintenance in the epidermis. However, whether Wnt/β-catenin signaling is involved in HD assembly is unknown. Here, we show that Wnt/β-catenin signaling regulates the qualitative and quantitative expression of HD components in keratinocytes through the protein kinase C (PKC) pathway. Wnt inhibition diminished HD components including COL17 and plectin in HD-rich fractions in vitro. In line with this, COL17 and plectin were reduced at the basal side of Wnt-inhibited cells and at the dermo-epidermal junction of Wnt-inactive murine skin. Plectin-knockout cells or epidermolysis bullosa keratinocytes with plectin-COL17 binding defects also showed COL17 reduction at the basal side of the cultured cells, as in Wnt inhibition. PKC inhibition alleviated the phenotypes of Wnt-inhibited keratinocytes. These findings demonstrate that Wnt/β-catenin signaling organizes the localization of HD components in keratinocytes and that the PKC pathway mediates Wnt inhibition-induced HD disarrangement. Our study points to the modulation of Wnt-PKC axis as a potential therapeutic target for diseases caused by hemidesmosomal defects, such as epidermolysis bullosa.

P05-05[O12-01]

Relationship between regulatory T cell distribution and interleukin -33 in a mouse model of skin barrier disruption

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Skin barrier function proffers frontline protection against invasion by foreign substances and retains water in the body. Little is known about the dynamics of regulatory T cells (Tregs) when the skin barrier is broken. In this study, we investigated the relationship between skin barrier condition and kinetics of cutaneous Tregs in a skin barrier disruption mouse model produced by repeated topical application of 4% sodium dodecyl sulfate (SDS). The numbers of $CD4^+$ and $CD4^+Foxp3^+$Tregs were significantly higher in skin of 4% SDS-treated than control mice, whereas the numbers of cutaneous mast cells and eosinophils were unchanged in 4% SDS-treated mice. The number of Tregs correlated positively with presence of acanthosis. Acanthosis induced by skin barrier disruption gradually normalized when 4% SDS treatment stopped. Concomitantly, the numbers of $CD4^+Foxp3^+$Tregs increased during skin barrier disruption treatment and decreased one week after. The numbers of interleukin (IL)-10^+ and transforming growth factor (TGF)- B^+Tregs were also higher in skin barrier disrupted than control mice. Localization of IL-33 in keratinocytes shifted from nucleus to cytoplasm after skin barrier disruption. Notably, IL-33 promoted migration of Tregs in chemotaxis assay. FACS analyses showed they expressed ST2, the IL-33 receptor. Skin infiltration of Tregs ceased in IL-33 neutralizing antibody-treated mice and IL-33 knockout mice. Since Tregs are involved in negative regulation of immune responses and maintain immunological self-tolerance and homeostasis through secretion of IL-10 and TGF- B, our findings suggest keratinocyte-derived IL-33 may induce Treg migration into barrier-disrupted skin to control the phase transition between healthy and inflammatory conditions.

P05-06[C06-04]

New transparent three-dimension and deep imaging for skin epidermal structure using a novel fluorescent solvatochromic pyrene probe

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Histopathological examination of the skin tissue has been an essential and fundamental method as one of the experimental procedures. For example, a sliced tissue prepared as the vertical-cross section stained with hematoxylin-eosin staining is routinely used for histopathological diagnosis. However, several cross-section views need a composite image to see a horizontal cross-section view, and the delicate technique for serial sectioning is required. For this purpose, a confocal scanning laser microscope or two-photon excitation fluorescent microscopy is suitable for drawing fine pictures of three-dimension and deep images. However, the autofluorescence of the skin tissue could not describe a high-quality picture with sufficient resolution. To solve the current problem, we have established a new three-dimension and deep imaging method, especially for skin epidermal structure combined with optical clearance using a transparency-enhancing technique and a novel fluorescent solvatochromic pyrene probe. The technique revealed fine skin features and detailed epidermal structures, including the stratum corneum (horny layer), keratinocytes, eccrine sweat glands, and peripheral nerves. Notably, we also have succeeded in obtaining a three-dimensional reconstruction of an entire acrosyringium. In summary, this new fluorescence microscopy technique yields high-quality epidermal images and will aid in histopathological analyses of skin disorders in addition to the conventional histopathological approach.

P05-07[C06-05]

IL-33 is a negative regulator in skin barrier homeostasis

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Background: The skin protects and maintains proper moisture to the human body by providing a mechanical, chemical, and biological barrier. The stratum corneum (SC), the outermost epidermal layer is predominately associated with the skin barrier function. Interleukin (IL)-33 is a new tissue-derived cytokine, mainly expressed by cells of barrier tissues, such as epithelial and endothelial cells, and is known to activate Th2 lymphocytes, mast cells, ILC2, and eosinophils. Objectives: We aimed to study the role of IL-33 in skin barrier function. Materials and methods: Wild-type (WT), IL-33 knockout (IL-33KO) mice were tape stripped, and trans-epidermal water loss (TEWL) was monitored to confirm that barrier disruption was achieved by tape stripping. Samples were collected and measured every 24 hours interval. Hematoxylin and eosin staining and immunohistochemical analyses were performed to evaluate structural alteration, cell proliferation, and protein expression. Total RNA was extracted from the skin samples and real-time PCR was performed. Results: Tape stripping increased the thickness and proliferation of the epidermis, the thickness of the granular layer. We observed a thicker granular layer, and higher proliferation of epidermis, increased level of filaggrin (FLG), decreased mRNA expression of TSLP, increased mRNA expression of CCL17, and CXCL12 in IL-33KO mice compared to WT mice, in tape stripped conditions. Conclusion: Barrier disruption by tape stripping increases epidermal thickness and proliferation, induces the expression of filaggrin, CCL17, and CXCL12, suppresses the expression of TSLP in IL-33KO compared to WT mice, suggesting that IL-33 is negatively involved in skin barrier homeostasis.

P05-08[C06-06]

Loricrin maintains Langerhans cell homeostasis and protects against cutaneous chemical carcinogenesis

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The epidermis is a frontline defence system that protects against a myriad of assaults. The thiol-rich protein loricrin (LOR) organises extensive disulphide (-S-S-) cross-linkages above the tight junction. Langerhans cells (LCs) adhere to keratinocytes (KCs) and constitute homeostatic units in the epidermis. We investigated the function of LOR through the two-stage chemical tumorigenesis model, which requires LC-KC interactions. LOR-knockout (LKO) mice exhibited severe oxidative damage and high mutation burden to the chemical carcinogen 7,12-dimethylbenz[a] anthracene, with concomitantly increased LC emigration from the epidermis. As a result, LKO mice developed a higher number of benign papillomas. However, epidermal LCs in LKO mice constitutively expressed high exofacial levels of CD207. Percutaneous LC activation by the tumour promoter 12-O-tetradecanoylphorbol-13-acetate augmented the E-cadherin expression levels and relatively attenuated emigration from the epidermis in LKO mice. Consequently, the altered LC behaviour appears to have delayed tumour promotion and lowered the carcinoma/papilloma ratio. The results indicated that LOR confers thiol-mediated cytoprotection and may constitutively instruct LCs to maturate in the epidermis.

P05-09[C06-07]

Effect of ceramide chirality on the lipid lamellar structure in stratum corneum

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The presence of ceramide (CER), which is a typical constituent lipid, is important for maintaining the skin barrier function. It is known that CER [NDS] in the stratum corneum exists as a (2*S*, 3*R*)-CER, using an intercellular lipid model, we investigated a nanostructure formed focusing on the chirality of CER. The lipid model was prepared by CER (optically active CER[NDS] or racemic CER[NDS]), cholesterol and palmitic acid (PA). In the phase transition around 50 degree Celsius, the heat absorption by the optically active model was about twice that of the racemic model in differential scanning calorimetry. In addition, the transition of the peak position derived from CH_2 symmetry and asymmetry vibration was investigated from the infrared absorption profile obtained from the measurement with temperature scanning, a peak was observed on the slightly blue shift in the racemic model, and the ratio of change was slightly increased. In the absorption of amide, a peak was clearly observed in the lower wave number in the optically active model. Moreover, in the absorption derived from C=O vibration, the shape of the spectrum was maintained up to high temperature in the racemic model. In the optically active model, it was suggested that the interaction with PA was attenuated by the temperature rise, and the PA was desorbed to form an environment-friendly nanostructure. The optically active CER formed a stable nanostructure near the skin surface temperature, and was able to reconstruct the nanostructure through interaction with surrounding lipids in response to changes in the external environment such as increase in temperature. It is considered that chirality of CER plays an important role in maintaining the barrier function of the skin in response to environmental changes.

P05-10[C07-01]

Development of a novel skin model combining SNF and collagen

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Silica nonwoven fabrics (SNF) prepared by the electrospinning method have high biocompatibility, thermal stability and high porosity, which enable the three-dimensional culture of cells. We have been investigated SNF to create skin models consisting of epidermis and dermis comparing them with collagen skin models. As a result, SNF skin models have enhanced functions in basement membrane, while collagen skin models have advantages in keratinization and barrier functions. The SNF skin model with mechanical strength formed a basement membrane mimic structure, suggesting the construction of a stable skin model. Here, we constructed a three-dimensional skin model consisting of SNF and collagen to further improve the previous model. We examined two models, sCS and tCS skin model. The sCS skin model in which the surface of SNF were modified with collagen, and tCS skin model in which void of SNF were filled with collagen gels. Fibroblast cell line NIH3T3 and epidermal keratinocyte line HaCaT were used to construct both models. Each model was evaluated by observation of hematoxylin and eosin staining, quantification of various epidermal/dermal-related gene expressions using real-time PCR. As a result, a significantly thicker epidermal layer was formed in the tCS skin model. Real-time PCR showed that both models significantly increased the expression of genes expressed in the basement membrane than collagen skin model and keratinization were enhanced than SNF skin model. In particular, the expression barrier function was significantly upregulated in the tCS skin model compared to the SNF skin model. Therefore, it is suggested that the tCS skin model can be a biomimetic model that takes advantage of both SNF and collagen and can be applied to various basic research.

P05-11[C07-02]

Nuclear factor erythroid 2-related factor 2 regulates epidermal keratinization under psoriatic skin inflammation

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Psoriasis is an autoinflammatory/autoimmune skin disease and the epitome of exaggerated primary inflammatory response in the surface barrier tissue. Despite the efficacy of dimethyl fumarate (DMF), an electrophilic drug for psoriasis management, there is a paucity of mechanistic evidence in vivo. In response to electrophiles, the Kelch-like ECH-associated protein 1 (KEAP1)/nuclear factor erythroid 2-related factor 2 (NRF2) system mediates a myriad of cytoprotective mechanisms, including the regulation of excessive inflammatory response and epidermal differentiation. Since the psoriasiform tissue reaction comprises neutrophil infiltration and parakeratotic scaling, we hypothesized that Nrf2 not only regulates inflammatory responses but is also required for the maintenance of epidermal differentiation, a hallmark of epidermal homeostasis. By utilizing the imiquimod-induced cutaneous inflammation model, we showed an exaggerated inflammatory response and impaired epidermal differentiation in *Nrf2*$^{-/-}$ mice. DMF treatment in *Nrf2*$^{+/+}$mice attenuated psoriasiform tissue reaction and rescued epidermal differentiation, which was not observed in *Nrf2*$^{-/-}$ mice. In accordance with the fact that psoriasis plaques form well-demarcated parakeratotic lesions in association with the psoriasiform tissue reaction, the lesional skin exhibited reduced expression levels of NRF2 and its downstream target genes compared with non-lesional skin. In conclusion, our results suggest that Nrf2 attenuates psoriasiform tissue reaction and underscore the mechanistic legitimacy of the electrophile-based approach for the management of psoriasis.

P05-12[O12-02]

Upregulation of the NMF producing enzyme PAD1 by low humidity and low temperature climate gives the skin adaptability to dry environments

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Background: How does our skin adapt to dry environment? We have previously reported that filaggrin-derived natural moisturizing factor (NMF), which plays a key role in skin moisturization, increases in the winter (low temperature and humidity) compared to the summer (high temperature and humidity). However, the mechanism has not been fully investigated. Therefore, we attempted to elucidate the mechanism by which filaggrin-derived NMF increases in the winter and to clarify the adaptive capacity of human skin against dry environments.
Method: The stratum corneum was collected from the same individual during the summer and winter (n=32) and the amount of NMF as well as the activity levels of representative NMF-producing enzymes, peptidyl arginine deiminase (PAD) and bleomycin hydrolase (BH) was analyzed. 3D skin models were then utilized to determine the impact of changes in temperature and humidity conditions on the gene and protein expression levels of PAD and BH. PAD1 knockdown 3D skin model was also established and analyzed NMF and citrullinated protein levels.
Results and Conclusion: The activities of NMF-producing enzymes, PAD and BH, and filaggrin-derived NMF were found to be increased in the winter compared to the summer, in vivo. Interestingly, the decrease in humidity and temperature did not change the gene expression level of BH but increased the gene and protein expression of PAD1. We therefore utilized PAD1 knockdown 3D skin model and found that citrullinated proteins and certain NMF were reduced. These results suggest that in dry environments such as during the winter, our skin senses the decrease in humidity and temperature in the external environment and increases the production of PAD1, thereby accelerating NMF production and adapting to the dry environment.

P05-13[O12-03]

The sweating disturbance aggravates contact hypersensitivity reaction in mice footpads

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Skin surface hydration (SSH) is one of the critical metrics to evaluate skin dryness and decrease of SSH may cause allergic diseases such as atopic dermatitis and hand eczema. Recently, sweating capacity is recognized as an essential factor for maintaining SSH. However, few studies have focused on the relationship between sweating and skin barrier function. In this study, we investigated the effect of sweating disturbance on contact hypersensitivity reaction (CHS) in mice footpads using anticholinergics agents-administrated the sweating impairment model. C57BL/6J mice were sensitized by an epicutaneous application of hapten solution to the ear a week before elicitation. The footpad was administered epicutaneously with anticholinergics agents and confirm a decrease of sweating, then elicited by hapten solution. CHS reactions were assessed by measuring footpads' thickness and swelling at 24 hours after elicitation. The footpad sweating condition was evaluated by the impression mold technique and SSH. In addition, hapten concentration in footpad skin was measured. When anticholinergics agent was applied on mice footpads, initial SSH (Mean ± SEM=352.2 ± 10.7) was significantly decreased (79.6 ± 12.5) in 30 minutes after treatment. Which lasted for 2 hours and gradually restored by time. Initial number of sweat droplets (71.7 ± 1.8) was also significantly decreased (12.8 ± 6.9) in the same manners. Thickness and swelling of footpads were significantly increased in anticholinergics agent-administered mice group compared with control mice. In this study, we showed that sweating disturbance related SSH decrease aggravated a CHS reaction in elicitation due to increased hapten absorption. These results concluded that sweating play an important role in development of CHS.

P05-14[O12-04]

TSLP impairs epidermal barrier integrity by the formation of nuclear IL-33/phosphorylated STAT3 complex in human keratinocytes

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Atopic dermatitis (AD) is an inflammatory skin disease characterized by skin barrier dysfunction. Although Th2 cytokines downregulate the expression of epidermal barrier proteins, the signaling mechanism underlying these effects remains unclear. IL-33 is a chromatin-associated cytokine and highly expressed in the nuclei of epidermal keratinocytes in AD skin. However, it is unclear whether the nuclear expression of epidermal IL-33 directly promotes the development of AD. TSLP, an epithelial cells-derived pro-Th2 cytokine, is elevated in the epidermis of AD patients. TSLP affects the pathogenesis of AD by activating Th2 responses and impairing epidermal barrier integrity. In this study, we stimulated post-confluent human keratinocytes and living skin equivalent with TSLP to investigate the role of nuclear IL-33 in TSLP-induced epidermal barrier defects. We observed that TSLP reduced the levels of FLG, hBD2, S100A7, and claudin-1, which required nuclear IL-33 expression. Similar to the Th2 cytokines IL-4, IL-13, and IL-31, TSLP was shown to upregulate IL-33 expression and trigger the formation of nuclear IL-33/phosphorylated STAT3 complex, which was bound to the FLG promoter, thereby inhibiting transcription. Moreover, nuclear IL-33 acted as a cofactor of STAT3 in the TSLP-induced transcriptional repression of hBD2, S100A7, and claudin-1. Therefore, epidermal nuclear IL-33 may be a key regulator of TSLP-mediated epidermal barrier dysfunction.

P05-15[C07-03]

The ligand of epidermal growth factor receptor, betacellulin, improves Th2 cytokine-mediated impairment of tight junction barrier

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Betacellulin (BTC) belongs to the epidermal growth factor family, whose members have been implicated in skin morphogenesis, homeostasis, repair and angiogenesis, however, the role of BTC in regulation of skin barrier remains unknown so far. To examine the role of BTC in skin barrier function, we analysed data from two independent Gene Expression Omnibus (GEO) datasets. We found that the gene expression of BTC was higher in skin lesions from patients with atopic dermatitis (AD), and this expression returned to normal levels following biological treatment, suggesting that the levels of BTC in the skin might be a biomarker for the therapy of AD. Moreover, following stimulation of normal human epidermal keratinocytes with different cytokines, we observed that the mRNA expression of BTC was significantly inhibited by only Th2 cytokines such as IL-4 and IL-13, which play a pivotal role in the pathogenesis of AD. Furthermore, the specific inhibitor of epidermal growth factor receptor abolished the BTC-mediated improvement of tight junction (TJ)-related proteins, including claudin-1 and claudin-4 and the increases in transepidermal electrical resistance, a functional parameter to monitor the TJ barrier. Importantly, BTC also rescued the downregulation of claudin-1 and claudin-4 in IL-4 plus IL-13-treated human keratinocytes. Together, we propose that BTC might be a novel potential biomarker and therapeutic target for the treatment of skin diseases with overproduction of Th2 cytokines and dysfunctional skin barrier such as atopic dermatitis.

P05-16[O12-05]

The contribution of single nucleotide polymorphisms of AKR1C3 to susceptibility of psoriasis

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Psoriasis is a multifactorial disease with a complex etiology involving genetic risk factors. In human epidermis, aldo-keto reductase (AKR) 1C3 regulates keratinocyte differentiation We hypothesized that single nucleotide polymorphisms (SNPs) in AKR1C3 is associated to onset of psoriasis. In 232 psoriasis patients, including 171 males and 61 females, a TaqMan SNP genotyping assay revealed that the rs12529 genotype distribution in our cohort was G/G: 75.0%, G/C: 22.8%, and C/C: 2.2%, and the rs12387 genotype distribution was A/A: 75.0%, A/G: 22.8%, and G/G: 2.2%. Surprisingly, these 2 SNPs were always observed in the same patients. The proportion of patients with both the rs12529 G/C, C/C and rs12387 A/G, A/A variants was 2-fold higher than that in 2 cohorts of healthy Japanese individuals in the NCBI database (rs12529, p=0.0088 [vs. ss69068306], p=0.024 [vs. ss71643788]; rs12387, p=0.037 [vs. ss 2827707], p=0.024 [vs. ss66361131] Fisher's exact test). The number of female patients with disease onset<23 years of age having both the rs 12529 G/C, C/C and rs12387 A/G, G/G variants was significantly higher than that having the rs12529 G/G and rs12387 A/A variants (p=0.0213, Fisher's exact test). Immunohistochemical staining of lesional psoriasis skin samples obtained from patients with the rs12529 G/C, C/C and rs 12387 A/G, G/G variants revealed significantly lower expression of AKR1 C3 in the epidermis compared to patients with the rs12529 G/G and rs 12387 A/A variants (p=0.0434, Student's t test). AKR1C3 downregulation in the epidermis induces abnormal terminal differentiation and skin barrier dysfunction. This may contribute to exposure to environmental factors such as tobacco smoke or environmental pollution, which may increase disease susceptibility of psoriasis.

P05-17[O12-06]

Sphingosine 1-phosphate receptor 1 (S1PR1) negatively regulates epidermal barrier function

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Background: Sphingosine 1-phosphate (S1P) is a bioactive sphingolipid mediator generated from ceramides and their metabolites. S1P is involved in various cell activities via different S1P receptor (S1PR) 1-5. We previously reported that the S1P-S1PR2 axis is essential to maintain skin homeostasis during epidermal barrier disruption. As a next step, we started to analyze other S1PRs in the epidermal barrier function. *Methods:* We used BALB/c mouse epidermis to evaluate the *S1pr1-5* mRNA expression before and after sequential tape stripping. We also used normal human epidermal keratinocytes (NHEKs) to analyze filaggrin (FLG), corneodesmosin (CDSN), and ZO1 expression. *Results:* The sequential tape stripping induced significantly increased *S1pr1* and *4* expressions in the mouse epidermis, so we considered that not only S1PR2 but also S1PR1 and 4 are involved in the epidermal barrier homeostasis. Since S1PR4 expression is the lowest in all S1PRs in NHEKs, we focused on analyzing the role of S1PR1 in NHEKs. *S1PR1* knockdown with siRNA in NHEKs increased FLG and CDSN expressions but did not affect ZO1 expression. *Conclusions:* Different S1P receptors perform different functions in the epidermis in keeping the barrier efficient. While the absence of S1PR2 causes an increase in permeability, the absence of S1PR1 has an opposite effect. Future studies will aim to understand better which mechanisms preferentially activate one of the two pathways.

P05-18[O09-05]

Antimicrobial peptide AG30/5C modulates tight junction barrier function in keratinocytes via EGFR, aPKC, GSK-3 and Rac1 pathways

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AG-30/5C is an antimicrobial peptide, which was discovered by the functional gene screening process for molecules with angiogenic properties. Similar to other antimicrobial peptides such as human β-defensins and LL-37, it was reported that AG-30/5C exerts pleiotropic functions, including the cytokine/chemokine production, angiogenesis and wound healing, in addition to its broad-spectrum antimicrobial activity. Given that human β-defensins and LL-37 improve the epidermal tight (TJ) barrier function, we aimed to investigate the role of AG-30/5C in regulation of TJ barrier in human primary keratinocytes. The expression of TJ-related proteins and activation of signaling pathways was determined by Western blot. Intracellular distribution of TJ-related proteins was examined by immunofluorescence. Transepithelial electrical resistance (TER), a parameter to assess the TJ barrier function, was measured using cellZscope. We found that AG30/5C increased the expression of various TJ-related proteins, including claudin-1 and claudin-4 and enhanced their intracellular membrane distribution in keratinocytes. Furthermore, AG30/5C elevated TER in keratinocyte monolayers. Investigation of the molecular mechanism suggested that AG30/5C-mediated regulation of TJ function was controlled by epidermal growth factor receptor, Rac1, atypical protein kinase C and glycogen synthase kinase-3 pathways, as evidenced by the inhibitory effects of pathway-specific inhibitors. Indeed, we confirmed that AG30/5C induced phosphorylation of above pathways. Our findings provide novel evidence regarding the contribution of AG30/5C in modulation of cutaneous immunity through improvement of epidermal barrier function, in addition to its antibacterial activity and other immunomodulatory properties.

P05-19[O09-06]

Mechanisms underlying the suppression of semaphorin 3A expression in atopic dermatitis

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Epidermal hyperinnervation causes itch sensitivity at the periphery and is mainly attributed to an imbalance between the expression of nerve growth factor and semaphorin 3A (Sema3A) in keratinocytes. We previously reported that Sema3A levels were lower in the lesional skin of atopic dermatitis (AD) than in normal skin. We more recently showed that *Sema3A* expression in normal human epidermal keratinocytes (NHEKs) was modulated by the calcium, MEK1/2, and AP-1 signaling axis. However, the mechanisms suppressing the expression of *Sema3A* in lesional skin of AD have not yet been elucidated. Several AD-mimicking models have recently been generated by silencing *filaggrin* (*FLG*) and adding cytokines overexpressed in the AD epidermis. Therefore, the present study investigated the mechanisms suppressing the expression of Sema3A in AD using AD-mimicking keratinocytes. We initially examined the effects of cytokines, such as interleukin (IL)-4, IL-13, IL-31, tumor necrosis factor (TNF)-α, interferon-γ, IL-1β granulocyte-macrophage colony-stimulating factor, IL-17A, IL-22, and IL-25, on the mRNA expression of *Sema3A* in NHEKs. *Sema3A* expression was increased by IL-4, IL-13, and TNF-α, but was not affected by the other cytokines tested. The combination of IL-4, IL-13, IL-22, and TNF-α significantly decreased *FLG*, *CASP14*, *CAPN1*, and *BH* mRNA expression in NHEKs, but increased *Sema3A*, *KAL-1*, and *CLDN1* mRNA expression. We then examined the effects of *FLG* silencing on the expression of *Sema3A* in NHEKs. *FLG* silencing in NHEKs suppressed the expression of *Sema3A*. This effect was not altered by the above-mentioned cytokine combination. Collectively, these results suggest that the suppression of Sema3A expression is influenced by skin barrier defects, but not by cytokines.

P05-20[O09-07]

A skin-derived antimicrobial peptide AMP-IBP5 regulates epidermal barrier function

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Background: Antimicrobial peptide derived from insulin-like growth factor-binding protein 5 (AMP-IBP5) not only displays antimicrobial activity but also shows pleiotropic immunomodulatory properties, including regulation of cutaneous immunity through cytokine/chemokine production and promotion of keratinocyte migration and proliferation. However, the role of AMP-IBP5 in the regulation of skin barrier remains unclear. Objective: To investigate the effects of AMP-IBP5 on skin barrier function and clarify the underlying mechanisms. Methods: Normal human epidermal keratinocytes were stimulated with AMP-IBP5 and Western blot was used to analyze the expression of differentiation markers and tight junction (TJ)-related proteins, and the signaling pathways. Immunofluorescence microscopy was used to examine the intercellular distribution of TJ proteins. Transepithelial electrical resistance (TER) was measured using CellZscope. Various inhibitors were used to clarify the molecular mechanism by which AMP-IBP5 regulates epidermal barrier function. Results: AMP-IBP5 increased the expression of various TJ proteins, including claudin-1, -2, -4, -7, occludin, zonula occludens 1 and enhanced their distribution along the cell-cell borders. AMP-IBP5 also enhanced the expression of differentiation markers such as filaggrin, loricrin, transglutaminase 1 and keratin 1, and improved the TJ barrier function by increasing TER. In addition, AMP-IBP5 increased the phosphorylation of aPKCZ and Rac1. Specific inhibitors against aPKCZ and Rac1 suppressed AMP-IBP5-induced expression of TJ-related proteins and TER. Conclusion: AMP-IBP5 might be a therapeutic target for skin diseases with skin barrier defects such as atopic dermatitis and psoriasis through improvement of the skin barrier function.

P05-21[O09-08]

Spatial distribution of KLK, SPINK, and SERPIN family proteins contributes to dense stratum corneum of normal sole skin and PPK phenotypes

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Human skin changes its biochemical and anatomical characteristics according to body site to secure specific functions. The palmoplantar skin lacks hair follicles unit but rich in eccrine glands, and the thick stratum corneum forms densely continuous structure distinct from that of the trunk skin. The purpose of this study was to understand the difference of keratinization process, innate and acquired immunity between human palmoplantar and non-palmoplantar skin by differential gene expression. RNA was extracted from trunk and sole for RNA-seq analysis. We could confirm that Langerhans cells, defined by CD1 and CD207, decreased in sole skin, while antimicrobial peptides were expressed higher than in trunk skin. Among KLKs and their inhibitor SPINKs and SERPINs which govern the thickness of stratum corneum, the expression of KLKs was generally decreased in plantar skin. SPINK5 and SERPINB7, a causative gene of Netherton syndrome and Nagashima-type palmoplantar keratosis respectively, were almost equally expressed in sole and trunk. Whereas SPINK6, and 9 were highly expressed in sole skin but not in trunk skin. We think that these distinct protease inhibitors expression and compensation contribute to dense cornified layer of normal palmoplantar skin and explain the reason why a Netherton syndrome patient with SPINK5 mutation show mild skin vulnerability in palmoplantar region. Although, the distribution of SERPINB7 expressed in both palmoplantar and non-palmoplantar skin reflects the symptoms of Nagashima-type palmoplantar keratosis whose hyperkeratosis extends beyond the margin of palmoplantar skin, it does not fully explain why keratinization is milder on trunk skin than on palmoplantar skin. Other SERPIN family members might compensate in trunk skin.

P05-22[O09-09]

Detergent-induced skin inflammation and itch in a mast cell-independent and antihistamine-resistant manner in C57BL/6 mice

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Background: Treatment with a detergent, sodium dodecyl sulfate (SDS), of shaved back skin for four days is known to induce itch in a manner sensitive to a histamine-1 receptor (H1R) antagonist in ICR mice. We examined responses induced by SDS treatment of ear skin of another strain of mice, C57BL/6. Methods: Ear skin of mice was treated with SDS for ten days to two weeks. Skin inflammation, barrier dysfunction, and hind paw scratching behavior were analyzed in wild-type and mast cell-deficient mice. Effect of administration of an H1R antagonist thirty minute before the measurement of the scratching behavior was examined. Results: The consecutive SDS treatment induced the inflammation, barrier dysfunction, and scratching behavior in wild-type C57BL/6 mice and mast cell-deficient mice. The H1R antagonist administration, which inhibited scratching behavior induced by intradermal injection of histamine, did not affect the SDS-induced itch in wild-type mice. Conclusions: We showed that SDS treatment of ear skin of C57BL/6 mice can induce itch-associated skin inflammation in a mast cell-independent manner, although more slowly than that of back skin of ICR mice previously reported by another research group. Different from the previous report for ICR mice, SDS-induced itch in the present C57BL/6 model showed resistance to an H1R antagonist. The mechanism of the inflammation and antihistamine-resistant itch in the model is yet to be elucidated.

P05-23[O09-10]

Possible roles of advanced glycated end-products in pathogenesis of acquired perforating dermatosis

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Background: Acquired perforating dermatosis (APD) is an uncommon group of skin disorders characterized by the transepidermal elimination of dermal connective tissue. The classic forms of APD include Kyrle's disease, acquired perforating folliculitis, acquired reactive perforating collagenosis (ARPC), and elastosis perforans. The rare forms include perforating granuloma annulare and chondrodermatitis nodularis chronica helicis (CNCH). **Objective**: To clarify pathomechanisms of two types of perforating dermatosis, ARPC and CNCH. **Methods**: We performed histological and immunohistochemical analyses of the skin lesions of ARPC and CNCH in a patient with type 2 diabetes mellitus and chronic renal failure. **Results**: Histopathologically, the transepidermal elimination of degenerated collagen fibers and cartilage were seen in the lesion of ARPC and CNCH, respectively. In addition, immunostaining revealed both the eliminated connective tissue and cartilage to positively stain with the anti-AGEs (advanced glycated end-products) antibody. **Conclusion**: The histopathological and immunohistochemical findings in the present study suggest that both ARPC and CNCH might share similar pathogenic mechanisms of degeneration of the connective tissue and/or cartilage associated with scratching and consequent trauma based on pruritus, and with the advanced glycation of proteins in the connective tissue and/or cartilage due to background systemic disease.

P05-24[O09-11]

Functional analysis of BCL6 in epidermal cells

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BCL6 is a transcriptional repressor which has emerged as a critical regulator of germinal centers, the sites where B cells are selected based on the production of antibodies with high affinity for the antigen. We previously found that tamoxifen-inducible BCL6 and Foxp3 double knockout (BCL6/Foxp3 cDKO) mice developed dermatitis and showed disturbed expression of epidermal differentiation markers. Since BCL6 is expressed not only in immune cells but also keratinocytes, loss of BCL6 in keratinocytes may contribute to differentiation defects in epidermis of BCL6/Foxp3 cDKO mice. However, the role of BCL6 in keratinocyte differentiation is largely unknown. In this study, we examined the role of BCL6 in keratinocyte differentiation using human keratinocytes. We found that BCL6 expression was increased during Ca^{2+} -induced differentiation of human keratinocytes. We further investigated the effect of BCL6 inhibitor on keratinocyte differentiation and found that inhibition of BCL6 impaired formation of cell-cell adhesion in response to differentiation-inducing stimuli. Real-time RT-PCR analysis revealed that inhibition of BCL6 also impaired induction of differentiation markers including K1, involucrin, loricrin, and filaggrin in human keratinocytes. Taken together, our results suggest that BCL6 is expressed in keratinocytes and positively regulates keratinocyte differentiation.

P06-01[I-1]

CRISPR/Cas9 targeting an intronic region for retrieving Col17 expression in junctional epidermolysis bullosa model mice

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Junctional epidermolysis bullosa (JEB) comprises a group of hereditary disorders characterized by mechanical stress-induced blistering. The *COL17A1* gene, which is a causative gene for JEB, encodes one of the major components of hemidesmosomes, namely type XVII collagen (COL17). CRISPR/Cas9 is known as the most powerful gene editing tool by two pathways: the inefficient but error-free homology-directed repair (HDRs) pathway and highly efficient but error-prone non-homologous end joining (NHEJ) pathway. Here, we report an efficient NHEJ CRISPR-mediated *Col17a1* editing to retrieve Col17 expression in JEB model mice. We first generated model mice with frameshift mutations in exon 2 ($Col17a1^{exon2fs}$) or exon 3 ($Col17a1^{exon3fs}$) of *Col17a1* leading to deficient Col17 expression. Then, compound heterozygous model mice ($Col17a1^{exon2fs/exon3fs}$) were produced by cross-breeding these mice. They showed the phenotype that resembled those seen in generalized intermediate JEB patients. The CRISPR/Cas9 system targeting intron 2 of *Col17a1* was designed to created DNA double-strand breaks (DSBs) in epidermal keratinocytes obtained from the compound heterozygous mice (*in vitro*) and in skin of these mice (*in vivo*). *In vitro*, after CRISPR/Cas9 treatment, recovery of Col17 expression in the mutant mouse keratinocytes were observed by immunofluorescence (IF) staining. Moreover, by flow cytometry analysis, in the treated mutant cell population, the high expression of Col17 was observed at a greater rate than non-treated cells. *In vivo*, one month after injecting CRISPR/Cas9 vectors into the skin, the high expression of Col17 in basal keratinocytes were seen by IF. In conclusion, our results demonstrated that CRISPR/Cas9 targeting an intronic region can retrieve Col17 expression in JEB model mice.

P06-02[C08-02]

Altered replication stress response due to *CARD14* mutations induces somatic genetic reversion

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Revertant mosaicism represents a naturally occurring somatic event in which pathogenic mutations are corrected in patients with hereditary diseases. This “natural gene therapy” phenomenon has been reported in only approximately 50 human genetic disorders including epidermolysis bullosa and ichthyosis, where genetic reversion occurs through back mutation, second-site mutation, and/or homologous recombination. However, the process by which mutant proteins induce somatic genetic reversion in these diseases remains unknown. In this study, we analyzed two unrelated Japanese patients with pityriasis rubra pilaris type V caused by heterozygous mutations in *CARD14*, and discovered that revertant mosaicism can occur mainly via homologous recombination in this disease. We next sought to elucidate the molecular mechanisms underlying this self-healing phenomenon by analyzing the impact of mutant CARD14 on DNA damage and replication stress, as well as the response to these events. Rather than altering the DNA damage response to exogenous stimuli such as X-irradiation or etoposide treatment, mutant CARD14 increased DNA double-strand breaks under replication stress conditions. Moreover, mutant CARD14 suppressed new origin firings without promoting crossover events in the replication stress state. Together, these results suggest that mutant CARD14 alters the replication stress response and preferentially drives break-induced replication, both of which may play important roles in homologous recombination-mediated genetic reversion observed in patients’ epidermis. Fully elucidating the molecular mechanisms underlying this phenomenon may pave the way for the development of innovative therapies for genetic diseases with currently limited therapeutic options.

P06-03[C08-03]

A novel keratin 14 mutation in epidermolysis bullosa induces more morphological abnormalities in keratin fiber than a hotspot mutation

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Epidermolysis bullosa simplex (EBS), a hereditary bullous disease, is mainly caused by *keratin (K)5* and *K14* mutation. We found a Japanese family with EBS generalized severe (EBS-gen sev) carries a heterozygous mutation for novel *K14* c.1087dupA (p. G364Rfr*118), which leads a frameshift and encodes an elongated protein due to a delayed terminal codon. The pathogenetic role of the novel *K14* mutation reminds unclear. To elucidate the pathogenic impact of K14 G364RFr*118 mutations, we generated doxycycline (Dox)-inducible K14 wild-type (WT), the hotspot mutation K14 R125C, or K14 G364Rfr*118 via a lentiviral vector in HaCaT cells. Transfected K14 exhibited dot- or ball-like aggregates in the cytosol of K14 R125C as well as K14 G364Rfr*118 cells. Notably, aggregated filaments of K14 G364Rfr*118 cells were large and prominent, and the number of keratin-aggregated cells was significantly higher in K14 G364Rfr*118 cells than in K14 R125C. To see if K14 G364R Fr*118 can affect the impairment of autophagy, expression of mitochondria and autophagy-related genes were analyzed. Mitochondria distributed around the nucleus in K14 WT cells, whereas that was decreased in K14 R125C and G364Rfr*11. Moreover, dot-like aggregation of mitochondria was observed to the same extent in two K14-mutated cells. RNA sequence revealed no significant difference in autophagy-related genes among the cells. The novel K14 G364Rfr*118 mutation causes morphological abnormalities in keratin fibers that are different from those of K14 R125C mutation but have the same level of impact on cellular homeostasis, including autophagy.

P06-04[C08-04]

Diversity of Mechanisms Underlying Dysregulating TGF-β Signaling in Recessive Dystrophic Epidermolysis Bullosa

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Injury- and inflammation-driven progressive and devastating dermal fibrosis is one of the most severe manifestations of recessive dystrophic epidermolysis bullosa, a genetic skin blistering disease caused by mutations in *COL7A1*. Activation of TGF-β signaling plays a crucial role in progressing dermal fibrosis. However, the underlying mechanisms are not fully elucidated. TGF-β is secreted in a latent form, which has to be activated for its biological functions. In this study, we determined that recessive dystrophic epidermolysis bullosa fibroblasts have an enhanced capacity to activate the latent form. Mechanistic and functional assessment demonstrated that this process depends on multiple latent TGF-β activators, including thrombospondin-1, RGD-binding integrins, matrix metalloproteinases, and reactive oxygen species, which act in concert and stimulate each other, in a vicious and self-perpetuating feedback loop to progress fibrosis. Importantly, our study also disclosed keratinocytes as prominent facilitators of fibrosis in recessive dystrophic epidermolysis bullosa. They stimulate microenvironmental latent TGF-β activation through enhanced production of the above latent TGF-β activators, suggesting that correction of both keratinocytes and fibroblasts will be needed for the most effective curative therapies. Collectively, our study offers new insights on the molecular mechanism behind dysregulated TGF-β signaling in recessive dystrophic epidermolysis bullosa, which are much needed for the development of evidence-based fibrosis-delaying treatments.

P06-05[C08-05]

Psoriasis-like skin lesions in a patient carrying *MEFV* variants

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Familial Mediterranean fever (FMF) is an autoinflammatory disorder associated with *MEFV* gene mutations. *MEFV* encodes pyrin, and aberrant pyrin function due to *MEFV* mutations leads to the hyperactivation of the interleukin (IL)-1β pathway. FMF is clinically characterized by self resolving bouts of fever accompanied by peritonitis, pleuritis and arthritis. There have been reports of psoriasis-like lesions in patients with FMF caused by *MEFV* mutations. IL-1β activation participates in the differentiation of Th17 cells. Therefore, it is predicted that Th17 cell activation through the aberrantly activated IL-1β cascade may be associated with the development of psoriasis-like lesions in patients with FMF. We studied an 18-year-old male with psoriasis-like skin lesions on the soles, the toes, the knees and the elbows that had been present since age 12. The plantar lesions were sometimes accompanied by pustules. A skin biopsy specimen from the plantar lesion showed features of psoriasiform dermatitis, such as parakeratosis, the absence of granular layers and the elongation of rete ridges in the epidermis, and the infiltration of lymphocytes in the papillary dermis. The patient’s maternal aunt and niece had been diagnosed with FMF, but the patient himself had no symptoms characteristic of FMF. Whole-exome sequencing (WES) showed that the patient had the compound heterozygous variants p.Glu 148Gln and p.Ser503Cys in *MEFV*, although WES revealed neither *IL36RN* nor *CARD14* mutations/variants in the patient. There have been no reports of psoriasis-like skin lesions in *MEFV* variant carriers. The findings in the present patient suggest that the psoriasis-like skin lesions might be associated with the *MEFV* variants.

P06-06[C08-06]

Transcriptional and translational interference of laminin-332 subunits in junctional epidermolysis bullosa with *LAMB3* mutations

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Junctional epidermolysis bullosa (JEB) is one of the four major subtypes of EB. About 80 percent of patients with laminin-332-deficient JEB have mutations in *LAMB3*, encoding the β3 subunit of laminin-332, a heterotrimeric protein (α3, β3 and γ2 laminin polypeptides) at the dermal-epidermal junction (DEJ). Although the laminin-332 molecular pathology in JEB involves mutations in any of the *LAMA3*, *LAMB3* or *LAMC2* genes encoding the respective polypeptides, it is not clear whether or how mutations in any one of these genes affect the expression of the other two genes or proteins, and how this impacts on phenotype. Here, we report three JEB patients with compound heterozygous *LAMB3* mutations presenting a variable degree of blistering, nail and teeth abnormalities. Quantitative PCR revealed a significant decrease of *LAMA3*, *LAMB3*, *LAMC2* transcripts in all three patients. Immunofluorescence microscopy showed either absence or decreased expression of the β3 and γ2 subunits at DEJ whereas α3 subunit immunoreactivity showed linear labelling at the DEJ, similar to control skin. To investigate whether *LAMA3* and *LAMC2* reduction is reproducible, siRNA knockdown of *LAMB3* in normal human epidermal keratinocytes was performed. The knockdown efficiency was greater than 90 percent, and *LAMA3* transcripts were significantly reduced. *LAMC2* was modestly reduced by one of the two *LAMB3* siRNAs. Furthermore, the interference by *LAMB3* knockdown was exclusive to laminin-332 since the transcription of other laminin genes expressed in keratinocytes and at the DEJ was not affected. Our study illustrates the complexity of laminin-332 heterotrimer pathobiology and the clinical challenge in delineating accurate genotype-phenotype correlation in this group of patients.

P06-07[O02-01]

Aberrant keratin assembly causes impaired mitochondrial movement and function: Implications for epidermolysis bullosa simplex pathogenesis

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Mitochondria is known as dynamic organelles, which move inside cells along the cytoskeleton and change their shape and size by mitochondrial fusion and fission. The role of mitochondrial dynamics in skin homeostasis is unknown. Abnormal mitochondrial distribution has been reported in epidermolysis bullosa simplex (EBS), a type of epidermolysis bullosa that is caused by a mutation in *KRT5* or *KRT14*. We hypothesized that keratin filaments may affect mitochondrial movement and function. In immunoprecipitation assays and proximity ligation assays, mitofusin 2, an outer mitochondrial membrane protein regulating mitochondrial fusion, was found to connect mitochondria with K5/14. Time-lapse imaging showed that the mitofusin 2 and to move along K14. Moreover, to evaluate mitochondrial movement and function in EBS patients, we generated HaCaT cell with mutant K14 harboring p.Arg125 Cys, the most common mutation in Dowling-Meara type of EBS. The mutant K14 caused keratin clumping in the cytoplasm, abnormal mitochondrial motility, increase of mitochondrial reactive oxygen species (ROS) and reduction of ATP production. These data indicate that keratin clumping disrupts normal mitochondrial motility, leading to unsuitable mitochondrial positioning and dysfunction. Mitochondrial dysfunction in EBS keratinocytes might cause failure of its homeostasis and be one of the reasons why skin fragility occur in EBS patients. We propose that the translocation of mitochondria is important for skin homeostasis and that mitochondrial dysfunction may be a pathogenic event in EBS.

P06-08[O02-02]

Mutations in SAM syndrome and palmoplantar keratoderma patients suggest genotype/phenotype correlations in *DSG1* mutations

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In *DSG1*, which encodes desmoglein 1, monoallelic mutations cause autosomal dominant palmoplantar keratoderma (PPK) and biallelic mutations cause severe dermatitis, multiple allergies, and metabolic wasting syndrome (SAM). We aim to clarify genotype/phenotype correlations in such patients with *DSG1* mutations. We studied the clinical, histopathological and ultrastructural features of the patients. In addition, we investigated desmoglein 1 expression in the epidermis of the SAM patient. We performed whole-exome sequencing and Sanger sequencing to detect causative mutations in the patients. The SAM patient had no extracutaneous symptoms. The PPK patient showed DPPK with hyperkeratosis on the dorsal aspect of the big toes and elbows. In *DSG1*, we found biallelic mutations in the SAM patient and a monoallelic mutation in the DPPK patient. We reviewed the literature on PPK and SAM cases caused by *DSG1* mutations including on heterozygous carriers of *DSG1* mutations in SAM families. Our review revealed that most PPK-causing *DSG1* mutations affect the extracellular or transmembrane domain (TMD) of desmoglein 1, in contrast to SAM-causing *DSG1* mutations, which are scattered throughout desmoglein 1 and affect various regions of desmoglein 1. Most of the *DSG1* mutation carriers had PPK. Heterozygous carriers of *DSG1* mutations affecting the cytoplasmic region of desmoglein 1 seemed to have mild or no PPK; heterozygous carriers with *DSG1* mutations in the extracellular or TMD of desmoglein 1 tended to have severe PPK. We speculate mild PPK symptoms in individuals with *DSG1* mutations affecting the cytoplasmic region of desmoglein 1 might be frequently overlooked and most *DSG1* mutations reported in PPK patients are those affecting the extracellular or TMD of desmoglein 1.

P06-09[O02-03]

Atypical epidermolytic palmoplantar keratoderma caused by *KRT1* mutation is considered as mild type epidermolytic ichthyosis

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Epidermolytic palmoplantar keratoderma (EPPK) is characterized by epidermolytic hyperkeratosis on the palms and sole, and caused by a mutation in the *KRT1* and *KRT9* gene. Epidermolytic ichthyosis (EI) typically presents at birth with erythroderma, skin fragility, and blistering and caused by a mutation in the *KRT1* or *KRT10* gene. While several patients caused by *KRT1* mutation have hyperkeratotic plaques over knuckles, knees, and elbows with palmoplantar keratoderma (PPK). The disease is known as atypical EPPK or Ichthyosis hystrix of Curth-Macklin. However, previous reports showed that identical *KRT1* mutations cause EI and atypical EPPK, and the exact mechanism for such variations has not been clear. Eight-year-old boy was referred to our hospital due to PPK and hyperkeratotic lesions on the knees, elbows, scrotum and axilla. Ichthyosis was not detected on his whole body. Histopathological findings from hyperkeratotic lesion showed papillomatous epidermis with hypergranulosis and marked hyperkeratosis. The patient was identified a mutation c. 623T>C (p.Leu208Pro) in the *KRT1* gene which was reported as EI. Therefore, we diagnosed him with atypical EPPK. We speculated that non-lesional skin might occur mild hypergranulosis change and observed the normal lesion by HE staining and electron microscopy. The results showed that the lesions were mild, but definite hypergranulosis change and keratin denaturation in non-lesional skin. Moreover, we investigated the difference of several cytokines between the patient and other EI patient for searching a possibility of treatment for EPPK. Although the differences of clinical findings between EI and atypical EPPK might be caused by genetic modifying factors and environmental factors, our research help the mechanism for atypical EPPK.

P06-10[O02-04]

Delineating the functional relevance of different lamin A domains that accelerate human ageing

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Hutchinson-Gilford Progeria patients age prematurely and exhibit alopecia, skin atrophy, aberrant pigmentation and die in their mid-teens due to cardiovascular complications. HGPS is a segmental premature ageing syndrome, caused by a aberrantly spliced form of LMNA that results in the production of a mutated form of lamin A, called progerin. Our goal is to understand the molecular mechanism that accelerate ageing in progeria and to find out whether these findings are relevant to normal ageing. On a cellular level, progerin expression causes heterochromatin loss, telomeric DNA damage, impaired proliferation and premature senescence, which are prevented by ectopic expression of telomerase, or by modulating the DNA damage response specifically at telomeres. However, the precise mechanism and structural features of the mutant protein that cause these disease phenotypes require further investigation. To address these questions, we generated a doxycycline-inducible system to express different lamin A mutants in human primary and telomerase-immortalized skin fibroblasts. This system, in conjunction with single-cell immunofluorescence microscopy, enabled us to delineate the temporal chain of events that occurs upon progerin expression and ultimately results in premature senescence. In addition, it allowed us to determine the structural domains essential to elicit a disease phenotype. These results provide mechanistic insight into how perturbations at the nuclear envelop disrupt cell physiology and trigger premature cell ageing. These findings may bear relevance to normal human ageing as aberrantly processed forms of lamin A, heterochromatin loss and telomeric DNA damage accumulate during chronological skin ageing.

P06-11[O02-05]

Evidence for a dominant-negative effect of a missense mutation in the *SERPING1* gene responsible for hereditary angioedema type I

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Hereditary angioedema (HAE) is a rare condition characterized by episodic local edema involving various organs, which can be life-threatening in some cases. Among the three subtypes of the disease, HAE types I and II are known to be caused by heterozygous mutations in *SERPING1* gene encoding C1 inhibitor (C1INH). Although a number of mutations in the *SERPING1* gene have been identified to date, the mechanisms how these mutations cause HAE are not completely understood. We herein performed detailed in vitro studies for a missense *SERPING1* gene mutation p.S150F which we recently identified in a Japanese patient with HAE type I. We showed that the p.S150F-mutant C 1INH was stably expressed within the cultured cells, while it was not secreted into the medium at all. Furthermore, we demonstrated that the mutant C1INH significantly prevented secretion of wild-type C1INH. Finally, the results suggested that the wild-type protein was not only retained but also degraded within the cytoplasm through interacting with the mutant protein. Our study clearly revealed a dominant-negative effect of the p.S150F-mutant C1INH against the wild-type C1INH.

P06-12[O02-06]

Hereditary mucoepithelial dysplasia/autosomal-dominant IFAP syndrome is a clinical spectrum due to *SREBF1* variants

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Ichthyosis follicularis with atrichia and photophobia (IFAP) syndrome is a rare genetic oculocutaneous disorder. Its mode of inheritance has been mostly reported to be X-linked recessive, caused by *MBTPS2* mutations. However, recently, it is revealed that mutations in *SREBF1* cause autosomal-dominant IFAP syndrome. *SREBF1* encodes sterol regulatory element-binding protein 1 (SREBP1), which is involved in promoting the transcription of lipogenesis that is associated with cholesterol and fatty acid biosynthesis. Morice-Picard *et al*. reported that seven patients from four independent families with hereditary mucoepithelial dysplasia (HMD) had *SREBF1* mutations. We had the opportunity to study one family from Japan. We identified that the family with autosomal-dominant IFAP syndrome had the recurrent hotspot mutation c.1669C>T (p.Arg557 Cys) in *SREBF1*. This hotspot mutation has been reported both in HMD families and autosomal-dominant IFAP syndrome families, independently (Morice-Picard *et al*., 2020, Wang *et al*., 2020). The present patients showed perineal lesions characteristic of HMD in addition to the typical clinical features of autosomal-dominant IFAP syndrome. The present family suggests that the mutation c.1669C>T (p.Arg557Cys) in *SREBF1* might be a recurrent hotspot mutation for HMD and autosomal-dominant IFAP syndrome and that HMD and autosomal-dominant IFAP syndrome due to the *SREBF1* mutations are diseases on the same clinical spectrum.

P06-13[O02-07]

Updated allele frequencies of *SERPINB7* founder mutations in Asian patients with Nagashima-type palmoplantar keratosis/keratoderma

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A number of *SERPINB7* mutations, including the common founder mutation c.796C>T (p.Arg 266*), have been reported in Nagashima-type palmoplantar keratoderma (NPPK) patients in East Asian populations. To determine the frequency of each *SERPINB7* mutation, of coexistent atopic dermatitis and of *FLG* mutations in NPPK patients, we sequenced the entire coding regions of *SERPINB7* in genomic DNA from NPPK patients. The detailed clinical features were analyzed for all the patients. Additionally, we performed comprehensive mutation screening for ten *FLG* mutations previously reported in the Japanese population. We report 14 Japanese NPPK patients from 14 independent families. All the patients had homozygous or compound heterozygous *SERPINB7* mutations, including one novel variant c.434G>C (p.Trp145Ser). According to the American College of Medical Genetics guidelines, the novel variant is judged to be 'likely pathogenic'. The mutant allele frequency of the East Asian *SERPINB7* founder mutation c.796C> T was 0.536 in the present 14 NPPK patients. 11 of the 14 (78.6%) NPPK patients had the founder mutation. NPPK families with the founder mutation accounted for 85.9% (55/64 families) of the previously reported and present Japanese NPPK families and accounted for 87.6% (78/89 families) of East Asian (Japanese, Chinese and Korean) NPPK families in the literature, including the present study. No significant association was found between *FLG* mutations and atopic dermatitis in our NPPK patients. The present updated data on the frequency of each *SERPINB7* mutation in East Asian NPPK families revealed that, although the East Asian common founder mutation c.796C>T is highly predominant, the other *SERPINB7* mutations in NPPK families are distinct among the Japanese, Chinese and Korean populations.

P06-14[O02-08]

Bradykinin pathogenesis in hereditary angioedema based on the discovery of novel genetic mutations in ACE and SERPING7 gene

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Hereditary angioedema is a dominantly inherited multiorgan disorder that causes sudden and severe edema of the subcutaneous, intestinal and respiratory tracts. The dysfunction of C1 inhibitor (C1INH) leads to episodic overproduction of bradykinin and persistent vascular hyperpermeability, which is much stronger than by histamine. To avoid repeated laparotomies and sudden death, it is essential to diagnose HAE based on acute abdomen, laryngeal edema, and Quincke's edema, and to confirm by genetic mutation. So far, mutations in SERPING1, F12, PLG, ANGPT1, KNG1, MYOF, and HS3ST6 have been identified. In addition, KLKB1 and NOS3 are known as disease modifying factors, and cases of ACE-I induced drug-induced HAE are also known. In our study, we identified novel gene mutations by exome analysis in two cases. Case 1: A patient in 20's presented with recurrent acute abdomen requiring repeated laparotomy with low C4 3mg/dl and C1INH activity 36%. A novel splice site mutation was found in an exon 4 of SERPING1, which defines C1INH. Case 2: A patient with recurrent laryngeal edema since late 20s. Compound heterozygous mutations were detected in ACE gene, those are very rare in the Japanese genome and are considered to be strongly involved in the pathogenesis. We hypothesized that mutation of ACE gene, which is an inhibitor of kininase to degrade bradykinin, impaired degradation of bradykinin and resulted in HAE as laryngeal edema. Since bradykinin is activated by a different pathway from that of C1INH, the serum C1INH value can be in normal range. Hereditary angioedema has a wide variety of phenotypes and lethal severity. To promptly introduce replacement therapy, it is essential to understand multiorgan symptoms and determine mutations including yet unknown causative gene.

P06-15[O02-09]

A microchip flow-chamber assay can be a powerful tool for detecting platelet function defects in Hermansky-Pudlak syndrome

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Hermansky-Pudlak syndrome type 1 (HPS1) is an autosomal recessive disorder characterized by oculocutaneous albinism, a bleeding diathesis and abnormal lysosomal ceroid-lipofuscin storage. In the absence of a history of bleeding, it is difficult to distinguish HPS from the other oculocutaneous albinism in childhood; and, therefore, it is important to accurately assess hemostasis function. We report here a 58-year-old male with HPS1. Whole-blood platelet impedance aggregometry induced by adenosine diphosphate (ADP), collagen, or ristocetin were comparable with those in normal controls. Next, we performed total thrombus-formation analysis system (T-TAS) assays to analyze the coagulability of whole blood in the bloodstream using a platelet (PL)-chip, and platelet thrombus formation was monitored with the time required for the flow pressure to increase by 10 kPa (T_{10}) from baseline, which can assess thrombogenicity mainly involving platelets (primary hemostasis). The T10 value of the patient (>10 min) was significantly prolonged compared with healthy controls. To the best of our knowledge, this is the first study to perform the T-TAS assay on HPS patients, and PL-chip T_{10} value successfully distinguished the HPS patient from healthy controls. Although this study was limited by a single patient, the results show that the T-TAS is useful for detecting platelet function defects in HPS1.

P07-01[I-2]

Migration and local adaptation of integrinβ7-positive mast cell progenitors in murine allergic skin

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Mast cells (MCs) are tissue-resident immune cells with two subsets: connective tissue-type MCs (CTMCs) and mucosal type MCs (MMCs). Although both CTMCs and MMCs are inducible from bone marrow (BM)-derived hematopoietic stem cells (HSCs) in vitro, research on ontogeny has revealed that only MMCs are maintained with a supply of BM-derived MC progenitors (MCps), while CTMCs are maintained locally by self-proliferation in a steady state. However, how skin MCs are maintained under allergic inflammation remains to be elucidated. In this study, we aimed to identify and characterize BM-derived MCs in allergic skin. In addition, we investigated whether migrated MCs differentiate toward CTMC at the late phase of inflammation. First, we confirmed that skin MCs were increased in allergic skin due to both local proliferation and migration in allergic skin by using CD45.1 BM-chimera mice and parabiosis. BM-derived MCs in allergic skin were derived from circulating MCps, and these migrated MCps were distinguished from resident MCs by integrinβ7 expression. MCps also expressed integrinα4 and their migration to allergic skin was dependent on integrinα4β7. Bulk RNA-seq of sorted rMCs and integrinβ7-positive MCs in NT and allergic skin showed that integrinβ7-positive MCs are increased in signature transcripts of both MMCs and CTMC. In addition, we investigated the fate of migrated MCps in allergic skin by analyzing expressions of CTMC markers and response with compound 48/80. We found that MCps proliferated and acquired a CTMC phenotype in the skin at the late phase of inflammation. In conclusion, in contrast to skin in a steady state, circulating integrinβ7-positive MCps migrate to skin under allergic inflammation, then differentiate toward CTMCs.

P07-02[I-4]

Type I IFN derived from inflammatory monocytes controls type 2 inflammation by suppressing basophil proliferation in atopic dermatitis

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Inflammatory monocytes, which have $Ly6C^{high}CD11b^{+}Ly6G^{-}$ phenotype, are quickly recruited to the site of inflammation or infection in a CCR2-dependent fashion. Numerous studies have demonstrated an inflammatory role for inflammatory monocytes, which have a dominant role in the control of the invading pathogen in various settings. Besides their role in immune defense against microbial pathogens, we recently demonstrated a specialized role of inflammatory monocytes in promoting autoimmune disease, in particular systemic lupus erythematosus. In this study, we demonstrated that inflammatory monocytes also play important role in the pathogenesis of inflammatory skin disease. Using mouse model of atopic dermatitis (AD), we found that blocking of type I IFN augmented type 2 inflammation as anti-IFNRα antibody or IRF7 deficiency resulted in exacerbation of AD-like inflammation. We also demonstrated inflammatory monocytes were major producer of type I IFN in AD lesion because both Ccr2 deficient mice and Irf7 deficient mice, which lack inflammatory monocytes themselves and type I IFN production from inflammatory monocytes, respectively, developed more severe disease. Further, we found that the percentage of basophil in the lesional skin was increased in Ccr2 deficient mice and Irf7 deficient mice compared with that in wild-type mice and that type I IFN suppressed the expansion of basophils from bone-marrow-resident progenitors elicited by thymic stromal lymphopoietin. Collectively, our results suggest that inflammatory monocytes are the first and dominant inflammatory cells reaching the inflamed location and modify type 2 immune responses.

P07-03[C01-01]

CCL2-CCR2 signaling in the skin drives surfactant-induced irritant contact dermatitis via IL-1β-mediated neutrophil accumulation

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Background: Surfactant-induced cumulative irritant contact dermatitis (ICD) is a common occupational skin disorder, but its pathogenesis is poorly understood. CCL2 is known to mediate inflammation following tissue damage in various organs. Objective: To investigate whether CCL2 contributes to the development of surfactant-induced cumulative ICD. Methods: ICD was induced by the topical application of 2% sodium dodecyl sulfate (SDS) on murine ears for 6 consecutive days. Results: Wild-type mice treated with SDS developed skin inflammation that recapitulated the features of human cumulative ICD, including barrier disruption and epidermal thickening. SDS-induced murine ICD was accompanied by the local accumulation of innate immune cells, particularly neutrophils. CCL2 was upregulated in SDS-treated skin, and local CCL2 blockade attenuated SDS-induced neutrophil accumulation and ICD. SDS-induced neutrophil accumulation and ICD were also attenuated in mice deficient in CCR2, the receptor for CCL2. Bone marrow chimera and parabiosis experiments revealed that SDS-induced neutrophil accumulation and ICD depended on CCR2 in the radioresistant compartment of the skin. Neutrophil depletion alleviated SDS-induced ICD, suggesting that impaired neutrophil accumulation was responsible for the amelioration of ICD in CCR2-deficient mice. RNA-seq analysis of SDS-treated skin revealed downregulation of *Il1b* in CCR2-deficient mice compared with wild-type mice. Local IL-1β neutralization attenuated SDS-induced neutrophil accumulation and ICD in wild-type mice. Furthermore, the intradermal administration of IL-1β reversed SDS-induced neutrophil accumulation and ICD in CCR2-deficient mice. Conclusion: Cutaneous CCL2-CCR2 signaling drives SDS-induced ICD via IL-1β-mediated neutrophil accumulation.

P07-04[C01-02]

IκBζ-deficient epidermis mediates systemic autoimmune inflammation via skin dysbiosis

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Skin microbiota affects systemic inflammation through mechanisms that have not been completely elucidated. We previously demonstrated that keratinocyte-specific IκBζ-deficient mice (*Nfkbiz*$^{\Delta K5}$) spontaneously develop autoimmune inflammation resembling human Sjögren syndrome. In this study, we examined how IκBζ-deficient epidermis dictates systemic autoimmune inflammation onset. We observed a decrease in antimicrobial peptides and an increase in Staphylococci colonization on *Nfkbiz*$^{\Delta K5}$ mice skin. Epicutaneous Staphylococcus aureus application on *Nfkbiz*$^{\Delta K5}$ mice caused epidermal apoptosis. Extracts of Staphylococci-induced apoptotic *Nfkbiz*$^{\Delta K5}$ keratinocytes showed enhanced neutrophil extracellular trap (NET) formation. NETs induced by apoptotic keratinocytes drove the IL-23/IL-17 immune response by activating dendritic cells and T cells. Anti-IL-23p19 antibody, but not anti-IL-12p40 antibody, alleviated systemic autoimmune responses including antinuclear antibody production and glomerulonephritis with IgG deposition, which are observed in human systemic lupus erythematosus. Thus, epidermal IκBζ controls skin microbiota, and skin dysbiosis on IκBζ-deficient epidermis induces systemic autoimmune inflammation by keratinocyte apoptosis, NETs, and the IL-23/IL-17 axis.

P07-05[C01-03]

T-cell receptor signaling pathways that regulate functional reprogramming of γδ T cells in the perinatal epidermis

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Resident epidermal T cells of the murine skin, called dendritic epidermal T cells (DETC), express an invariant γδ T-cell receptor (Vγ3 TCR) that recognizes an undetermined self ligand expressed on epidermal keratinocytes. DETC rapidly produce IL-13 upon TCR stimulation, but their fetal thymic precursors produce predominantly IFN-γ. We found that IFN-γ-producing Vγ3 T cells were reprogrammed to produce IL-13 in the perinatal epidermis during ontogeny. Analyses of cytokines produced by the resident epidermal T cells in *Tcrd*$^{-/-}$ and *Tcrd-V1*$^{-/-}$ mice revealed that only epidermal T cells with the TCR recognizing the self ligand on epidermal keratinocytes produced IL-13, indicating that the TCR signaling promotes differentiation of epidermal T cells into IL-13-producing cells. We established an in vitro model of Vγ3 T-cell differentiation, in which neonatal epidermal Vγ3 T cells were cultured in the presence of stimulating anti-TCR monoclonal antibody. By adding inhibitors of TCR downstream signaling pathways to this model, we identified p38 MAPK and PI3K-Akt-mTORC1 pathways as candidate signaling pathways that positively and negatively regulate the functional reprogramming of γδ T cells in the perinatal epidermis, respectively.

P07-06[C01-04]

Proteomics analysis of bacterial and fungal composition in skin and serum extracellular vesicles

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Recent study proposed that skin microbial alteration as dysbiosis contribute to pathogenesis of atopic dermatitis (AD). Besides, extracellular vesicles (EVs) have been found to be secreted by various cells and work as mediator to communicate between cells and transport of cellular components. Previously, we found that serum EVs contained *Helicobacter pylori*-derived peptide and associated with an immune recognition of this bacteria by proteomic analysis. Recent skin microbiome analysis has mainly done by metagenomics, however there are no reports of skin microbiome and mycobiome analysis by proteomics. Protein level analysis may correlate with actual bacterial and fungal composition. Therefore, we aimed to analyze proteomic profile of microbiome and mycobiome. Additionally, we also analyzed microorganisms in serum EVs to assess the differences from the skin microenvironment. We collected skin and serum samples from AD and non-atopic groups for mass spectrometry. Metagenomic analysis was also used to assess bacterial components in skin samples. The result showed that our protocol enabled to find bacterial and fungal composition of skin and serum samples. Notably, we found high *Staphylococcus aureus* loads in AD skin compared to healthy control in proteomic and metagenomic analysis. Moreover, we also identified proteomic profile of *Malassezia sp.* that have been known to be involved in AD. We detected specific bacteria peptides in EVs of AD serum. Finally, the compositions of bacteria and fungus are different between results of proteomics and metagenomics. Herein, we report the first observations with proteomic analysis of the relationships AD and human microbiota. We suppose that the bacterial and fungal peptides in serum EVs may influence the immunity in AD patients.

P07-07[C01-05]

TREM2/APOE-double positive macrophages as possible pathogenic cells in sarcoidosis

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Sarcoidosis is an inflammatory disease associated with granulomas that appear in multiple organs. Pathologically, it is characterized by non-caseating epithelioid cell granuloma. Recent studies have shown that TNF-alpha neutralizing antibodies are effective in some cases of sarcoidosis and that Janus kinase inhibitors improve the disease. However, the detailed pathological mechanism remains unclear. In this study, we analyzed macrophages in scar sarcoidosis of the face using single-cell RNA-sequencing. The number of TREM2-positive APOE-positive macrophages was increased in sarcoidosis compared to normal skin. These macrophages expressed genes such as ACE and CYP27B1, which are considered to induce active vitamin D, characteristic of sarcoidosis. Interestingly, TREM2-positive APOE-positive macrophages were not increased in the skin of atopic dermatitis, psoriasis vulgaris, or granuloma annulare. These findings were confirmed by immunostaining (n=5; each disease), suggesting that TREM2-positive APOE-positive macrophages are characteristic to sarcoidosis. Previous reports have shown that APOE is a ligand for TREM2, suggesting that that APOE may activate macrophages in an autocrine manner. Overall, TREM2-positive APOE-positive macrophages increased specifically in sarcoidosis and expressed genes specific for sarcoidosis. We will also discuss the function of APOE in sarcoidosis and its potential therapeutic application.

P07-08[O05-01]

Dysbiosis mediates inflammatory destruction of the hair follicles

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Hair follicles (HFs) are active hubs for stem cells, immune cells, and commensal microbes suggesting the presence of active mechanisms that maintain host-microbial symbiosis. Indeed, transient inflammation such as those caused by viral infections can obscure tissue functions, triggering autoimmunity or rendering the host susceptible to bacterial infections. Here, we utilized an experimental anti-viral immunity model and show that ADAM10-Notch signaling axis in type I/III interferon-responsive upper HF area was crucial for regulating skin microbiota. Inhibition of ADAM10-Notch signaling axis altered the innate epithelial barrier via the downregulation of the anti-microbial peptide gene, *Defb6*, that allowed *Corynebacterium* species to predominate the microbiome. Dysbiosis triggered inflammation mediated by group 2 innate lymphoid cells in CCL 20-CCR6 axis-, IL-7 receptor-, and sphingosine-1-phosphate receptor 1-dependent manners, leading to pyroptotic cell death of HFs, resulting in irreversible alopecia. Targeting dysbiosis, group 2 innate lymphoid cells, and the inflammatory caspases-1 and -4/11 attenuated alopecia. Thus, regulation of host-microbial symbiosis via ADAM10-Notch signaling axis crucially protects HFs and the stem cell niche from inflammatory destruction, which has implications for strategies to sustain tissue integrity during chronic inflammation.

P07-09[C01-06]

Purinergic molecules in murine bone marrow-derived mast cells

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In the skin, adenosine triphosphate (ATP) is released from various types of cells by various environmental stimuli via nonlytic mechanisms, cell damage, or acute cell death. Because ATP is a potent inducer of skin inflammation, it has to be promptly hydrolyzed for the skin to achieve homeostasis. Mast cells (MCs) are predominantly present in the upper dermis and are known to promote skin inflammation. Of note, ATP activates MCs through P2X7, leading to the enhanced skin inflammation. However, MC involvement in the impairment of skin inflammation via ATP hydrolysis remains largely unknown. Thus, we sought to determine the expression of ATP-hydrolyzing molecules such as Entpd-1 (CD39), -2, -3, and -8; Enpp-1, -2, -3; and alkaline phosphatase (ALP), and an adenosine monophosphate (AMP)-hydrolyzing molecule (CD73) in the murine bone marrow-derived MCs (BMMCs). Bone marrow cells recovered from female B6 mice were cultured in the presence of stem cell factor and IL-3 for 5 weeks, resulting in differentiation into CD45+FcεRI+ c-kit+ BMMCs. A culture of BMMCs with 1 mM ATP-γ-S, a non-metabolizable ATP analogue, or 1 μM ionomycin for 60 min or 10 min, respectively, induced their degranulation. PBS-treated steady-state BMMCs strongly expressed Entpd-1 (CD39) and Entpd-3 and weakly expressed Enpp-1 and CD73, but not Entpd-2, Entpd-8, Enpp-2, Enpp-3, and ALP. While ionomycin upregulated Entpd-1 (CD39), Entpd-3, and Enpp-1 expressions approximately 4 times, ATP-γ-S upregulated only Entpd-1 (CD39) expression approximately 4 times. These data suggest that MCs might participate in ATP hydrolysis via Entpd-1 (CD39) and Entpd-3. In addition, ATP-activated degranulated MCs upregulate Entpd-1 (CD39) expression possibly to inhibit ATP-mediated excess skin inflammation.

P07-10[C01-07]

Granzyme K cleaves protease-activated receptor-2 and induces itch

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Itch is a significant and unpleasant symptom that accompanies many skin diseases. Current standard treatment relies on antihistamines, which often fail to control the itchy sensation. This antihistamine resistant itch is suggested to be controlled by histamine-independent mechanisms such as protease-activated receptor-2 (PAR-2) activation on sensory neurons in the skin. PAR-2 is activated through proteolytic cleavage by many serine proteases, however, itch-inducing proteases have not been fully explored. The serine protease granzyme K (GzmK) is increased in a number of inflammatory skin diseases associated with itch, such as atopic dermatitis and psoriasis. Therefore, we hypothesized that GzmK may induce itch through PAR-2 activation in skin. Chinese Hamster Ovarian (CHO) cells transfected with the nluc-hPAR2-eYFP cleavage reporter were incubated with GzmK or trypsin (standard agonist against PAR-2) to evaluate PAR-2 cleavage. Relative to 100 nM trypsin, a 15-minute incubation with 100 nM GzmK induced 20% cleavage of PAR-2, suggesting that GzmK activates PAR-2. To investigate the role of GzmK in itch, GzmK was intradermally injected into the cheeks of mice and scratch behavior was recorded and quantified. 10 ng tryptase and GzmK injections induced 31 and 49 seconds of total scratch time in 30 minutes, respectively, while vehicle injection induced 21 second over the same time period. In addition, GzmK-induced calcium influx in mouse dorsal root ganglion cells was tested. In summary, GzmK may induce itch through a PAR-2-dependent mechanism.

P07-11[C08-01]

Involvement of V δ1+ epithelial type of γδT cells in the systemic form of hydroa vacciniforme-like lymphoproliferative disorders

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Hydroa vacciniforme-like lymphoproliferative disorder (HV-LPD) is a form of cutaneous chronic active Epstein-Barr virus infection (CAEBV) mediated by EBV+ T cells. We studied the ability of atypical T cells from HV-LPD patients to express natural killer (NK)-cell antigens such as CD16 and CD56, mimicking a natural killer T (NKT)-cell phenotype. We examined the immunophenotypes of peripheral blood mononuclear cells in 10 patients with HV-LPD: five with systemic HV (sHV) and five with classic HV (cHV). The use of T-cell receptor (TCR) was examined in two sHV and one cHV cases by high throughput sequencing. The five sHV patients included two with the γδT-cell-dominant type, two with the αβT-cell-dominant type, and one with the mixed type. CD3+ T cells expressed CD16/CD56 at 7.8%-42.3% and 1.1%-9.7% in sHV and cHV, respectively. CD3+CD16/CD56+ cells were accumulated in large granular lymphocyte or atypical T-cell fractions in sHV. The epithelial type of Vδ1+ γδT-cells were increased in two sHV patients examined, whereas the Vδ2+ γδT cells were of dominant in one cHV patient and healthy individuals. One fatal sHV patient's blood contained a major CD3+CD56+ αβT-cell clone, distinct from Vα24+ invariant NKT cells, and another Vδ1+ γδT-cell clone, without NK cell lymphocytosis. In conclusion, both atypical αβT and γδT cells in HV-LPD frequently coexpress NK-cell antigens such as CD16 and CD56, and the epithelial Vδ1+ γδT cells might be involved in sHV.

P07-12[O05-02]

An antimicrobial peptide cathelicidin triggers skin inflammation with other DAMPs via multiple receptors

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An antimicrobial peptide cathelicidin is upregulated in inflammatory skin diseases such as psoriasis and rosacea. Cathelicidin and its active form LL 37 induces various cytokines and chemokines. We have demonstrated that LL37 enables keratinocytes and macrophages to recognize self-non-coding RNA by facilitating its binding to cell surface scavenger receptors and intracellular pathogen recognition receptors (PRRs) in human psoriatic skin. However, other specific pathways by which LL37 exerts its immunomodulatory effects are not clear. In this study, we investigated the mechanism how LL37 and/or other damage-associated molecular patterns (DAMPs) induces inflammation in human skin. We performed DNA microarray and immunoblotting in keratinocytes with LL37 and/or poly(I:C), a synthetic double-stranded RNA. Sole LL37 induced genes related to metabolism and biological processes including cyclooxygenase (COX)-2 and vascular endothelial growth factor (VEGF)-A. This induction was reduced by inhibition of formyl peptide receptor (FPR)2, a known cell surface LL37 receptor. On the other hand, the complex of LL37 and poly(I:C) induced immune-related genes such as retinoic acid-inducible gene-I (RIG-I), tumor necrosis factor (TNF)-α, CXCL10, and interferon (IFN)-β. This induction was attenuated by inhibition of clathrin-dependent endocytosis and toll-like receptor (TLR)3, an intracellular RNA receptor. The inhibition of FPR2 did not change the expression of those genes. These results suggest that LL37 induces inflammation through various pathways depending on the presence or absence of coexistent DAMPs. Moreover, with appreciation of the dependence on this interaction it becomes possible to devise new therapeutic interventions to block inappropriate inflammation driven by LL37.

P07-13[O05-03]

Potential role of neutrophil elastase (NE) in the development of nephrogenic systemic fibrosis (NSF) in an in vivo model of renal failure

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Nephrogenic systemic fibrosis (NSF) is a fibrosing dermopathy which has been associated with the exposure of gadolinium (Gd)-based contrast agents (GBCAs) in patients with renal impairment. It characterized by thickening of the skin and multiorgan Gd deposition. Studies showed that Gd stimulates the proliferation of dermal fibroblast *in vitro*. Moreover, fibroblasts collected from NSF patients showed a marked increase in collagen production. In scleroderma, another fibrotic disease, neutrophil and neutrophil elastase (NE) were shown to be increased which may be involved in the stimulation of collagen synthesis. However, there has not been a report on NE activity in NSF patients. Our aim is to investigated NE activity after a series of GBCAs injection on renal failure mouse model. GBCAs injection (gadodiamide) was intravenously administered for a total of nine injections. Mice were observed daily and skin samples were collected two weeks after. Blood samples were collected from facial vein to quantify the NE enzymatic activity. After the administration of gadodiamide, a variety of skin lesions (erosion, erythema, hair loss) were developed in different places. Dermal thickness was significantly higher and the collagen bundles in gadodiamide group increased compared to control group. The mRNA expression of collagen 1a, TGF-b, CTGF, and aSMA were also significantly increased after gadodiamide administration. The infiltration of $CD3^+$ T cell, $CD68^+$ macrophages, and the expression of NE on the skin were significantly increased in gadodiamide mice. NE activity observed from blood serum also shown a significant increment after GBCAs injection. It is suggested that NE may play a role in the development of fibrosis linked to the administration of GBCAs in renal failure mice model.

P07-14[O05-04]

Coordinated expression of retrotransposon and type I interferon with distinct interferon pathways in autoimmune diseases

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Type I interferon (IFN) plays a crucial role in immunity, and aberrant IFN responses are involved in systemic autoimmune diseases, such as systemic lupus erythematosus (SLE) and dermatomyositis (DM). Type I IFNs can be induced by transcribed retrotransposons. Long interspersed nuclear element-1 (LINE-1) is a representative retrotransposon, is observed in some autoimmune diseases. The regulation of retrotransposons and type I IFN, and the downstream IFN pathways in SLE, DM and autoimmune blistering disease (AIBD) were investigated. The gene expression levels of retrotransposons, including *LINE-1*, type I-III IFNs, janus kinases, signal transducers and activators of transcription factors (STATs), and IFN-stimulated genes (ISGs) and IFN-stimulated genes (ISGs) in peripheral blood cells from patients with DM (n=24), SLE (n=19), AIBD (n=14) and healthy controls (n=10) were assessed by quantitative polymerase chain reaction. Upregulation of retrotransposons and IFNs was characteristically detected in DM, as compared to HC, although ISGs were not always upregulated. In contrast, retrotransposons and IFNs, except for type II IFN, were not upregulated in SLE, but STAT1/2 and ISGs were significantly increased. In AIBD, only part of retrotransposons and type I interferons was upregulated. DM, SLE and AIBD showed coordinated expression of retrotransposons and type I IFNs, and distinct expression spectra in IFN signalling. The expression of retrotransposons and type I IFNs showed synchronicity despite the disease, suggesting that various pathways of type I IFN activation may be mutually correlated with retrotransposon activation. These factors may participate in the pathogenesis of these autoimmune diseases.

P07-15[O05-05]

Macrophages express βKlotho in skin lesions of psoriasis patients and the skin of imiquimod-treated mice

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Psoriasis is a common inflammatory skin disease in which the expression levels of interleukin (IL)-17A and tumor necrosis factor-α (TNFα) are elevated. Macrophages are vital to innate immunity, and persistent macrophage activity results in the development of psoriasis and other chronic inflammatory skin diseases. βKlotho is a member of the Klotho family, which regulates the function of fibroblast growth factor (FGF). Pro-inflammatory cytokines increase Klotho expression by macrophages, and Klotho acts directly on macrophages, stimulating their secretion of TNFα. Thus, we investigated the expression of βKlotho in the lesional skin of psoriasis patients using immunohistochemistry. We also examined the effects of IL-17A neutralization therapy on βKlotho expression in the skin of imiquimod (IMQ)-treated mice, a model for psoriasis-like skin inflammation. The results of the immunohistochemical analysis revealed that βKlotho was strongly expressed in cells infiltrating the lesional dermis of psoriasis patients compared to control or atopic dermatitis patients. βKlotho-expressing cells were positive for CD68, a human macrophage marker. We also investigated βKlotho expression in the skin of IMQ-treated mice. Similar to psoriasis patients, βKlotho was more strongly expressed in cells infiltrating the skin of IMQ-treated mice than in untreated mice. βKlotho-expressing cells were positive for F4/80, a mouse macrophage marker. IL-17A neutralization therapy reduced the number of βKlotho-expressing cells infiltrating the dermis and βKlotho-positive/F 4/80-positive macrophage cell ratio as well as βKlotho protein expression levels in the skin of IMQ-treated mice.

P07-16[O05-06]

Skin Inflammation and Testicular Function

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The medical comorbidities including skin diseases are associated with male infertility. The most common cause of male infertility is the inability of testes to produce sperm; however, the influence of persistent dermatitis on testicular function has not been elucidated so far. We investigated the relationship between skin inflammation and impaired sperm production using a spontaneous dermatitis mouse model. We examined the breeding records of dermatitis mice and their wild-type littermates. Sperm count, motility, and viability were analyzed by direct microscopic observation and flow cytometry. In addition, testis and epididymis were histologically examined. Finally, sperm viability was evaluated in another dermatitis mouse model and in wild-type mice in which inflammatory cytokines were intraperitoneally administered. Compared to wild-type littermate mice, the number of children born was lower in mice with dermatitis. The body weight and testis size were decreased age-dependently. In the skin disease group, the sperm count and movement ratio were clearly decreased, and reduced sperm viability was observed. Histological examination revealed the detachment of Sertoli cells and reduced spermatogenesis. The fibrosis of epididymal stroma was severe, and it might affect defective sperm maturation in the epididymis. In addition, this phenomena was reproduced by a hapten applied dermatitis mouse model and the intraperitoneal administration of inflammatory cytokines. Once the skin is inflamed, inflammatory cytokines are produced and released, which may affect testicular and sperm function. Additional studies are needed to determine the relationship between male infertility and severe dermatitis in human.

P07-17[O05-07]

Roles of interferon regulatory factor 3 in murine models of allergic and irritant dermatitis

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Interferon regulatory factor 3 (IRF3) is a transcriptional regulator of cellular responses in many cell types and is known to be important for innate immunity, including toll-like receptor 3 (TLR3) signaling. We previously demonstrated that TLR3 signaling is closely associated with the pathomechanisms of allergic and irritant dermatitis using murine models. However, the roles of IRF3 in allergic and irritant dermatitis have not been clarified yet. In this study, we examined the roles of IRF-3 in allergic and irritant dermatitis by applying a hapten/stimulant once or repeatedly to the auricular skin of IRF3-deficient mice. The IRF3-deficient mice demonstrated significantly stronger ear-swelling responses than the wild-type mice in both the acute/chronic allergic dermatitis and irritant dermatitis experiments. In addition, IRF3 deficiency increased leukocyte infiltration into the inflamed skin. Furthermore, the IRF3-deficient mice produced greater amounts of some cytokines in the epidermis than the wild-type mice. These findings suggest the IRF3 signaling may regulate allergic and non-allergic skin inflammation.

P07-18[O05-08]

Internalization of live atopic dermatitis-derived Staphylococcus aureus into HaCaT cells and inhibition by Staphylococcus epidermidis

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Background: Staphylococcus aureus (S. aureus) is frequently detected on the skin of patients with atopic dermatitis (AD). On the other hand, Staphylococcus epidermidis (S. epidermidis) is more prevalent in healthy skin. Previously, we reported that HaCaT, immortalized human keratinocyte cell line, cells internalize heat-killed S. aureus derived from the skin of patients with AD (AD-derived S. aureus). However, it is still unclear whether keratinocytes internalize live S. aureus. The effect of S. epidermidis on this internalization is also unknown. Objective: In this study, we investigated the internalization of live AD-derived S. aureus into HaCaT cells. In addition, we examined the effect of S. epidermidis on the internalization of live AD-derived S. aureus. Methods: HaCaT cells were treated with live AD-derived S. aureus. The amount of live AD-derived S. aureus taken up into HaCaT cells was measured by a high throughput high content imaging system (Opera PhenixTM). Results: HaCaT cells took up live AD-derived S. aureus. The internalization was inhibited by the presence of S. epidermidis. Examination of the culture supernatant of S. epidermidis revealed that S. epidermidis secretes a substance that inhibits the uptake of S. aureus into HaCaT. Conclusion: Further validation is needed on the association between S. aureus colonization of AD skin and keratinocytes uptake of AD-derived S. aureus. However, S. aureus uptake inhibitors secreted by S. epidermidis may control the bacterial flora of the skin.

P07-19[O05-09]

Low heterogeneity among isolates of *Cutibacterium modestum*: Resident of human skin with possible infectious nature

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In 2020, we established the species concept of *Cutibacterium modestum*, a sister species of *Cutibacterium acnes* (Dekio et al. 2020). The species is a minor but common member of skin microbiome and include a group of bacteria tentatively named as "*Propionibacterium humerusii*". To understand the characteristics of this bacterial group and search for possible disease-related subtypes, we investigated the biochemical features of eight live strains and the digital comparison of nine genomes. The live strains were all human isolates obtained from skin, meibomian gland, bone, and pacemaker device. All isolates were Gram-stain positive short rods. Pairwise comparisons of the genomes by *in silico* DNA-DNA hybridization showed similarity values of 98.1% or larger, which were far higher than the subspecies cutoff of 79-80%. *16S rRNA* gene sequences of thirteen isolates and genomes were identical. Their *recA* sequences were identical except for two strains, HM-510 (HL037PA2) and Marseille-P5998, which showed unique one-gene polymorphisms. Biochemical features using API kits showed slight differences but were far closer than the nearest species, *C. acnes* and *Cutibacterium namnetense*. Spectra of MALDI-TOF mass spectrometry showed slight differences in the presence of *m/z* 10,512 (10 kD chaperonin GroS) and three other peaks, further clustering the eight isolates into three subtypes. These results indicated that the intra-species variation *C. modestum* is relatively small compared with that of *C. acnes*, and these isolates did not separate to form subspecies-level clusters, at least with the analysed strains/genomes. However, the subtyping was shown to be possible by using *recA* gene sequences or MALDI-TOF spectra.

P07-20[O05-10]

Cutaneous adverse events caused by EGFR inhibitors may result from reduced expression of human β-defensins induced by staphylococci

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EGFR inhibitors (EGFRIs) frequently cause cutaneous adverse events such as acneiform rashes and paronychia. Although staphylococci are commonly detected in the skin lesions, the mechanism underlying development of these adverse events remains unclear. We previously reported that expression of human β-defensins which have a broad spectrum of antimicrobial activity decreased in the skin lesions of EGFRIs-induced acneiform rashes by a tape stripping procedure. In this study, we aimed to determine the involvement of EGFRIs on β-defensins in acneiform rashes. First, normal human epidermal keratinocytes cultured in the presence of EGFRIs showed markedly reduced human β-defensin expression induced by staphylococci. Therefore, to clarify whether EGFR ligands induce the expression of human β-defensins, EGFR ligands, such as EGF, HB-EGF, and TGF-α, were administered to the culture medium; however, human β-defensins were only slightly secreted from keratinocytes. On the other hand, the expression of human β-defensins was significantly increased in keratinocytes stimulated by staphylococci in the presence of EGFR ligands compared to the absence of EGFR ligands. These results suggest that staphylococcal infections induce the expression of human β-defensins in synergy with EGFR ligands under normal conditions, but in the patients with EGFRIs, the expression of human β-defensins is significantly reduced, which may exacerbate staphylococcal and other skin infections and lead to cutaneous adverse events.

P07-21[O05-11]

Alternation of the cutaneous microbiome of herpes zoster lesion in a patient with severe coronavirus disease 2019

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Main symptoms of coronavirus disease-2019 (COVID-19) are acute respiratory syndrome and some patients are at risk for illness and death. The control and therapy were analyzed COVID-19 from a different point of view. So, recent reports have focused on the relationship between the microbiome and COVID-19. However, the skin microbiomes of patients with COVID-19 have not yet been investigated. We report an alteration in the skin microbiome of trigeminal herpes zoster (HZ)-infected lesions, which underwent necrosis in a patient with severe COVID-19. A 57-year-old-man was hospitalized with high fever accompanying with COVID-19. His respiratory status rapidly worsened and required extracorporeal membrane oxygenation (ECMO) for uncontrolled hemodynamically unstable bradycardia. 30 days after admission, He developed HZ over the right side of his forehead lesion located in the first division of the trigeminal nerve. The lesion immediately underwent necrosis. We thought the change of HZ lesion was possible involvement of imbalance in skin microbiome. We analyzed the sequence genome data of fungal ITS and bacterial 16srRNA from the extracted DNA using next-generation sequencing at the diagnosis of HZ and 14 days after diagnosis of HZ. The dominant species was Ralstonia both of two points. Controlling Ralstonia genus may be a viable treatment for skin necrosis and COVID-19 infection.

P07-22[O05-12]

Postbiotics power in supporting skin

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Prebiotics and probiotics are known for their use for gut health, and now they are increasingly seen as an ingredient source in topical skin treatments. In particular, postbiotics show numerous advantages for the skin.

Postbiotics are non-viable molecules/metabolites produced by the bacteria during fermentation, and they are functional bioactive compounds. Research has shown that postbiotic metabolites have health benefits on the guts by helping against inflammation and oxidative stress. Postbiotics use does not require having live bacteria in the product. Only the molecules that the bacteria have produced are introduced in the product.

Lactobacillus strains have been shown to have positive effects on skin for decades now. Here, we investigated the benefits of postbiotic metabolites, like pinitol and amino acids, produced during the lactobacillus fermentation process.

After treatment with these postbiotics, we were able to measure an increase of cell viability and energy and an increase of cell differentiation markers such as involucrin and filaggrin, which resulted in an increased thickness of viable epidermal layers. Over time, such activity can help the skin reinforce its epidermal layer and build a very strong barrier to defend itself better against environmental factors.

P08-01[III-5]

Estimation of cutaneous squamous cell carcinoma incidence attributable to arsenic in U.S. water supplies

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Arsenic in water supplies potentially exposes millions of people to increased disease risk worldwide. Despite strengthened regulation by the U.S. Environmental Protection Agency (EPA) for public water supplies, arsenic at current levels in U.S. water supplies may increase the incidence of cutaneous squamous cell carcinoma (cSCC). However, no prior studies have quantified this arsenic-associated incidence. We analyzed three national-scale datasets: urinary arsenic from the National Health and Nutrition Examination Survey, public water supply data from the EPA Six-Year Review 3, and private well user data from Ayotte et al. (2017). These data were combined with published odds ratios for cSCC incidence in order to estimate arsenic-attributable cSCC incidence among U.S. non-Hispanic whites, a demographic with disproportionately high skin cancer incidence, at national and county levels. Based on urinary arsenic data representative of U.S. non-Hispanic whites, we estimate that 32,058 out of 2,548,845 cSCCs annually in the U.S. are attributable to arsenic in water supplies: 25,861 cSCCs among public water users and 6,196 among private well users. Separately, water supply data suggest that 10,159 and 4,414 cSCCs are attributable to arsenic in public water supplies and in private wells, respectively. Private well users have twofold greater risk of arsenic-attributable cSCC than public water supply users. In this first estimation of arsenic-attributable cSCC incidence, 1.3% of cSCC incidence in the U.S. is due to arsenic in current water supplies. Thousands of cSCCs may be prevented by further restricting arsenic in U. S. water supplies.

P08-02[C02-01]

Plasma metabolome-wide analysis in Japanese identifies potential biomarkers of psoriasis and clinical subtypes

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Psoriasis is an immune-mediated skin disease for which the crosstalk between genetic and environmental factors is responsible. To date, no definitive diagnostic criteria for psoriasis yet, and specific biomarkers are required. We performed metabolome-wide analysis using a non-targeted metabolomics approach. We constructed metabolomics profiling of 130 plasma samples (50 cutaneous psoriasis [PsC] patients, 42 psoriatic arthritis [PsA] patients, and 38 healthy controls). Psoriasis case-control association tests identified one metabolite (ethanolamine phosphate) significantly increased in psoriasis cases than in the controls, and three metabolites decreased in cases (false discovery rate [FDR]<0.05; XA0019, nicotinic acid, and 20alpha-hydroxyprogesterone). In the clinical subtype association test between PsA and PsC, tyramine significantly increased in PsA than in PsC, whereas mucic acid decreased (FDR<0.05). Molecular pathway analysis of the PsA-PsC association test identified enrichment of vitamin digestion and absorption pathway in PsC (P=1.3x10^{-4}). Correlation network analyses elucidated that a subnetwork centered on aspartate was constructed among the psoriasis-associated metabolites; meanwhile, saturated fatty acids primarily formed the major subnetwork among metabolites with differences between PsA and PsC. Our large-scale metabolome-wide analysis highlights novel characteristics of plasma metabolites in psoriasis and the differences between PsA and PsC, which could be used as potential clinical biomarkers of psoriasis and its clinical subtypes. These findings contribute to our understanding of psoriasis pathophysiology.

P08-03[C02-02]

Prevalence, comorbidities, and treatment patterns of Japanese patients with alopecia areata: a descriptive study using JMDC claims database

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Background: Real-World data on alopecia areata (AA) demographics, comorbidities and treatment patterns is sparse, not only in Japan, but in all the world.
Objective: To elucidate the current prevalence of AA, including alopecia totalis (AT), alopecia universalis (AU), alopecia ophiasis (AO), and widespread alopecia (WA). Frequency of comorbidities, and unmet medical needs related to treatment were also assessed.
Methods: Subjects registered in JMDC claims database from January 2012 to December 2019 were analyzed. Prevalence was calculated yearly, most common comorbidities were evaluated, and treatments described in the AA Japanese guidelines were included in the analysis.
Results: A total of 61,899 patients were diagnosed with AA during the study period. AA prevalence has been gradually increasing in recent years, from 0.16% in 2012 to 0.27% in 2019. The principal comorbidities are atopic dermatitis, allergic rhinitis, and asthma. Depression and anxiety are also frequent in AA patients, as well as autoimmune diseases such as vitiligo, thyroid diseases. Intriguingly, the analysis found Down syndrome as a comorbidity associated with severe AA. The principal treatment is topical steroid, followed by carpronium chloride, and cepharantine. The use of systemic steroids (oral and intravenous) and antihistamine increase in severe patients (AT, AU, AO, WA). The AA guidelines does not support the use of oral steroids in children; however, the medication has been prescribed to up to 2.5% and 9.8% of all and severe pediatric AA cases respectively.
Conclusion: AA prevalence has gradually increased in recent years. Allergic diseases are the most common comorbidities. The data implied that there is a need of a more effective and safe therapy, especially for severe and pediatric cases.

P08-04[O11-01]

Pork allergies in Japanese urban areas are predominantly classified as pork-cat syndrome

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Background: Mammalian meat allergies are mainly classified into two categories; pork-cat syndrome and alpha-gal syndrome. Pork-cat syndrome is a meat allergy due to cross-reactivity to mammalian serum albumins, which patients are primarily sensitized to via the respiratory tract. Currently, pet ownership is globally on the rise. However, there are few reports about the impact of increased pet ownership on the onset of pork-cat syndrome. We investigated the prevalence of pork-cat syndrome in patients with pork sensitization. Methods: We enrolled 147 patients with suspected pork allergy based on clinical history. We measured specific IgE levels against pork, cat and dog dander, nSus s 1, rFel d 2, n Can f 3 and thyroglobulin (alpha-gal), using ImmunoCAP (Thermo Fisher Scientific). Furthermore, to investigate cross-reactivity between pork and live animal dander, IgE-immunoblotting was performed. Results: Eight (5.4%) of the 147 patients (M:F=1:7, mean age 33.9 yrs) had positive ImmunoCAP results for pork. ImmunoCAP for cat and/or dog dander were positive in five (62.5%) of the eight patients with pork allergy. One of the five patients owned a cat; one, a dog; two, a dog and cat; one, two dogs, five hamsters and three hedgehogs and one, no pets. All three patients, who gave informed consent for additional examination, also had positive ImmunoCAP results for nSus s 1, rFel d 2 and n Can f 3, however not for alpha-gal. IgE-immunoblotting using serum from two patients with higher serum specific IgE levels against pork showed cross-reactivity between pork and animal dander. Conclusion: Patients with pork allergies were mainly sensitized to nSus s 1, however not for alpha-gal. The results indicated that pork allergies in urban areas are predominantly pork-cat syndrome.

P08-05[C02-03]

Prevalence of malignancies in Japanese psoriasis patients and selected treatments in the West Japan Psoriasis Registry

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A lot of evidence has been suggesting the association between psoriasis and malignant tumors, however, all reports are from overseas and there is no evidence from Japan. Although the revised Japanese guidance of psoriasis allowed the use of biologics in psoriatic patients with malignancy in 2018, it could be still hard for dermatologists in Japan to use biologics to these cancer carriers. We investigated to reveal the prevalence of malignancies in Japanese psoriasis patients and selected treatments in real world through West Japan Psoriasis Registry.1397 psoriasis patients were enrolled in the Registry in 2019 and 2020. Five cases were excluded because of missing values. The overall complication rate of malignancy was 9.0% (124/1392). Among complicating tumors, gastric cancer (n=19) was the most common, followed by colon cancer (n =16) and breast cancer (n=15). In 1002 male patients, gastric cancer (n= 16), colon cancer (n=14), and prostate cancer (n=12) were the most common. Breast cancer (n=15), uterine cancer (n=9), and thyroid cancer (n=8) were the most common in 390 women. Non-melanoma skin cancer and melanoma were 8 and 1, respectively. Compared to the general population, thyroid cancer and non-melanoma skin cancer tended to be highly incident. Biologics were used in 68.1% (864/1268) of patients without cancer, whereas 49.2% (61/124) of those with cancer, which was statistically significantly lower (p<0.001). Although certain amount of psoriatic patients with malignancy were treated with biologics, complicating malignant tumors had a strong influence on treatment selection, even if not prohibited.

P08-06[O11-02]

The Clinical Significance of a Shortened Activated Partial Thromboplastin Time in Patients with Connective Tissue Disease

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Introduction: Connective tissue disease (CTD) patients have been reported to have an increased risk of venous thromboembolism (VTE). Deep venous thrombosis represents a potential emergency that may have a fatal outcome. The D-dimer test is the most widely accepted screening marker for VTE; however, elevation of the plasma D-dimer level without demonstrable thrombosis sometimes accompanies CTD activity itself, infection, and other conditions. Thus, the accuracy of a diagnosis of VTE based on a D-dimer test result is lower in CTD patients. The activated partial thromboplastin time (APTT) test is a very common and simple test. Method: The medical records of 535 CTD patients were retrospectively investigated. The following data were extracted: APTT, D-dimer, thrombotic events, laboratory data and systemic corticosteroid therapy. Results: The rates of thrombotic events and VTE were significantly increased in patients with a shortened APTT (<26 seconds) (PSAPTT) in comparison to those without a shortened APTT (p=0.004, 0.0009, respectively). The number of PSAPTTs was significantly increased in patients with VTE in comparison to those without VTE (p=0.0009). In the diagnosis of VTE in CTD patients, the specificity and positive predictive value (PPV) of the D-dimer test were 71.6% and 83.8% and 12.7% and 19.4%, respectively. The combination of a shortened APTT and elevated plasma D-dimer level improved the specificity and PPV to 94.7% and 97.3% and to 25.0% and 36.4%, respectively. Conclusions: For the evaluation of possibility of accompanying VTE in CTD patients, APTT shortened was useful and should be evaluated with careful attention.

P08-07[O11-03]

Prevalence and Characteristics of Prurigo Nodules in Adults With Moderate-to-severe Atopic Dermatitis in Japan: a 2-year Observational Study

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Background: Prurigo nodules (PN), sometimes associated with atopic dermatitis (AD), may have a negative impact on patients. The objective of this analysis was to describe baseline (BL) characteristics and 2-year treatment outcomes of AD-associated PN in a Japanese registry of patients with moderate-to-severe AD (UMIN000022623).
Methods: An exploratory analysis was performed measuring the presence, number, and size (corresponding to diameter of most significant nodule) of PN. Outcome measures included Investigator's Global Assessment (IGA), peak pruritus Numerical Rating Scale (NRS), Eczema Area and Severity Index (EASI), Dermatology Life Quality Index (DLQI), Patient Oriented Eczema Measure (POEM), and % body surface area (BSA) affected by AD.
Results: 288 patients were studied (median age 34 years; 37.5% had PN at BL). Patients with BL PN had numerically higher mean EASI/POEM scores, greater % BSA, and similar mean DLQI and weekly peak pruritis NRS scores vs those without BL PN.
Over 2 years, PN persisted in 53.4% of patients with BL nodules, and newly developed in 11.6% of those without. Patients with BL PN had mean % BSA affected>30% at all 3-month data points, and EASI/POEM values consistently numerically higher. At 2 years, there were no apparent differences in mean POEM between patients with vs without BL PN. Fewer patients with vs without BL PN achieved IGA 0/1 (6.5% vs 22.6%) at 2 years, with more remaining at IGA 3/4 (55.8% vs 33.0%). At each time-point, lower proportions of patient with vs without PN achieved EASI25/ 50/75 (25%, 50%, and 75% reduction, respectively, in EASI from BL).
Conclusion: Patients with BL PN had consistently higher disease severity and less favorable treatment outcomes than those without BL nodules.

P08-08[O11-04]

Withdrawn

P08-09[O11-05]

Psoriasis Epidemiology Screening Tool (PEST) is a useful tool for psoriatic arthritis in the Japanese population

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Psoriasis is a systemic organ involved in inflammatory skin diseases and the early time point detection of inflammatory reaction in other organs is a current highlighted issue for clinicians. Psoriasis Epidemiology Screening Tool (PEST) is an easy questionnaire consisting of 5 questions to predict the presence of psoriatic arthritis in psoriasis patients and widely investigated in Europe and United States, however, there has been no report on the usefulness of PEST questionnaire in the Asian population. The aim of this study is to clarify the actual usefulness of the PEST questionnaire in the Japanese population. Total 143 patients of psoriasis patients were enrolled in this study and 29 patients were diagnosed with psoriatic arthritis, and the prevalence of psoriatic arthritis among total psoriasis patients in this study was 20.7%. The PEST scores of more than 3 showed an increased frequency of psoriatic arthritis (P<0.0001) with a sensitivity of 93.1% and a specificity of 78.9%, respectively. Among the 5 questions of the PEST questionnaire, "Have you ever had a swollen joint?" showed the highest frequency in psoriatic arthritis patients. Univariate and multivariate analysis revealed that high PEST scores of more than 3 showed a significantly high odds ratio (P<0.0001 and P= 0.0003, respectively), suggesting that a high PEST score is an independent variable in psoriatic arthritis patients. Our study shows that the PEST questionnaire is useful for the detection of psoriatic arthritis among Japanese psoriasis patients.

P08-10[O11-06]

The impact of atopic dermatitis on health-related quality of life in Bangladeshi adults

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Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disorder that can impose profound patients' burdens including quality of life (QoL) impairment in people of all ages. Yet, poorly understood its psychological impacts on adults in low- and middle-income countries. The objective of this study was to assess the impact of AD on health-related quality of life (HRQoL) in Bangladeshi adults. A cross-sectional study of 184 eligible adults (83 males and 101 females, with a mean age of 33.46±15.44 years) was conducted at a dermatology outpatients department of a tertiary hospital in Dhaka, Bangladesh. AD was determined with the UK diagnostic criteria. A structured questionnaire was used to obtain patients' characteristics and Dermatology Life Quality Index (DLQI) for HRQoL. The severity of AD was measured with self-reported global AD severity, and Eczema Area and Severity Index (EASI). The mean DLQI score for the entire sample was 11.29±5.27, and 51.60% reported having a poor QoL. In bivariate analysis, significant differences in DLQI scores were found concerning self-reported AD severity, overall health, and EASI. In multivariable regression models, severe AD group reported a significantly higher DLQI score (Coef. =4.42; 95% CI=2.06-6.78, p<0.001) compare to that of a mild group. Concurrently, patients who had moderate and severe EASI, reported significantly higher DLQI score (Coef. =3.51; 95% CI=1.68-5.40, p<0.001 and Coef. =4.63; 95% CI=2.38-6.88, p<0.001 respectively) compare to that of mild EASI group, suggesting a marked impairment in HRQoL along with disease severity. AD severity markedly diminished HRQoL in Bangladeshi adults, thereby, a more patient-oriented approach in the management of AD would ease patients suffering and improve HRQoL.

P08-11[O11-07]

A clinical investigation for superficial type atypical lipomatous tumor

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We often face a difficult situation to examine superficially covered skin disease, especially subcutaneous tumor. Therefore, clinical findings of subcutaneous tumors are helpful for dermatologists to predict the diagnosis. Atypical lipomatous tumor (ALT) is recognized as a well-differentiated liposarcoma showing a higher frequency of a local recurrence after surgical resection. ALT is divided into 2 subtypes, namely superficial type and deep type. In contrary to deep type ALT, superficial type ALT is rarely observed, and it is difficult to make a diagnosis or predict the presence of superficial type ALT before surgical resection. To clarify the clinical characteristics of superficial type ALT, 15 cases with superficial type ALT and 118 cases with benign lipoma were enrolled in this study, and their differences in clinical characteristics and the findings of magnetic resonance imaging (MRI) test were investigated. As the clinical characteristics, the tumor size of superficial type ALT was significantly larger than that of benign lipoma. Superficial type ALT showed a significantly higher frequency of the tumor size of more than 4 cm. In addition, the characteristics of poor tumor mobility and hardness with elastic soft were observed in superficial type ALT. A significantly higher frequency of tumor site of superficial type ALT was seen in extremities. Buttocks and shoulder showed significantly higher frequent location in superficial type ALT. An MRI examination showed superficial type ALT exhibited a significantly higher frequency of the septal structures. Taken together, the combinations of clinical characteristics and MRI findings are useful to predict the presence of superficial type ALT.

P08-12[O11-08]

A single-center survey of psoriasis patients on biologics during the COVID-19 pandemic

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Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The ongoing COVID-19 pandemic has affected both daily life and medical care. The aim of this study was to analyze the use of biologics for psoriasis during the COVID-19 pandemic in our hospital. The observation period was between January 1, 2020, and February 28, 2021. A total of 227 patients with psoriasis were enrolled in this study, of which 159 (70.0%) were male and 68 (30.0%) were female. The average (mean±standard deviation) age of the patients was 54.4±14.4 years. The most prevalent type was psoriasis vulgaris (131 cases [57.7%]), followed by psoriatic arthritis (84 cases [37.0%]), generalized pustular psoriasis (9 cases [4.0%]), and erythrodermic psoriasis (3 cases [1.3%]). Current therapy included adalimumab (36 cases [15.9%]), certolizumab pegol (5 cases [2.2%]), infliximab (18 cases [7.9%]), ustekinumab (22 cases [9.7%]), guselkumab (30 cases [13.2%]), risankizumab (30 cases [13.2%]), tildrakizumab (2 cases [0.9%]), brodalumab (23 cases [10.1%]), ixekizumab (31 cases [13.7%]), and secukinumab (30 cases [13.2%]). Biologics were discontinued in 14 patients (6.2%). By contrast, the introduction of biologics was observed in 27 patients (11.9%). Bioswitch was performed in 25 patients (11.0%). The use of telephone consultation was observed in only 4 patients (1.8%). One patient, who received adalimumab for the treatment of psoriatic arthritis, suffered from COVID-19 and recovered after a mild course. In conclusion, we report our experience regarding the use of biologics for psoriasis. The use of biologics seemed safe for use amidst COVID-19 infection during the observation period.

P09-01[II-5]

Basal sweating as unrecognized machinery to maintain skin hydration in the finger: a long-standing paradox in dry skin resolved

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A long-standing paradox was why skin dehydration can be triggered by repeated water exposure in fingers despite the action of water to help hydrate skin tissue. Potential clues could be provided by identifying water-holding machinery in the glabrous skin, such as fingers. Therefore, we hypothesized that the water-holding machinery would be impaired after repeated water exposure. We investigated whether there could be a glabrous skin-specific water-holding machinery and if this machinery could be impaired in dry skin/hand eczema: this was examined by using an impression mold technique, which allows accurate quantification of sweat gland/duct activity at skin fold or ridge. Sweat pores were rarely detected at the folds in the finger at baseline, contrary to those in the hairy skin. Surprisingly, after water exposure, sweat pores opened at the folds while those at the ridges closed in healthy volunteers. The basal sweating response from the folds appearing after water exposure was significantly declined in patients with dry skin/hand eczema. We, therefore, investigated whether basal sweating responses from sweat pores at the folds could be exhausted after repeated water exposure cycles. Water exposure cycles were repeated up to twelve times, and sweating responses after each cycle were examined. Importantly, this basal sweating response from the folds appearing after repeated water exposure was sustained in healthy control and decreased in patients with dry skin/hand eczema. This exhaustion of sweating response was rescued in part by exposing individuals at high humidity conditions. Because basal sweating from the folds as water-holding machinery was severely impaired in these patients, basal sweating defects would be a potential target for dry skin/hand eczema.

P09-02[II-6]

Increased serum levels ofCCL2 and IL-8 in patients with toxic epidermal necrolysis accompanied by acute respiratory distress syndrome

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Background: Toxic epidermal necrolysis (TEN) is fatal adverse skin reactions, which are occasionally affected various organs. Although acute respiratory distress syndrome (ARDS) is rare complication, it can cause rapid and potentially fatal pulmonary dysfunction. However, the mechanism of TEN-induced ARDS was unknown. We investigated the potential biomarker predicting the onset of ARDS in TEN patients. Methods: Pre-treatment serum samples were collected from 16 TEN patients and 16 healthy controls (HC). The serum levels of cytokine were determined using Luminex Assay Human Premixed Multi-Analyte Kit. TEN patients were divided into two groups: those with ARDS (3 patients) and those without ARDS (13 patients). Among them, the serum from 2 patients with ARDS were collected one day before the onset of ARDS. The other one was collected on the day of onset. Results: Levels of CCL2, IL-6, and IL-8 were significantly increased in TEN patients with ARDS compared to those without ARDS and HC while there was no significant difference between TEN patients without ARDS and HC on serum levels of CCL2 and IL-8. Interestingly, there were no differences on levels of these cytokines between TEN with other organ damages such as the liver, kidneys, and eyes, and TEN without. These results suggest that CCL2 and IL-8 may be specific markers in TEN-induced ARDS. We further analyzed changes in cytokine levels before and after treatment in 2 TEN patients with ARDS. CCL2, IL-6, and IL-8 were decreased after systemic treatment compared to baseline levels at an early stage. Conclusion: Increased serum levels of CCL2, IL-6, and IL-8 were observed in TEN patients with ARDS. IL-8 and CCL2 may be involved in the pathogenesis of TEN-induced ARDS and be useful as a predictive marker for the onset of ARDS.

P09-03[C12-01]

Decomposition of skin RNA-seq data by Non-negative matrix factorization reveals various pathways in pathogenesis of Atopic dermatitis

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Transcriptomic analysis has revealed molecular expression characters in Atopic dermatitis(AD); however, there have been difficulties interpreting the complex RNA-seq data to show the pathophysiological variation in AD patients and collecting a sufficient number of samples for analysis. Our study aims to collect many human AD skins and utilize analytical methods to understand the heterogeneous expression patterns in AD skin samples. We chose 1mm punch biopsy for sampling bulk skins, with minimal invasion. We collected 735 skin samples from 142 AD patients, 20 normal and 14 psoriasis vulgaris patients as controls. In data analysis, we used the Non-negative matrix factorization method(NMF). NMF decomposes the gene expression data to a smaller number of metagenes, representing groups of genes co-expressed in the samples. By NMF, we revealed metagenes associated with inflammatory pathways and skin structures, including skin appendages, which enabled us to interpret the immunological characters of the samples while discarding noisy information due to the various inclusion of skin appendages. Notably, we identified distinct metagenes that included Th1 or Th2 pathway-related genes in high ranks: most psoriasis samples and some AD samples were associated with Th1 metagene, whereas Th2 metagene was mainly associated with AD samples. This study also suggested that evaluation as metagenes are more informative than focusing on a single gene when assessing prediction markers for therapeutic response and disease monitoring markers. Thus, our study has the potential to discover unique molecular pathways in diseases or responsive to targeted therapies, which could eventually help realize personalized medicine in the future.

P09-04[C12-02]

Automated assessment of the severity of psoriasis by AI

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In recent years, artificial intelligence (AI) plays a major role in modern society. In the medical field, AI research is progressing in the fields of radiology, ophthalmology, gastrointestinal endoscopy, pathology, etc., and AI is already being used in clinical settings. In the Japanese dermatology field, since 2018, the Japanese Dermatological Association (JDA) has been developing a reliable National Skin Disease Database (NSDD) evaluated by dermatologists and developing an AI diagnosis support system using NSDD. We showed the progress of our AI research at JSID meeting last year. Recently, we have established a novel AI platform for the evaluation of psoriasis skin severity by using deep convolutional neural networks (CNNs). We trained a CNN using a dataset of 750 psoriatic clinical pictures scored the rash state of psoriasis from erythema, induration, desquamation, and skin lesion area. Our AI can instantly evaluate the disease activity of psoriasis from one clinical picture. This technology replaces disease assessment with highly reproducible AI and provides it as a handy mobile app. Doctors at each institution can use a mobile app to evaluate the severity of psoriasis. Rookie doctors can use this app to check their skills. Patients can take pictures by themselves and use this app to understand their disease condition. In this presentation, we tested this disease scoring system with board-certified dermatologists, resident dermatologists, and student doctors, and we will report the score changes in each group after AI reference.

P09-05[C12-03]

Stimulator of IFN genes (STING) expression is a prognostic marker in patients with Merkel cell carcinoma

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Merkel cell carcinoma is a rare aggressive cutaneous neuroendocrine malignancy with an unfavorable clinical behavior. Approximately 80% of cases with Merkel cell carcinoma are directly linked to Merkel cell polyomavirus (MCPyV) infection, which is known to enhance the stimulator of IFN genes (STING) for the tumorigenesis of Merkel cell carcinoma. On the contrary, STING also contributes to driving antitumor immunity, suggesting that STING expression in the tumor might show a beneficial impact on the prognosis of Merkel cell carcinoma. The aim of this study is to confirm whether STING is a prognostic marker and the clarify the molecular mechanism how STING drives antitumor immunity against Merkel cell carcinoma. Statistical analysis based on the cohort study revealed that the degree of STING expression is associated with the prognosis of Merkel cell carcinoma. Consistently, RNA sequencing analysis also identified that STING expression was significantly increased in metastatic tissues Merkel cell carcinoma compared with that in primary cutaneous Merkel cell carcinoma, suggesting that STING expression in the tumor might regulate antitumor effect. Consistently, STING expression is related to the degree of infiltration of CD4+ and CD8+ T cells in the tumor. Taken together, STING expression is a prognostic factor to predict the prognosis of Merkel cell carcinoma, possibly due to the positive driver for antitumor immunity against Merkel cell carcinoma.

P09-06[C12-04]

Ultra high-frequency ultrasound provides a novel noninvasive diagnostic method for hair diseases complementing conventional modalities

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Trichoscopy and scalp biopsy are major diagnostic methods globally used to diagnose hair diseases; however, both have limitations to be covered by other modalities. Ultra high-frequency ultrasound (uHFUS) is an emerging technology equipped with 70mHz transducer which has the potential to assess minute structures including hair follicles (HFs)/shafts (HSs) and surrounding abnormalities. In this study, scalp images of uHFUS from patients with hair diseases (n=103) and healthy controls (n=40) were analyzed adopting both descriptive and numerical parameters and the data were compared to those of trichoscopy and scalp biopsy samples. As a result, disease-specific findings associated with pattern of inflammation and fibrosis, hair cycle abnormality, and subcutaneous changes, which were not directly observable in trichoscopy, were detected in hair diseases with statistical significance in frequency. For instance, active lesions of lichen planopilaris demonstrated perifollicular hypoechogenicity in mid-dermis (50%, $p<0.01$) and distal ambiguity of HFs (38%, $p<0.01$) reflecting inflammatory and fibrotic changes of upper HFs, whereas scarring lesions manifested homogeneous dermis without structure (100%, $p<0.01$), reflecting diminished skin appendages and increased collagen tissue. Numerical parameters representing dermal echogenicity, HFs/HSs numbers, hair diameter and its diversity were significantly different between patients and controls. Based on the outcome of the analyses, major diagnostic findings for each hair disease were proposed and the patients not otherwise diagnosed were given probable diagnoses. The outcome highlighted advantages of uHFUS in diagnosing hair diseases, while overcoming the weaknesses of other diagnostic techniques.

P09-07[C12-05]

Persistent HHV-6 infection has an increased risk of autoimmune disorders in patients with DIHS

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DIHS is a severe drug eruption characterized by reactivation of HHV-6. In addition, autoimmune diseases such as type 1 diabetes and thyroiditis may develop long-term after resolution of DIHS. We found that 27% (11 of 41) of patients harbor high levels of HHV-6 DNA (>1000 copies/10^6 PBMC) during the entire follow-up period for at least six months after onset of DIHS, except in cases of death. The other 30 patients were associated with 28 cases of HHV-6 and 2 cases of CMV transient infection. However, it is unclear what effects persistent HHV-6 infection has on DIHS in chronic phase. In this study, we analyzed clinical symptoms, blood test findings, reactivation of herpes virus, expression of serum cytokines (IL-4, IL-5, IL-10, IFN-Γ) and soluble IL-2 receptor (sIL-2 R) for 11 DIHS patients with persistent HHV-6 infection and 30 patients with transient HHV-6 or CMV infection. Compared to transient HHV-6 infection group, persistent HHV-6 infection group showed 1) more severe acute phase cutaneous and mucosal eruptions, 2) higher levels of HHV-6 and CMV DNA, 3) higher levels of IL-5 in acute phase and higher levels of sIL-2R in both acute and late phase, 4) higher rate of long-term complications (ie, interstitial nephritis, arthritis, thyroiditis). We additionally investigated the relationship between HHV-6 persistent infection and development of long-term complications. We examined the levels of HHV-6 DNA in five patients had long-term complications after DIHS from other medical institutions. All five patients had significantly high level of HHV-6 DNA even after a long period of onset of DIHS. In conclusion, persistent HHV-6 infection after resolution of DIHS may lead to prolonged imbalance in host immune responses that may alter the clinical course and prognosis.

P09-08[C12-06]

S100A2 is a potent biomarker of severe drug reaction

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The development of medications gives us a beneficial impact on various diseases; however, these medications accidentally cause an adverse drug eruption. In addition, the severe type of drug eruption sometimes causes a life-threatening adverse event, namely Stevens-Johnson syndrome and toxic epidermal necrolysis. Therefore, a useful biomarker to predict the clinical course of severe cutaneous adverse reactions is desired. The aim of this study is to search for a novel biomarker of severe cutaneous adverse reactions. To clarify this issue, we first conducted RNA sequencing analysis to identify a high expression of S100A2 in keratinocytes by telaprevir and trichloroethylene, which are potent to cause a drug eruption. The skin in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis showed a high expression of S100A2 in the epidermis with a significantly increased frequency of S100A2 positive staining in patients with severe type drug eruption. Finally, we also investigated whether S100A2 is a specific biomarker in severe type drug eruption. Atopic dermatitis and psoriasis patients also increased S100A2 expression compared with healthy subjects and the severity of atopic dermatitis showed a positive correlation with S100A2 expression, suggesting that S100A2 is a biomarker of toxic damaged skin not limited to severe type drug eruption. However, S100A2 might be helpful to predict the clinical course of severe cutaneous adverse reactions in the early time point.

P09-09[C12-07]

Inflammatory type of acquired idiopathic generalized anhidrosis is characterized by dysregulation of sweat gland immune privilege

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Collapse of immune privilege (IP) has been speculated to play a key role in the pathogenesis of autoimmune skin appendage disorders. Indeed, we recently demonstrated the presence of human sweat gland (SwG) IP and dysregulation of IP-related molecules in syringotropic collagen diseases. In this study, we attempted to evaluate the state of SG-IP in acquired idiopathic generalized anhidrosis (AIGA), by a newly invented digital image analysis combined with immunohistochemistry. Six AIGA patients were included in this study. All the patients were male, and the average age was 27.3±8.8. Five out of 6 patients were received corticosteroid pulse therapy and four cases achieved remission. In histology, lymphocytic cell infiltration surrounding the dermal portion of the sweat duct (SwD) was observed in four cases and so the cases were categorized as the inflammatory type of AIGA (infAGIA). In infAIGA, but not in non-inflammatory AIGA, MHC class I was significantly upregulated in SwD ($p < 0.01$) at the site where MIF expression was down-regulated prior to the treatment, suggesting regional IP collapse. In a refractory infAIGA case, syringotropic cell infiltration and dysregulation of IP-related molecules remained even after the treatment. Local increase in IP-10 was tendentiously observed in infAIGA case with claudin-1 downregulation. In all AIGA cases, acetylcholine receptor was downregulated in SwGs, however the extent was greater in non-inflammatory AIGA. Further accumulation of the cases is essential, however, the findings in this suggested a putative association between IP collapse and the elicitation of proinflammatory stimuli leading to fragility of the tight junction in SwD in infAIGA, which might distinguish infAIGA from its non-inflammatory counterpart.

P09-10[C12-08]

Lymphocyte count and neutrophil-to-lymphocyte ratio at the onset of herpes zoster are useful biomarker for predicting life prognosis

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Background: Although patients with malignant and immunosuppressants run higher risk of developing herpes zoster (HZ), it is not clear the life prognosis after the event of HZ induced by immunosuppression.
Objectives: We sought to determine the risk of specific mortality and a biomarker that can predict the outcomes after the event of HZ.
Methods: A retrospective study of 954 patients with HZ was performed. HZ patients were divided into 3 groups; HZ with malignancies (n=91), HZ with immunosuppressants (n=113), and others (n=750). We analyzed the mortality rate within 180 days after HZ, and neutrophil and lymphocyte counts at the onset of HZ.
Results: The mortality rate showed 2.57% (n=24) (median: 91 days) in total, and 15.4% (n=14) (median: 86 days), 2.65% (n=3) (median: 115 days), and 0.93% (n=7) (median: 96 days) with malignancies, with immunosuppressants, and others, respectively. The most frequent cause of death was primary disease associated with malignancy (41.7%) followed by infections (33.3%) in total. All HZ patients with malignancies were died of primary disease or fatal infection. Lymphocyte counts at the onset of HZ were significantly decreased in lethal patients within 180 days (median: 665/μL) than in patients with alive more than 180 days after HZ (median: 1310/μL). NLR at the onset showed significantly higher in lethal patients within 180 days (median: 7.70) than in patients with alive more than 180 days after HZ (median: 2.55). Marked decrease in lymphocyte counts and increase in NLR accurately predicted subsequent risk of death after the event of HZ (cut off: 940 and 4.84, respectively).
Conclusion: Lymphocyte count and NLR at the onset of HZ as a useful biomarker can predict the risk of specific mortality, especially fatal infection after the event of HZ.

P09-11[O06-01]

Investigation of the involvement of TIF1γ expression in tumors in the pathogenesis of cancer-associated dermatomyositis

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Anti-transcription intermediary factor 1γ (anti-TIF1γ) antibody (Ab) is significantly associated with internal malignancies in adult patients with dermatomyositis (DM). Although pathogenesis of cancer-associated DM is unknown, TIF1γ overexpression in tumors has been considered to be critical for the development of DM. Objective was to investigate clinical characteristics of patients with anti-TIF1γ Ab-positive DM and elucidate risk factors that are potentially associated with internal malignancy. In addition, we compared the expression of TIF1γ in tumor tissues of patients with anti-TIF1γ Ab-positive DM, anti-TIF1γ Ab-negative DM and without DM in order to investigate the pathogenesis of cancer-associated DM. We analyzed 77 Japanese patients with DM, and found 19 patients to be positive for anti-TIF1γ Ab. Patients with anti-TIF1γ Ab-positive DM were older and presented heliotrope rash and flagellate erythema more frequently than patients without anti-TIF1γ Ab. Furthermore, internal malignancy and dysphagia were significantly more frequent in the anti-TIF1γ Ab-positive group. Male sex and dysphagia were significantly associated with internal malignancy in patients with anti-TIF1γ Ab-positive DM. Using immunohistochemistry, we examined the TIF1γ expression in tumors of 11 patients with cancer-associated DM and 25 patients without DM. TIF1γ was highly expressed in all tumors, and there was no significant difference in TIF1γ expression between patients with and without DM. Furthermore, TIF1γ expressions in tumors were similar irrespective of the presence of anti-TIF1γ Ab. These results suggest that anti-TIF1γ antibody may not be simply induced by overexpression of TIF1γ in tumors in patients with DM, but that other mechanisms may exist.

P09-12[O06-02]

Identification of serum biomarkers predicting the therapeutic effect of dupilumab in atopic dermatitis by a targeted metabolomics approach

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Dupilumab is the first biologic for atopic dermatitis (AD). Despite its high expense, it is unknown in what kind of patient group the drug is effective. Therefore, in this study, we aimed to identify novel and reliable biomarkers predicting the efficacy of dupilumab, which can be measured before the administration of dupilumab. The serum samples of 20 AD patients treated with dupilumab were analyzed for metabolomics using gas chromatograph-mass spectrometer (GCMS-TQ8040; Shimadzu Co.). The serum levels of metabolites in the patients who achieved EASI75 (high responders, n=12) were compared with those in the patients who did not achieve it (low responders, n=8). Of the 148 metabolites, 10 showed significant difference between high responders and low responders; ribose, lactic acid, alanine, oxalic acid, glyceric acid, fumaric acid, nonanoic acid, xylulose, ornithine, and sorbitol. As a result of principal component analysis, it was possible to distinguish high responders from low responders. Furthermore, ribose and nonanoic acid were the specific metabolites that were useful for predicting the effect of dupilumab. Thus, several metabolites that could predict the efficacy of dupilumab were identified. These metabolites may be used as serum biomarkers to establish new personalized medicine.

P09-13[O06-03]

Predicting RNA sequences of small patch image for Treatment of Atopic Skin Disease by Deep Convolutional Neural Networks

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Recently new type of medicine for atopic disease has been released, which inhibits the action of cytokines such as Dupilumab. Patients should get generic test to know which cytokines is inflamed or not. However, generic test is high cost and takes time so generic test is not common. We propose a deep convolutional neural network (CNN) which predicts amount of each RNA from the small skin surface image. Generic test using image may become fast and easy way to know which cytokines is high and can propose best treatment for atopic dermatitis patients. This research is actually challenging, and it is difficult to predict all type of RNA, so we investigated which cytokines was predictable by CNN from image through experiment. We build the new dataset which includes skin surfaces and its RNA sequence. There are 160 subjects and total 821 RNA sequences and 90% of them are from atopic dermatitis patients. We separate the dataset to training set and validation set. 32 subjects are used in training and others are in validation. Skin specimens for RNA sequencing were obtained from the patient's upper back region with a 1 mm biopsy punch. The number of RNA types is more than 10,000, and we choose some RNAs such as IL4 or IL13 for treatment of atopic disease. In preprocess, we use Transcripts Per Kilobase Million (TPM) for normalization. We took a picture of the skin surface where we punched to get RNA sequences. The picture is strongly zoomed to the punched area to remove noisy information. Finally, we build the CNN model to predict each RNA sequence. We use regression method and root mean squared log error as a loss function. We compared some back born CNN networks and proposed new regression method for skin RNA sequence prediction.

P09-14[O06-04]

Dermoscopic diagnostic performance of non-dermatologists for skin tumor is improved by a computer-aided diagnosis system

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Background: Dermoscopy is an indispensable technique when making a correct diagnosis of pigmented skin tumors. Recently, several deep neural networks (DNN) have been developed on the purpose for classifying dermoscopic images of skin tumors, however, a few studies demonstrated the usefulness of those DNNs as a computer-aided diagnosis (CAD) system. **Objective:** To examine the dermoscopic diagnostic performance of non-dermatologists for pigmented skin tumors and clarify whether a CAD system improves the performance. **Methods:** 52 non-dermatologists (29 dermatology residents and 23 non-dermatology doctors) and 17 dermatologists were asked to decide malignancy prediction for 200 dermoscopic images of pigmented skin tumors obtained from multi-centers. The diagnostic performances of the human readers with/without CAD system were calculated and compared between those with/without CAD system. Three CAD systems containing different amount of information (#1: simple, #2: median, #3: detailed) were created mostly based on the previous reported DNN (J Dermatol 2021;48:232) and one of the three systems was provided to each reader. **Results:** The mean sensitivity and specificity for malignancy without CAD system were 0.82 and 0.71 in dermatology residents, 0.71 and 0.65 in non-dermatology doctors, and 0.82 and 0.81 in dermatologists. Those with CAD system were 0.85 and 0.82, 0.79 and 0.82, and 0.86 and 0.88, respectively. When comparing among CAD #1, 2, and 3, the mean sensitivity and specificity of dermatology residents were 0.83 and 0.79 in CAD #1, 0.84 and 0.81 in CAD #2, and 0.87 and 0.87 in CAD #3. **Conclusions:** The CAD system can improve the dermoscopic diagnostic performance of non-dermatologists and may lead them to the similar level as dermatologists.

P09-15[O06-05]

A possible role of surgical deroofing procedure to cover the disadvantage of adalimumab treatment for hidradenitis suppurativa

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Hidradenitis suppurativa is refractory chronic, inflammatory skin diseases characterized by recurrent follicular disease located in the axillae, groin, and anal. Although only conservative treatment with oral antimicrobials and surgical treatment such as skin implantation has been traditionally conducted, anti-TNF-alfa antibody treatment adalimumab shows a beneficial impact on the clinical outcome of hidradenitis suppurativa. The aim of this study is to clarify the clinical characteristics of refractory hidradenitis suppurativa by adalimumab administration and a possible therapeutic option to obtain more therapeutic outcome of adalimumab treatment. Total 7 patients, who were diagnosed with hidradenitis suppurativa and received adalimumab treatment, were enrolled in this study. As the clinical characteristics, 6 males and 1 female, with a mean age of 45.8 years; all patients had a history of smoking, 3 patients had a high BMI more than 25. Adalimumab administration showed favorable clinical outcome in moderate type based on physician's global assessment for HS. On the contrary, severe type patients showed refractory skin eruption by the treatment of adalimumab alone and insufficient superficial epithelization is thought as the problem of recurrent skin eruption, due to TNF-alfa-inhibitor-mediated suppressive effects on keratinocyte migration. However, antecedent deroofing surgery and subsequent adalimumab treatment prevents the recurrence of skin eruption. Taken together, severe type hidradenitis suppurativa patients might be a therapeutic candidate for the treatment of adalimumab following deroofing surgery.

P09-16[O06-06]

Dermcidin is a prognostic factor in patients with extramammary Paget's disease

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Extramammary Paget's disease is recognized as an apocrine-derived skin tumor and is basically localized in the epidermal skin lesion. In contrast, dermal invasion is closely associated with lymph node metastasis and poor prognosis, and there are a limited number of biomarkers to estimate the prognosis of extramammary Paget's disease. Therefore, a potential biomarker has been desired to identify for estimating the tumor advancement in extramammary Paget's disease. Dermcidin is an antimicrobial peptide derived from the eccrine gland and is identified as a biomarker in various malignancies. Extramammary Paget's disease has been believed as a malignant tumor derived from apocrine glands which show a negative expression of dermcidin in normal tissue. However, it has not been intensively investigated whether dermcidin is expressed in patients with extramammary Paget's disease. To investigate a possible potential of dermcidin in extramammary Paget's disease, we investigated dermcidin expression in the tumor by immunostaining technique. Among a total of 60 patients with extramammary Paget's disease enrolled in this study, 14 patients showed positive immunostaining of dermcidin. We next investigated the clinical characteristics of positive dermcidin extramammary Paget's disease patients. Dermcidin positive patients showed a significantly high frequency of lymph node metastasis. The overall survival curves using the Kaplan-Meier method showed unfavorable clinical behavior in patients with dermcidin-positive patients. Univariate analysis identified that positive dermcidin showed a significantly increased hazard ratio in the overall survival, suggesting that dermcidin might be a prognostic factor in extramammary Paget's disease.

P09-17[O06-07]

Immediate impact of granulocyte and monocyte adsorption apheresis on generalized pustular psoriasis

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Granulocyte and monocyte adsorption apheresis (GMA) is an extracorporeal circulation therapy that removes activated granulocytes and monocytes. GMA demonstrated effectiveness for generalized pustular psoriasis (GPP) with tolerable safety in the clinical setting; however, its evidence is very limited due to the rarity of GPP. Furthermore, to date, its immediate impact on GPP has not been assessed yet. We herein report the real-world data on 14 GPP patients, and its immediate impact on GPP. Data on GPP patients treated with GMA in our department were collected retrospectively from their charts. Patients were evaluated for the affected body surface area (BSA) of erythema, pustule, and edema before and at two weeks after the last GMA. Patient's body temperature (BT), the number of circulating leukocytes (WBC), and serum levels of C-reactive protein (CRP) and albumin (Alb) were assessed before, at two days after the first GMA, and at two weeks after the last GMA. Fourteen patients were included. Their mean age was 64.5 ± 12.6 years. All patients except one received systemic therapy including oral drugs or biologics prior to GMA. All patients showed significant improvement in the affected BSA of erythema, pustules, and edema at two weeks after the last GMA therapy. As for immediate impact of GMA, BT, WBC, and CRP significantly decreased at two days after the first GMA. No serious adverse events were observed during GMA therapy. Its good safety profile allows a wide range of patients including old patient and those with complications, possible active infection, or malignancy to receive it. Moreover, our study revealed immediate improvement in BT, WBC, and CRP, indicating that GMA contributes to rapid suppression of acute inflammation in GPP.

P09-18[O06-08]

Safety and efficacy of bexarotene for Japanese patients with CTCL: Real-world experience from a result of post marketing survey

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To establish a real-world evidence about safety and efficacy of bexarotene for Japanese patients with CTCL, we conducted a nation-wide cohort study using a result of post marketing survey. In total, 294 patients with CTCL are identified between June 2016 and June 2018. Of the 294 patients, 267 are included in the safety analysis set (SAS). Common treatment-related adverse events include hypothyroidism (85.8%), hypertriglyceridemia (68.5%), hypercholesterolemia (43.8%), and neutropenia (21.6%). Hypertriglyceridemia, hypercholesterolemia and neutropenia occur more frequently in patients of the regular-dose (bexarotene at 300mg/m^2) cohort than those of the low-dose cohort (less than 300mg/m^2) (76.4, 49.0 and 28.0% vs 57.0, 36.4 and 12.1%; p=0.001, 0.045 and 0.002, respectively). Of the 267 patients, 175 are included in the efficacy analysis set (EAS). In the EAS population, 139 patients have mycosis fungoides (MF), including 46 (33.1%) with early-stage and 93 (66.9%) with advanced-stage diseases, respectively. In the 139 patients with MF, the objective response rate is 46.8% (95% CI, 38.3-55.4). A significant difference in response between the regular- and low-dose cohorts is detected (61.6%; 95% CI, 50.5-71.9 vs. 22.6%; 95% CI, 12.3-36.2; P<. 001). Of the 139 patients with MF, 92 (66.2%) are treated with a combination of bexarotene plus photo(-chemo) therapy. A significant difference in response between two patient groups with bexarotene plus photo(-chemo) therapy and with bexarotene monotherapy is detected (57.6%; 95% CI, 46.9-67.9 vs 25.5%; 95% CI, 13.9-40.3; P<. 001). This study indicates that a combination of photo(-chemo) therapy and low-dose bexarotene may provide one of promising therapeutic strategies for patients with CTCL, when emphasizing safety.

P09-19[O06-09]

MicroRNAs in neutrophils as markers of psoriasis

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MicroRNA(miRNA)s belong to the class of short, non-coding, RNAs that can negatively regulate gene expression at a post-transcriptional level by binding to target messenger RNA to block mRNA translation or induce mRNA cleavage. We performed comprehensive analysis of miRNA in sera of patients with psoriasis and healthy control. Three miRNAs related to neutrophils were chosen. These miRNAs significantly increased in patients compared to control subjects. For in vitro study, we used an all-trans retinoic acid (ATRA)-induced differentiated HL-60, a human acute promyelocytic leukemia cell line. When HL-60 was treated with ATRA, the cells were differentiated to neutrophilic cells which show increased cytoplasm to nucleus ratio, increased condensated chromatin, and nuclear segmentation. The expression of above-mentioned miRNAs increased during the differentiation of these cells. Moreover, miRNAs regulate proliferation of cultured keratinocytes. These data suggest that miRNAs play important role in neutrophil differentiation and proliferation of keratinocyte in psoriasis.

P09-20[O06-10]

Chronic hepatitis B virus infection in dupilumab-treated atopic dermatitis patients

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Chronic hepatitis B virus (HBV) infection can lead to death in de novo acute hepatitis or chronichepatitis with HBV reactivation caused by immunosuppressive drugs including biologics forpsoriasis and other diseases. Atopic dermatitis (AD) is one of the most common inflammatory skindiseases. Dupilumab, an inhibitor of IL-4 and IL-13, is a highly effective biologic that controls skinrash and itching in AD (Matsutani M, et al. J Cutan Immunol Allergy, 2020). However, dupilumabclinical trials did not include HBV-positive patients due to the exclusion criteria, and little wasknown concerning its safety in these patients. Therefore, we aimed to investigate the safety ofdupilumab in HBV-positive patients. Of the AD patients who started dupilumab at our hospital fromApril 2018 to July 2020, 103 patients were measured for HBs antibodies (HBsAb), and 6 patients(5.8%) were HBsAb positive. Of six, one had previously received the HBV vaccination and wasexcluded from the study. We performed HBV-DNA quantification by TaqMan PCR in all 5 patientsperiodically after the introduction of dupilumab. As a result, no patients showed HBV reactivation. Recently, we reported that dupilumab selectively suppresses Th2 immune responses (Imai Y, et al. JID Innovations, 2021). Given that HBV suppression is considered primarily dependent on the Th1immune response, we hypothesize that dupilumab is unlikely to induce HBV reactivation. Insummary, dupilumab was given to HBV-positive AD patients without any major problems.

P09-21[O06-11]

Comparison of treatment goals between users of biological and non-biological therapies for treatment of psoriasis in Japan

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Background: Previously, our cross-sectional observational study in Japan revealed high (68%) discordance within treatment goals between psoriasis patients and their physicians. Objective: This secondary analysis aimed to determine whether patient and physician users of biologics have higher treatment goals than users of non-biologics. Methods: A survey for both patients and physicians on background characteristics, disease severity, treatment goals, treatment satisfaction, and health-related quality of life was conducted at 54 sites. Association between treatment goals and biologic/non-biologic users was assessed using ordinal logistic regression models. Results: In total, 449 patient-physician pairs agreed to participate; 425 completed the survey and were analyzed. More biologic users than non-biologic users reported complete clearance (Psoriasis Area and Severity Index 100) as a treatment goal (patient-reported: 23.6% vs 16.1%; physician-reported: 26.9% vs 2.2%). Biologic users were significantly associated with higher treatment goals than non-biologic users (patient-reported: 1.8[1.15-2.87](odds ratio[95% CI]), P=0.01; physician-reported: 11.0[5.72-21.01], P<0.01). Among biologic users, higher treatment goals were associated with higher treatment satisfaction (patient- and physician-rated); lower treatment goals were associated with back lesions and increasing patient age (patient-rated) and higher disease severity (physician-rated). Conclusion: Use of biologics among patients with psoriasis was associated with higher treatment goals. Further use of biologics contributed to treatment satisfaction. Appropriate treatment goals that are shared among patients and their physicians may improve treatment outcomes.

P09-22[O06-12]

A patient with atopic dermatitis and psoriasis vulgaris presenting an unusual reaction for dupilumab

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Cases of concurrence of atopic dermatitis and psoriasis vulgaris in a single patient have been recently reported in spite of their different pathogenesis. In such cases, it is suggested that different cytokine profiles are found in each skin lesion. A case report showed the possibility that atopic dermatitis of the patient may be aggravated after the treatment of his psoriasis using ustekinumab was administered. Here, we present a case who exhibited cutaneous manifestations of both atopic dermatitis and psoriasis vulgaris treated with dupilumab. A Japanese female in her fifties was diagnosed clinically with the concurrence of atopic dermatitis and psoriasis vulgaris. She had been received many kinds of treatment mainly for atopic dermatitis in our institution over a long period. Dupilumab was administered due to the intractable atopic dermatitis. After dupilumab was started, the patient exhibited annular and papular scaly lesions widely distributed on her trunk. Most of the lesions disappeared after dupilumab was continued. Atopic dermatitis was also improved. However, psoriatic lesions on her knees were residual. We will investigate the cytokine profiles in her lesions and discuss the treatment of such cases who have both atopic dermatitis and psoriasis vulgaris, reviewing the literature.

P10-01[III-6]

Blockade of CX3CL1-CX3CR1 pathway inhibits mouse sclerodermatous chronic graft-versus-host disease model

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Systemic sclerosis (SSc) is a connective tissue disease characterized by fibrosis and vascular injury of skin and internal organs. CX3CL1 (fractalkine) and soluble CX3CL1 are involved in selective migration of CX3CR1-expressing leukocytes into the lesional tissue. We previously reported that the expression of CX3CL1 and CX3CR1 was both augmented in patients with SSc, and anti-mouse CX3CL1 monoclonal antibody (mAb) suppressed inflammation, fibrosis, and vascular injury of the skin in bleomycin- or growth factors-induced skin fibrosis models. However, these animal models do not develop apparent fibrosis and inflammation in internal organs including lungs. Therefore, we investigated the utility of anti-mouse CX3CL1 mAb therapy in a murine sclerodermatous chronic graft-versus-host disease (Scl-cGVHD) model. Allogeneic bone marrow transplantation into sublethally irradiated BALB/c mice induced skin and lung fibrosis resembling human Scl-cGVHD or SSc. An intraperitoneal injection of anti-CX3CL1 mAb increased survival rate in a dose dependent manner. The mAb therapy significantly attenuated the fibrosis of the skin and lungs as well as the local infiltration of T lymphocytes in the skin and lungs and macrophages in the lungs. Furthermore, the mAb suppressed the expression of proinflammatory cytokines such as IL-6, TNF-α, and profibrotic cytokine IL-4 in the skin and the TNF-α expression in the lungs. Anti-CX3CL1 mAb therapy showed no obvious side effects. Together with our previous results in other murine models, these findings indicate that the systemic administration of anti-CX3CL1mAb can be one of the key candidates for the treatment of human Scl-cGVHD and SSc.

P10-02[C02-04]

Vitamins and their derivatives synergistically promote hair shaft elongation *ex vivo* via PlGF/VEGFR-1 signaling activation

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Hair loss often impacts on quality of life and therefore vast demand exists for products promoting hair growth. Despite that vitamins (Vit) or their derivatives, such as panthenyl ethyl ether (Vit B5 derivative), tocopherol acetate (Vit E derivative), or pyridoxine (Vit B6) have widely been used in topical hair care products, their efficacy and mode of action have been insufficiently studied.
In this study, we aimed to elucidate the effect of Vits and their derivatives on hair follicles and dissect underlying mechanisms. In the mouse vibrissa organ culture model, the supplementation of a triple combination of panthenyl ethyl ether, tocopherol acetate, and pyridoxine (namely PPT) significantly promoted hair shaft elongation, when compared to single- or double-agent treatments ($p<0.05$). In histology, PPT-treatment enhanced hair matrix cell proliferation by 1.89 folds compared to vehicle-treated controls, as demonstrated by Ki-67 positive immunoreactivity. Intriguingly, PPT-treated mouse follicular dermal papillae up-regulated *Placental growth factor (Plgf)* by 1.60 folds, compared to non-treated controls, which was the only markedly up-regulated growth factor among those examined, such as *Fgf7, Igf1, Hgf, Vegfa*, and *Pdgfa*. Importantly, the addition of PlGF neutralizing antibodies to the ex vivo culture diminished the promotive effect on hair growth and the increase in VEGFR-1 phosphorylation achieved by PPT. Moreover, PPT treatment increased PlGF secretion in cultured human dermal papilla cells.
Taken together, these findings suggested that PPT promoted hair shaft elongation via activating PlGF/VEGFR-1 signaling. The current study can shed light on the previously underrepresented advantage of utilizing Vits and their derivatives for ameliorating hair care products.

P10-03[C02-05]

Formyl peptide receptor 1 triggers cell death signals in keratinocyte as SJS/TEN model

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Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but severe skin eruptions induced by an adverse drug reaction. The patients suffer from acute inflammation on their skins and mucosa, leading to vast skin detachment and loss of eyesight. Specific drugs for SJS/TEN have not been established due to the lack of knowledge about the molecular mechanism of SJS/TEN. Previously, we have revealed that formyl peptide receptor 1 (FPR1) induced necroptosis of keratinocytes in the lesional skins of SJS/TEN patients. Here, we reconstituted in vitro cell death model cells by inducing FPR1 expression in HaCaT cells to analyze the mechanism of keratinocyte death in SJS/TEN. The membrane expression of FPR1 was measured with FACS, and mRNA level was measured by qRT-PCR. The cell death was quantified by LDH release and by in vitro fluorescent staining of the live and dead cells. The presence of signal transduction, such as phosphorylation of ERK and cleavage of PARP, was measured by Western blot. As a result, ATP stimulation induced a transient increase in the expression level of FPR1 in HaCaT cells. Ligand stimulation to FPR1 triggered transient phosphorylation of ERK, demonstrating the functionality of the induced FPR1. The FPR1-expressing cells showed spontaneous cell deaths upon ligand stimulation. The cell death was inhibited by an apoptosis inhibitor but not by a necroptosis inhibitor, suggesting that stimulation for FPR1 induced apoptosis for HaCaT cells. Induction of cleaved PARP further confirmed the apoptotic signal transduction in HaCaT cells. Collectively, expression and following activation of FPR1 in HaCaT cells mainly triggered apoptosis instead of necroptosis.

P10-04[C02-06]

Konjac-ceramide (kCer) induces semaphorin 3A production in normal human epidermal keratinocytes

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Epidermal hyperinnervation has been identified as one of the causes of itch sensitivity. We previously proposed that keratinocyte-produced semaphorin 3A (Sema3A) plays a role in the modulation of epidermal innervation in skin barrier dysfunction. We also demonstrated that Sema3 A replacement therapy reduces epidermal nerve fiber density, and improves the dermatitis score in AD model NC/Nga mice. However, the mechanisms by which endogenous Sema3A induction in keratinocytes have not yet been elucidated. Konjac ceramide (kCer), prepared by the deglucosylation of konjac glucosyl ceramide (kGlcCer), was recently exerted similar neurite outgrowth inhibitory effects to those of Sema3A. Our preliminary study demonstrated that kCer significantly induces the production of Sema3A in normal human epidermal keratinocytes (NHEKs). Therefore, the present study investigated the mechanisms by which kCer induces the expression of Sema3A in NHEKs. In NHEKs incubated with 0-100 μM kCer, kGlcCer, and C24Cer, Sema3A mRNA and protein levels were dose-dependently increased by kCer and kGlcCer. kCer exerted more potent effects than kGlcCer. Similar results were obtained when kCer was applied to medium or the stratum corneum side of reconstructed human epidermal models. kCer-induced *Sema3A* mRNA expression was suppressed by MEK1/2, JNK, and PI3K inhibitors. In addition, increased RORα expression in NHEKs was observed by kCer treatment. These results participation of the MAPK and/or RORα signaling pathways may implicate in the mechanism of kCer-induced Sema3A production in NHEKs. kCer might be potential for a topical antipruritic treatment for epidermal hyperinnervation in skin diseases caused by skin barrier dysfunction, such as xerosis and AD.

P10-05[C02-07]

A calpain inhibitor ALLN attenuates bleomycin-induced skin fibrosis in a mice model

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Objection : Systemic sclerosis (SSc) is a collagen disease representing fibrosis of the skin and internal organs. TGF-β1 has been considered to play a central role in the pathogenesis of SSc. Calpains are family members of $Ca2^{+}$-dependent cysteine proteases for which the biological action may contribute to fibrosis in various organs. However, the precise mechanism of calpain-dependent fibrosis and the potential utility of their inhibitors in SSc remain unclear. In this study, we investigated if one of calpain inhibitors ALLN could offer an innovative therapeutic approach for skin sclerosis in SSc.
Method: Normal human dermal fibroblasts pretreated with various doses of ALLN were stimulated with recombinant TGF-β1, followed by real-time RT-PCR, western blotting, and immunostaining for assessment of TGF-β1/Smad signaling and fibrogenic molecules. ALLN (3mg/kg/day) was intraperitoneally administered 3 times a week in bleomycin-induced SSc model mice.
Result: ALLN treatment significantly inhibited over-phosphorylation and nuclear transport of Smad3 in TGF-β1-stimulated fibroblasts. TGF-β1-dependent increase of collage type 1, fibronectin 1, α-smooth muscle actin, and epithelial mesenchymal transition markers including SLUG and ZEB1 was attenuated in mRNA and protein expression by ALLN. In consistent with these findings, intraperitoneal administration of ALLN remarkably suppressed the development of skin fibrosis in bleomycin-induced SSc model mice. The number of $F4/80^{+}$ macrophages and $CD3^{+}$ T cells tended to decrease in number in the ALLN-treated mice compared to the control-treated mice. No obvious side effects were observed.
Conclusion: Calpain may be a primary contributor and novel therapeutic target for skin fibrosis in SSc.

P10-06[O04-08]

Spesolimab improves patient-reported outcomes (PROs) in patients with generalized pustular psoriasis (GPP) in the Effisayil 1 study

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GPP is a rare and potentially life-threatening skin disease characterised by widespread sterile pustules and recurrent flares. Here, we report PROs for measures of pain, symptoms of psoriasis, fatigue and impact on quality of life (QoL) in patients treated with spesolimab in the Effisayil 1 study. Effisayil 1 (NCT03782792) is a multicentre, randomised, double-blind, placebo-controlled study in patients with a GPP flare. Patients were randomly assigned (2:1) to receive a single intravenous dose of 900 mg spesolimab (n=35) or placebo (n=18) on Day 1 and followed for 12 weeks. At Week 1, patients with qualifying clinical assessment scores who did not receive escape medication before Day 8 could receive a 900 mg open-label dose of spesolimab. Secondary and further endpoints were assessed throughout the study using the following scales: Psoriasis Symptom Scale (PSS), pain Visual Analogue Scale (pain VAS), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and the Dermatology Life Quality Index (DLQI). Patients receiving open-label spesolimab at Week 1 were considered non-responders for analysis. At baseline, patients in the spesolimab arm had a high clinical burden and impaired QoL, as indicated by median PSS (11.0), pain VAS (79.8), FACIT-F (14.0) and DLQI (19.5) scores. Patients receiving spesolimab saw improvements in these scores from baseline to Week 12. Pain improved as early as Week 1 (-21.3), with further improvements at Week 4 (-53.4) that were sustained to Week 12 (-52.6). Other PROs improved as early as Week 1 and continued to improve through to Week 12. In this study, patients who received up to two doses of 900 mg spesolimab showed marked improvements from baseline in PROs and QoL. These improvements were sustained for up to 12 weeks.

P10-07[O04-09]

Induction of Type XVII collagen decreases cellular senescence in Human hTert/KER-CT keratinocytes

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Background: Aging is related to the accumulation of reactive oxygen species caused by an imbalance of redox homeostasis with the declined function of the mitochondrial antioxidative process with decreased removal of ROS, resulting in cellular damage including DNA, proteins, and lipids, leading to cellular senescence. The Type XVII collagen (COL 17A1) expressed in epithelial hemidesmosomes plays a crucial role in maintaining hair follicle stem cells. It has been reported that chronological aging in the skin is positively correlated with the accumulation of senescent cells and downregulation of COL17A1. Apocynin is an inhibitor of NADPH oxidase. It has been known to induce COL17A1 in epithelial cells. Here, we aimed to study whether induction of COL17A1 by apocynin can decrease H2O2-induced cell senescence or not. Methods: hTert/KER-CT keratinocytes were pretreated with apocynin (10 μM) for 24 hours and exposed to H2O2 (500 μM) for 2 hours. The expression of COL17A1 was measured by immunofluorescence, cellular senescence was measured by senescence associated-β-galactosidase (SA-β-gal) staining and WST-1 was used to measure cell viability. Results: Treatment with H2O2 significantly increased the percentage of SA-β-gal expression, altered cell morphology, decreased COL17A1 expression, and cell viability. Pre-treatment with apocynin restored COL17A1 expression, cell viability, and decreased SA-β-gal activity. Conclusions: Results demonstrate that apocynin significantly increased COL17A1 expression and decreased H2O2-induced cell senescence in hTert/KER-CT keratinocytes. We conclude that NADPH oxidase inhibition is useful in reducing cell senescence and the induction of COL17A1, which would result in epidermal anti-aging.

P10-08[O04-10]

An antimicrobial peptide derived from insulin-like growth factor-binding protein 5 alleviates imiquimod-induced psoriatic skin inflammation

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Antimicrobial peptide derived from insulin-like growth factor-binding protein 5 (AMP-IBP5) is expressed in keratinocytes and displays both antimicrobial and immunomodulatory properties. In contrast to many antimicrobial peptides (AMPs), insulin-like growth factor-binging protein 5, the parent protein of AMP-IBP5, is downregulated in psoriasis, an inflammatory skin disease characterized by epidermal hyperplasia, erythematous plaques, abnormal epidermal differentiation, and neutrophil infiltration into the epidermis. Although several AMPs are implicated in the pathogenesis of psoriasis, the role of AMP-IBP5 remains unknown. To investigate the effects of AMP-IBP5 in psoriasis, we established imiquimod-induced psoriasis-like mouse model. Following subcutaneous administration of AMP-IBP5 into the psoriatic mice, AMP-IBP5 reduced the presence of dry scales and plaques, epidermal thickness, hyperkeratosis, parakeratosis, hyperplasia of dermal vessels and neutrophil infiltration, compared with normal mice. Consistently, AMP-IBP5 diminished the expression of differentiation markers, including involucrin and loricrin, inflammatory cytokine TNF-A, AMPs (cathelicidin and S100A proteins), and angiogenesis factors such as vascular endothelial growth factor and platelet-derived growth factor from the psoriatic lesional skin. Interestingly, administration of receptor-associated protein, an antagonist of low-density lipoprotein receptor-related protein 1 (LRP1), exacerbated psoriasis and abolished AMP-IBP5-mediated improvement in psoriasis, suggesting that LRP1 is crucial in the pathogenesis of psoriasis and that AMP-IBP5 improves psoriasis via LRP1 pathway. Collectively, we provide evidence that AMP-IBP5 might be a novel potential therapeutic target for the treatment of psoriasis.

P10-09[O04-11]

Difamilast, a novel PDE4B inhibitor, topically improves chronic idiopathic dermatitis induced by persisting psychological stress in mice

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Psychological stress can trigger or exacerbate atopic dermatitis (AD) symptoms, and AD is associated with significant psychiatric morbidity. Difamilast is a PDE4B selective inhibitor for topical use synthesized by Otsuka Pharmaceutical Co., Ltd. The NDA for the treatment of AD has been submitted to PMDA in Japan. We have reported that difamilast shows therapeutic effects to an allergic chronic contact dermatitis model in mice (Presented at: American Academy of Dermatology Annual Meeting; March 1-5, 2019; Washington, DC). In this study, we investigated the effects of difamilast in a murine psychological stress (social isolation) induced idiopathic dermatitis model (Journal of Investigative Dermatology 2014 134, 1561). Mice were sensitized and repeatedly challenged by an epicutaneous application of hapten (1% TNCB) on the right ear three times per week for 16 weeks. The long-standing allergic contact dermatitis mice were individual housing (social isolation) for 6 months. The idiopathic dermatitis is caused by persistent self-scratching during social isolation. The therapeutic effects upon repeated topical application of the difamilast, tacrolimus and betamethasone valerate were examined for 6 weeks. Difamilast (1%, 3%) significantly improved skin symptoms as measured by the clinical skin score, and significantly decreased MIP-1α and MIP-2 content in the skin lesion. Tacrolimus (0.1%) slightly improved skin symptoms, but betamethasone valerate (0.1%) exacerbated the skin symptoms. Unfortunately difamilast shows no effect on the number of scratching in this model. In conclusion, difamilast ameliorates psychological stress-induced idiopathic dermatitis in mice. The mechanism of the interesting effect of difamilast is unknown well. We are planning further studies.

P10-10[O04-12]

Investigation of *in-vitro* antibacterial activity of selected plant extracts and its combination with a view of developing a face wash

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Though the wide variety of treatment regimens exist in the market for acne vulgaris none of those regimens are free of side effect and demand for natural formulations are continuously increasing. The present study was carried out to investigate in vitro antibacterial activity of *Azadirachta indica* (AI), *Curcuma longa* L (CL) and *Allium sativum* L (AS) singly and in combination with a view of developing a low cost, effective herbal face wash with minimum side effects. Aqueous extracts were prepared from fresh leaves of AI, dried rhizomes of CL, and dried cloves of AS. The extracts were used to determine minimum inhibitory concentration (MIC) against *Staphylococcus epidermidis* (ATCC 12228), *Staphylococcus aureus* (ACTT 49775), *Acinetobacter calcoaceticus* (ATCC 23055) and *Escherichia coli* (ATCC 25922), which are the causative microorganisms for acne vulgaris. Synergistic activity was investigated by combining the three extracts and two extracts in different concentrations. When considering the individual plant extracts; AI showed lowest MIC against all tested pathogens. Combination of three and two different extracts showed comparatively less MIC than single extracts. However, combination of AI and CL extracts showed the highest synergistic activity. Accordingly, it is confirmed that the synergistic antibacterial activity of selected plant extracts against tested pathogens. Due to high antibacterial activity, availability and affordability; formulation of a face wash for the treatment for acne is possible with combination of aqueous extracts of AL and CL with lowest concentrations.

P11-01[I-6]

Skin regulatory T cells producing proenkephalin expand upon ultraviolet B exposure without ST2-IL33 axis and promote keratinocyte outgrowth

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Foxp3+CD25+CD4+ regulatory T (Treg) cells play an important role in controlling immune responses, but recent studies have shown that Treg cells have distinct roles in tissue such as visceral adipose tissue, muscle, brain and skin. Here we report an unusual facet of skin Treg cells expanded by ultraviolet B (UVB) exposure. Gene expression analysis by RNA-sequencing showed that skin Treg cells expanded by UVB exposure expressed a unique set of genes compared to Treg cells in visceral adipose tissue, muscle, brain and naïve skin. Skin Treg cells expanded by UVB exposure highly expressed Penk, encoding proenkephalin, a precursor of endogenous opioid. Not only gene expression, but also protein expression analyzed by flow cytometry, revealed that skin Treg cells expanded by UVB exposure possessed high expressions of CD25 and proenkephalin. Notably, proenkephalin derived from Treg cells contributed to enhancing keratinocyte outgrowth in a skin explant model. We also showed that skin Treg cells expanded by UVB exposure play a key role in would healing in a mouse model in vivo. Surprisingly, UVB-induced expansion of skin Treg cells did not require the ST2-IL33 axis in contrast to the expansion of Treg cells in visceral adipose tissue, muscle and brain. Therefore, upon UVB irradiation, skin Treg cells expand through a unique mechanism and show a healing function by producing proenkephalin. Our data highlight a novel feature of skin Treg cells expanded by UVB exposure, which might contribute to an innovative therapy. (H.S. and M.O. contributed equally to this work.)

P11-02[C09-02]

Analysis of anti-inflammatory effects and the underlying mechanisms of CO2 on skin

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Carbon dioxide (CO2) is the predominant gas molecule emitted during aerobic respiration. In recent years, the effects of CO2 have attracted attention in the areas of beauty and health care. CO2 has been scientifically proven to improve wound healing and seasonal barrier dysfunction. Although inflammation is known to be strongly involved in these skin conditions, little is known about the relationship between CO2 and skin inflammation. Our study aimed to elucidate the effects of CO2 on skin inflammation and the mechanisms. We investigated inhibitory effects of CO2 on UVB-induced inflammation in human keratinocytes. In addition, using multiphoton laser microscopy, the pH change caused by CO2 was observed by loading a three-dimensional (3D)-cultured epidermis with a high-CO2 concentration formulation. Finally, the effect of CO2 on UVB-induced erythema was confirmed and we performed transcriptome analysis of mRNA in sebum of the face before and after CO2 administration in skin. CO2 suppressed the UVB-induced inflammatory responses via reduction in extracellular pH in keratinocytes. Moreover, we found that GPR65, one of the pH-sensitive receptors, may be involved in the suppression of the inflammatory response by CO2. In human skin, the high-CO2 concentration formulation suppressed UVB-induced erythema. In addition, transcriptome analysis of mRNA in sebum indicated that CO2 administration repressed the expression of inflammatory genes and increased the expression of genes involved in mitochondrial function. These results showed that CO2 may be a potential therapeutic agent in restoring skin immune homeostasis.

P11-03[C09-03]

Epigenetic regulation in melanocytes differentiated from induced pruripotent stem cells originated from xeroderma pigmentosum

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Xeroderma pigmentosum (XP) is a DNA repair disorder characterized by photosensitivity, resulting in occurrence of freckle-like pigmented maculae and depigmented maculae on sun-exposed areas. In Japan, patients with XP complementation group A (XP-A), who have the most severe cutaneous and neurological symptoms of the disease, is the most frequent. We have successfully generated melanocytes from induced pluripotent stem cells (iPSCs) derived from a patient with XP-A via melanocyte precursor cells (MPCs). We performed a comprehensive analysis of XP-A-iPSC-derived melanocytes (XP-A-iMCs) and healthy control iPSC-derived melanocytes (HC-iMCs) 12 hours after high-dose (150 J/m^2) UV-B irradiation to elucidate the molecular mechanism of the disease. The results showed that the major GO term category of genes specifically down-regulated in XP-A-iMCs was cell cycle regulation. Among these genes, we focused on Histone Deacetylase 4 (HDAC4) because HDAC4 has been implicated in autophagy and mitophagy, which partly explain the pathology observed in XP-A. HDAC4 reportedly plays an important role in histone modifications and is essential for cell proliferation, cell cycle progression, differentiation, and development. We showed that decreased HDAC4 affected cell proliferation and cell cycle regulation, and also reduce migration ability. These results suggested that this phenotype of XP-A-iMC may cause the characteristic hyperpigmentation and depigmentation of patients with XP-A.

P11-04[C09-04]

Identification and Quantification of Senescent Cells In UV-induced Skin Pathologies

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Skin ageing is an inevitable consequence of human life and accelerated by extrinsic factors including exposure to ultraviolet radiation, smoking and pollution. Senescence is an irreversible growth arrest and senescent cells accumulate in ageing tissues, including human skin, at sites of age-related pathologies and in pre-neoplastic lesions. Actinic keratosis (AK) is a common skin condition associated with prolonged sun exposure and age. If untreated, AK can progress towards squamous cell carcinoma (SCC). Despite its prevalence, current diagnostic tools are limited to visual and histological examination of lesions and frequently fail to distinguish benign AK from cancerous SCC lesions. To test if senescent cells accumulate in pre-neoplastic AK and malignant SCC lesions, we multiplexed novel senescence markers with cell-type specific markers to detect and quantify senescent cells within different compartments in normal skin, AK and SCC lesions, using an in-house software developed in collaboration with the A*STAR Microscopy Platform. Using lamin B1 and HMGB1 as senescence biomarkers, in conjunction with proliferation and celltype specific markers, we found that senescent cells accumulate within the epidermis of pre-neoplastic AK lesions as compared to non-affected isogenic control skin, while the dermis remained unaffected. In contrast, SCC lesions contained a heterogenous mixture of senescent and proliferative cells. The characterization of senescence biomarkers and tools developed in this study lay the foundation to investigate how different environmental factors may impact skin aging and regeneration, and shed light on the role of senescence in agerelated skin pathologies, including pigmentation disorders, skin wrinkling, skin cancer and chronic wounds.

P11-05[O09-01]

Deficiency of epidermal ferroportin enhances UV dermatitis in mice

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We reported that keratinocyte-specific ferroportin knockout (Fpn^{Epi-KO}) mice significantly increased epidermal iron content compared to control mice and became anemic on a low iron diet, suggesting that iron metabolism in the epidermis affects systemic iron homeostasis. In this study, since iron produces hydroxyl radical with strong cytotoxicity by Fenton reaction, we examined whether UV exposure that is known to increase ROS in the epidermis produces more ROS in Fpn^{Epi-KO} mice and consequently much stronger inflammation in the skin. We irradiated 1 kJ/m^2 and 5 kJ/m^2 of UVB on the shaved back skin of Fpn^{Epi-KO} and wild mice. Twenty-four hours after irradiation, Fpn^{Epi-KO} mice showed significantly increased thickness of dermis and subcutaneous tissue and inflammatory cell numbers in the skin. The mRNA expression of *Il6, Cxcl1, Cxcl2, Cxcl3,* and *Il1b* by 1kJ/m^2 irradiation and *Il6, Tnfa, Il1a, Cxcl1, Cxcl2* and *Cxcl3* by 5 kJ/m^2 irradiation, respectively, were significantly augmented in Fpn^{Epi-KO}mice after 24 hours. Immunohistochemical staining of 8-hydroxy-2-deoxyguanousine revealed greater oxidative stress in Fpn^{Epi-KO}mice. Finally, we confirmed that the skin inflammation in Fpn^{Epi-KO}mice was rescued by deferiprone treatment, an iron chelator. Taken together, we revealed exacerbation of UV dermatitis in Fpn^{Epi-KO} mice, suggesting that epidermal ferroportin plays an important role not only in systemic iron homeostasis, but also in reducing harmful ROS production in the epidermis.

P11-06[C09-05]

Rapid pustule fixation of palmoplantar pustulosis by UVA1-LED phototherapy

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Palmoplantar pustulosis (PPP) is a chronic inflammatory skin disease effectively treated by some phototherapy. UVA1 phototherapy has been widely applied to treat T cell-mediated skin disorders such as atopic dermatitis and cutaneous T-cell lymphoma, and connective tissue disorders. However, UVA1 availability is limited, perhaps due to the relatively high energy consumption and heat generation. Therefore, a light-emitting diode (LED) that emits UVA1 will be a more desirable and feasible light source, particularly if it has a high enough intensity level to treat skin diseases. Here, we successfully treated PPP using UVA1-LED phototherapy. A retrospective observational study was conducted from August 2019 to September 2020. In this study, a new treatment device (modified based on the TheraBeam R UV-N, USHIO INC, Tokyo, Japan) incorporating LEDs rather than methyl halide lamps were used. This device emits a peak wavelength of 365 nm UVA1 and utilizes a short wavelength cut-off filter to reduce excessive immediate tanning theoretically. As a result, 9 of 13 patients showed amelioration of PPP lesion, and PPSI was decreased significantly by UVA1-LED irradiations (N =13, one-way ANOVA $p<0.0001$, additional statistics by Wilcoxon matched-pairs signed-rank test; ** $p=0.0044$). The pustular 0-1 achievement was 46.2% (week1) and 76.9% (week5). In conclusion, the newly developed UVA1-LED device provided therapeutic effects for PPP. No safety concern was found. There are good features of UVA1-LED phototherapy including no requirement of 8-methoxypsoralen and unnecessary to avoid sunlight after the treatment.

P11-07[C09-06]

Switching the light source of phototherapy from a lamp to a deep ultraviolet light-emitting diodes

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The luminous efficiency of deep UV light-emitting diodes (DUV-LEDs) are now remarkably improved and expected to be applied to phototherapy. The full width at half maximum (FWHM) of DUV-LEDs differs from that of traditional light sources such as the narrowband UVB and excimer lamps. Because the absorption coefficient of DNA greatly changes at wavelengths around 300 nm, slight differences in the spectral distribution may cause large differences in the clinical effect. Therefore, we studied the optimum wavelength characteristics when using DUV-LEDs for phototherapy. Jurkat cells were used to investigate apoptosis and DNA damage as an in vitro model of T cell-mediated disease. The cells were irradiated with UVB light ranging from 280 nm to 320 nm in 5-nm steps and apoptosis and CPD was measured. For verification, we calculated the action coefficient of apoptosis and CPD from the dose-apoptosis curves and the dose-CPD curves. We defined the slope in the linear region as the action coefficient and normalized it by each maximum value. The wavelength at which the apoptosis action coefficient exceeded the CPD action coefficient was 285 nm to 297 nm and longer than 312 nm. The wavelength range from 285 nm to 297 nm is not suitable for clinical use because it has a high erythema action coefficient. On the other hand, the longer the wavelength, the longer the irradiation time needed for treatment. Therefore, we concluded that the optimum peak wavelength when using DUV-LEDs with an approximately 15-nm FWHM for ultraviolet phototherapy is 312 nm. If the spectrum can be narrowed and the short wavelength can be cut off, the peak wavelength may be able to slide to 308 nm, which is the same as the excimer light.

P11-08[O09-02]

Effect of M1 and M2 Macrophages on Production and Degradation of Extracellular Matrix in Dermal Fibroblasts

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The balance between the production and degradation of the dermal extracellular matrix (ECM) is altered during aging, specifically with solar elastosis, a skin aging phenomenon that occurs in sun-exposed areas. However, the detailed mechanisms and correlation with immune cells are still unknown. Among the immune cells in skin, macrophages are well elucidated in the area of wound healing, a phenomenon where the balance between the production and degradation of the ECM is a significant factor. There are two phenotypes: the M1 phenotype that causes inflammation and the M2 phenotype that is involved in the anti-inflammatory function. Last year, we reported that an imbalance between M1 and M2 may cause the senescence of human dermal fibroblasts.
Here, we analyzed the correlation between the M1/M2 balance and homeostasis of the ECM in the dermis. RNA sequencing (RNA-seq) and differential gene expression analysis were performed on human dermal fibroblasts cultured with M1 and M2 supernatants. Regarding the collagen-related differentially expressed genes between M1 and M2, the expression levels of *COL1A1*, *COL1A2*, *COL3A1*, *COL5A1*, *COL5A2* and *COL5A3* --which encode type I, III and V collagen respectively--were increased in dermal fibroblasts cultured with the M2 supernatant. Moreover, the expression levels of collagenase genes such as *MMP1*, *MMP2* and *MMP9* were increased in dermal fibroblasts cultured with the M1 supernatant. In addition, immunocytochemistry and ELISA were performed on type I collagen, which is a typical constituent of dermal collagen. M1 macrophages have the potential to decompose collagen via dermal fibroblasts, and M2 macrophages have the potential to maintain the production of collagen.

P11-09[O09-03]

Downregulation of IL-34 Associated with the Skewing of M1/M2 Balance of Macrophages Induces Senescence in Human dermal fibroblasts

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Macrophages are one of the immune cells that were found more than a century ago. They can be polarized into two subsets, pro-inflammatory phenotype (M1) and anti-inflammatory phenotype (M2). Recently, the association between a skewed M1/M2 balance and diseases, such as cancer, fibrosis and rheumatoid arthritis, has been reported. Last year, we reported that M1/M2 ratio is increased with aging in sun exposed area of skin and induces senescence of dermal fibroblasts. Here, to understand why the M1/M2 ratio is altered in sun-exposed aged skin, we analyzed the expression of factors which is known to be involved in macrophage differentiation. We found that IL-34 inhibited the effect of M1 macrophages on inducing senescence in dermal fibroblasts. In addition, the number of IL-34+ cells were decreased in aged epidermis and negatively correlated with the M1/M2 ratio. To test whether IL-34 can regulate macrophage phenotype, we stimulated macrophages with IL-34 and found that it could not induce CD206 mRNA expression that is known for M2 marker, however, it induced significantly higher IL-10 mRNA expression that is known for anti-inflammatory cytokine. This study suggests that IL-34 from epidermis may control the homeostasis of dermis via controlling the M1/M2 balance of macrophages.

P11-10[C09-07]

Bath-PUVA therapy targets keratinocytes to suppress the secretion of pathogenic chemokines

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Psoriasis is a chronic inflammatory proliferative skin disease involving various types of chemokines regulating immune cell migration, localization, and activation. Bath-psoralen plus ultraviolet A (PUVA) treatment is an established phototherapy for psoriasis and could induce remission, but its effects on chemokine levels remain unknown. The aim of this study was to identify the chemokines involved in the pathogenesis of psoriasis and to investigate the chemokine-based mechanisms of bath-PUVA therapy. The levels of 22 serum chemokines were measured by using a flow cytometry bead-based immunoassay in 20 psoriasis patients first treated with bath-PUVA therapy between 2007 and 2011 in our hospital. The median PASI score before bath-PUVA therapy was 23.8. All patients showed a decrease in the PASI score following treatment (median score 2.0). Before bath-PUVA therapy, the PASI scores correlated with the serum levels of CCL17 (r=0.581), CCL18 (r=0.462), CCL19 (r=0.477) and CXCL16 (r=0.524). After bath-PUVA, the serum levels of CCL17, CCL22, CXCL1 and CXCL9 were significantly decreased. And heatmap clustering and network analysis based on Spearman correlations among chemokines showed distinctive pattern changes in the chemokine signature between before and after the therapy. We identified 4 chemokines correlated with the disease severity of psoriasis. In addition, together with earlier reports, our data revealed the suppression of 4 keratinocyte-derived chemokines, which induce the migration of pathogenetic immune cells in psoriasis, is a key action of bath-PUVA therapy.

P11-11[O09-04]

Non-invasive assessment of diameter-dependent cutaneous vascular alterations with age using Optical Coherence Tomography Angiography

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Dermal blood vessels are composed of not only thick blood vessels that regulate blood flow and pressure, but also the micro-vessels which are responsible for the nutrition. As dermal vessel alterations affect homeostasis, a non-invasive assessment method is crucial to evaluate the skin's condition. Here, optical coherence tomography angiography (OCTA) is a non-invasive method that can visualize dermal blood vessel structure. Changes in dermal vessels due to aging can be detected by the OCTA (Hara et al, JDS, 2018). However, classifying the type of dermal blood vessels was previously limited.

In this study, we applied 3D analyses to the OCTA data to expand its functionality to identify blood vessel types based on their diameters. With this technique, we looked at diameter-dependent dermal vascular alterations with age. 150 Japanese women aged 20-79 years were enrolled and the dermal blood vessels in their cheeks were assessed using the OCTA.

As a result, we found that alterations with age were dependent on vascular diameter. The number of micro-vessels, defined at 20-39 microns, decreased with age, which was inversely true for thick vessels (160-179 micron diameter). The averaged diameters observed by the OCTA appear thicker than they are. While decreased micro-vessels may cause malnutrition, the increase of thick blood vessels potentially indicates the body compensating for the loss of micro-vessels resulting from the photoaging. Our results suggest that the degree of photoaging is uniquely assessed by analyzing the age-related alterations of micro-vessels using the OCTA.

In conclusion, we found diameter-dependent vascular alterations with age using the OCTA. In the future, the OCTA may be beneficial for assessing photo-aging, and validating medical applications.

P11-12[O03-01]

Excimer light downregulates interleukin-17 production and induces regulatory T cells in imiquimod-induced psoriasiform dermatitis

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Psoriasis is a chronic inflammatory skin disease, and impairs patients' quality of life tremendously. The efficacy of biologics and other research revealed that interleukin (IL)-17A plays a key role in the pathogenesis of psoriasis. Narrow band UVB (nbUVB) is broadly used; however, its detailed mechanism remains to be elucidated. Although an ex-vivo study utilizing human peripheral blood mononuclear cells revealed that nbUVB restored the function of regulatory T cells, it has yet to be studied what is occurring in the lesion skin of psoriasis irradiated with nbUVB in vivo. We investigated an effect of nbUVB on psoriasis in vivo utilizing an imiquimod-induced psoriasiform model. Psoriasiform dermatitis was induced by imiquimod (IMQ) application on shaved back skin of mice for 6 days. The mice were irradiated with 100 mJ/cm2 of 308nm excimer light (nbUVB) every other day. Irradiation with excimer light ameliorated dermatitis clinically and pathologically in imiquimod-induced psoriasiform dermatitis. Immunostaining revealed increased number of Foxp-3-positive cells and IL-10-positive cells infiltrating into the skin of the IMQ-applied mice irradiated with excimer light compared with those without irradiation. IL-17 mRNA expression levels were decreased and those of IL-10 were elevated in mice irradiated with excimer light in comparison with mice without irradiation. Furthermore, the percentage of Foxp3-positive cells in the inguinal lymph nodes was higher in mice irradiated with excimer light than in mice without phototherapy. Our study demonstrated that nbUVB not only downregulated IL-17 production but also induced regulatory T cells in vivo.

P11-13[O03-02]

Characterization of the DNA damage response in human skin cell types

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Skin aging and the development of age-related skin diseases are accelerated by sun exposure and intricately linked to the accumulation of DNA damage. Human skin is comprised of at least 20 different cell types and little is known how these various cell types respond to extrinsic stressors such as UV-irradiation and other genotoxic stressors. Understanding how the various resident skin cell types respond to different genotoxic stressors will provide fundamental insight into the development of age-related skin conditions, and is essential for the advancement of better anti-aging interventions. In an attempt to provide answers to these important questions, we studied the temporal dynamics of the DNA damage response factors p53-binding protein-1 (53BP-1) and phosphorylated H2A-X (gamma-H2A-X) in human dermal fibroblasts and keratinocytes in 2D and 3D organotypic cultures upon UV-irradiation, using immunofluorescence microscopy and live cell imaging. Concomitant with the recruitment of DNA repair factors, we also monitored the accumulation and clearance of UV-induced CPD lesions over time. Surprisingly, we find that different cell types and different cell states exhibit vastly differing responses to genotoxic stress. Going forward, our goal is to elucidate the fundamental mechanisms underlying these differences. Collectively, these findings will provide novel insight into how different human skin cell types respond to genotoxic stress, and may have implications for the development of skin aging phenotypes and how they are linked to inflammaging and diseases, including cancer.

P11-14[O03-03]

A role of elastogenic factors in the pathogenesis of Solar Elastosis

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Solar elastosis is the accumulation of disorganized and non-functional elastotic material in photo-aged skin. Solar elastosis occurs through a cycle of elastic fiber degradation followed by extracellular matrix production and reassembly into an organization that differs from the original structure. To clarify the pathomechanism underlying solar elastosis, we examined the expression of elastogenic factors by immunofluorescence using eight samples of skin tissue with solar elastosis. Sun-exposed aged skin without solar elastosis (n=7), sun-protected aged skin (n=11) and young skin (n=5) were used as controls. In solar elastotic skin, intense staining of elastin was observed in a thick structure, whereas elastin deposition was decreased in aged skin samples without solar elastosis. In addition, intense staining of fibrillin-1, LTBP-2, and fibulin-4 was colocalized with a thick dermal structure that was positive for elastin in solar elastotic skin. The expression of these proteins was decreased in aged skin samples without solar elastosis. Notably, the LTBP-4 expression was largely decreased in both solar elastotic skin and control aged skin samples. Five of the eight solar elastotic skin samples showed intense fibulin-5 signals, while the rest of the samples showed decreased fibulin-5 staining, although all samples of aged skin tissue without solar elastosis showed a decreased expression of fibulin-5. Accordingly, we hypothesized that the increased expression of fibrillin-1, LTBP-2, and fibulin-4 in combination with the decreased expression of LTBP-4 might be associated with the development of solar elastosis.

P11-15[O03-04]

Photodynamic therapy using portable devices

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We have been studying photodynamic therapy (PDT) using 5-aminolevulinic acid (ALA-PDT) as a photosensitive substance as a novel treatment for bacterial skin ulcers. We have found that ALA-PDT is effective in the treatment of bacterial-infected skin ulcers, and we believe that it is a promising new treatment method. Conventional PDT requires hospitalization or outpatient treatment, but in view of the recent coronary disasters and the aging of society, it is necessary to enable easy treatment at home, and we have moved to the development of ALA-PDT using a portable device. We are planning to use a portable device called iOLED™, which is powered by a lightweight battery. The advantage of iOLED™ is that it is safe even in a wet environment and fits the human body. The iOLED™ has an irradiation wavelength of 545 nm and a low luminance. Since the treatment was to be performed at home, we thought that a once-daily treatment like gauze replacement would be appropriate, and the irradiation time was set at 24 hours. Under these conditions, ALA-PDT using iOLED™ was performed in vitro, and a significant bactericidal effect was observed. We plan to conduct in vivo experiments using this new device in the future. iOLED is a trademark of NIPPON SHOKUBAI CO.,LTD.

P11-16[O03-05]

Usefulness of UVA lamps for the diagnosis of green nail syndrome with or without onychomycosis

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Green nail syndrome (GNS) is *Pseudomonas aeruginosa* infection of the nails and is sometimes referred to as Goldman-Fox syndrome. Previous studies reported that the association of fungal co-infection with GNS is over 60%. In this study, we demonstrated the usefulness of UVA lamps for the diagnosis of GNS with or without onychomycosis. We presented UVA lamp examination images of two cases of GNS with onychomycosis and one case without onychomycosis. Under UVA light, the nail plate of GNS with onychomycosis exhibited pastel yellow fluorescence against a green background. Although this study was limited by the small number of cases and fungal viability, it revealed that UVA lamps are useful for the diagnosis of GNS with or without onychomycosis.

P12-01[II-4]

A mechanism of cooling hot tumors: lactate and its induced EGR1 are novel key factors that turn hot tumors into cold tumors

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Since the demonstrated clinical success of immune checkpoint inhibitors (ICIs), one of the most active research focuses today is augmenting the responses to ICIs by targeting the tumor microenvironment. Tumors with an inflamed tumor microenvironment are considered “hot tumors” and show good responses to ICIs. Therefore, turning non-inflamed (cold) tumors into inflamed (hot) tumors is important for maximizing the effect of ICIs against malignancies. We showed that lactate, a product of the Warburg effect, inhibited the efficacy of ICIs and suppressed IL-12 p40 expression in dendritic cells (DCs) through reducing NF-κB p65, p50 and c-Rel DNA-binding activity to the IL-12 p40 promoter. Additionally, lactate promoted the expression of early growth response protein 1 (EGR 1), whose expression was significantly increased in human invasive melanoma compared with non-invasive melanoma. Additionally, the expression levels of EGR1 were correlated with tumor thickness and 5-S-CD. Although there were no significant differences in the expression levels of IL-12 p40 between *Egr1*$^{-/-}$ and WT DCs, ChIP-Seq analysis showed a region that suggested the interaction of EGR1 in the CD80 promoter. We also found that EGR1 interacts with serum response factor (SRF) and represses the expression of CD80 in DCs. Taken together, these results suggested that the expression of IL-12 p40 can be suppressed by lactate but this is independent of EGR1, while the expression of CD80 may be dependent on both lactate and EGR1, which is induced by lactate. In conclusion, our results suggest that lactate and its induced EGR 1 may be novel key factors that determine the inflamed or non-inflamed tumor status and may be new targets for stimulating antitumor immunity in treatment with ICIs.

P12-02[C05-01]

TIGIT/CD155 axis mediates resistance to immunotherapy in cancer patients with the inflamed tumor microenvironment

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Melanoma patients gain clinical benefits from treatment with immune checkpoint inhibitors (ICIs). Especially, patients with inflamed tumor microenvironment (TME) tend to respond to ICIs. However, some patients fail to respond to initial treatment (initial resistance) and the others acquire resistance after initial response (acquired resistance), despite inflamed TME. In this study, we analyzed mechanisms of acquired resistance to ICIs in melanoma patients, using clinical samples. We established four pairs of autologous tumor cell lines and tumor-infiltrating lymphocytes (TILs) from melanoma patients treated with ICIs. Two patients were durable-responders, and the others acquired resistance after initial response. Unexpectedly, in one of the patients with acquired resistance, highly inflamed TME and extremely high tumor mutation burden were observed. The tumor cell line and paired TILs derived from this patient showed high CD155, TIGIT ligand, and TIGIT expression, respectively. In the co-culture assay of these cells, TIGIT blockade or CD155-deletion activated TILs. Moreover, CD155 expression on the tumor cell line derived from a durable responder increased after co-culturing with autologous TILs, and which suppressed activation of TIGIT+ T-cell in the TILs. Consistently, TIGIT blockade or CD 155-deletion overcame resistance to ICIs in vivo mouse models. Finally, we confirmed that CD 155 was upregulated in the clinical samples with ICI resistance despite inflamed TME. These findings indicate that the TIGIT/CD155 axis mediates resistance to ICIs in melanoma patients with inflamed TME, promoting the development of TIGIT blockade therapies in such patients.

P12-03[C05-02]

IPS cell-derived myeloid cells expressing OX40 ligand amplify tumor-infiltrating T cells in advanced melanoma

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Immune checkpoint inhibitors improved the survival rate of patients with unresectable melanoma. However, some patients do not respond, and variable immune-related adverse events have been reported. Therefore, more effective and antigen-specific immune therapies are urgently needed. We previously reported the efficacy of an immune cell therapy with immortalized myeloid cells derived from induced pluripotent stem cells (iPS-ML). In this study, we generated OX40L-overexpressing iPS-ML (iPS-ML-OX40L) and investigated their characteristics and in vivo efficacy against mouse melanoma. We found that iPS-ML-OX40L suppressed the progression of B16-BL6 melanoma, and prolonged survival of mice with ovalbumin (OVA)-expressing B16 melanoma (MO4). The number of antigen-specific CD8+ T cells was higher in spleen cells treated with OVA-peptide-pulsed iPS-ML-OX40L than in those without OX40L. The OVA-peptide-pulsed iPS-ML-OX40L significantly increased the number of tumor-infiltrating T lymphocytes (TILs) in MO4 tumor. Flow-cytometry showed decreased regulatory T cells but increased effector and effector memory T cells among the TILs. Collectively, these results indicate that iPS-ML-OX40L therapy might be a new method for antigen-specific cancer immunotherapy.

P12-04[C05-03]

Impact of a *SLC24A5* novel mutation identified in the first Japanese patient with oculocutaneous albinism 6 on retinal pigment epithelium

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Oculocutaneous albinism (OCA) 6 is a non-syndromic type of OCA. Typical OCA6 patients have severe eye symptoms such as nystagmus and amblyopia, but the pigment in their skin and hair are relatively retained. The causative gene is *SLC24A5*, which encodes NCKX5, a K+-dependent Na+/Ca2+ exchanger. The role of NCKX5 has been reported in the maturation of melanosomes, but its function is still unclear. In this study, we experienced the first case of a Japanese patient with OCA6. The patient revealed light skin, brown hair, hazel irises, obvious nystagmus and amblyopia. Genetic analysis revealed compound heterozygous variants in *SLC24A5*, c.590 +1dupG and c.598G>A (p.G200R). To clarify the functional significance of the missense variant, we generated a knock-in mouse model (KI) carrying the mouse homolog of the p.G200R variant and a knock-out mouse (KO) using CRISPR/Cas9 system. Chemical analysis showed decreased amount of eumelanin in hair and skin of the KI mice as well as KO mice, while benzothiazine units in pheomelanin was significantly increased in their hair which was consistent with data from the patient. And notably, histopathologic study on the eyes revealed significant pigment loss in retinal pigment epithelium (RPE) rather than pigment in choroid. Furthermore, the expression of Nckx5 in RPE was decreased, whereas that in choroid was maintained in the KI mice. Also, the expressions of Pmel, a marker of immature melanosomes, in both RPE and choroid were increased in the KI mice. Together, the p.G200R variant in *Slc24a5* caused severe pigment loss in the RPE rather than other pigmented area, which could explain the dissociation of the phenotypic severity between eye and skin/hair in OCA6.

P12-05[C05-04]

Molecular and functional characterization of melanocyte subpopulations in the human hairy skin epidermis based on single-cell RNA sequencing

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We genetically, phenotypically and functionally studied heterogeneity in primary epidermal melanocytes which were freshly purified from human hairy skin. At first multiple novel melanocyte identities were molecularly determined by single cell RNA sequencing. One identity which was represented by upregulation of ribosome biogenesis and the expression of Neurotrophic receptor tyrosine kinase 2 (NTRK2) showed progenitor-like molecular characteristics and distinct differentiation trajectory in RNA velocity and pseudotime analysis. The differentially expressed gene profile and anatomical localization of the melanocytes with the identity were corresponding to melanoblasts. Melanocytes with the identity dominated and showed increased survival, clonogenicity and resistance to UVB-stress in mono-culture without feeder cells as well as in ex vivo organ skin. Inhibition of the identity by inhibiting ribosome biogenesis with CX5461 or NTRK2 signaling with Cyclotraxin-B resulted in suppression of the subpopulation. These results indicate a novel molecular identity of human melanoblasts and their direct regulatory mechanism by UVB.

P12-06[C05-05]

Melanocyte stem cell dynamics underlie de novo melanomagenesis

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The origins of different melanomas have been debated for a half century. To study the impact of cellular origin in melanoma development on the non-haired volar skin, we developed fate tracing technologies of melanocyte stem cells (McSCs) in sweat glands and disease modeling technologies in mice and compared the cellular dynamics with human disease. Here we report that McSCs in sweat glands self-renew to expand their migratory progeny in response to genomic stress and trauma to generate melanomas that mimic human acral melanoma in mice. The analysis of melanocytic lesions on human volar skin revealed that genetically unstable McSCs expand in sweat glands and in the surrounding epidermis in all melanomas examined. The detection of such cell spreading dynamics in human skin provides an innovative method for an early diagnosis of acral melanomas.

P12-07[C05-06]

Liquid biopsy-based analysis by CAPP-Seq and ddPCR in patients with melanoma

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The development of BRAF/MEK inhibitors in patients with metastatic melanoma harboring BRAF mutations has garnered attention for liquid biopsy to detect BRAF mutations in cell-free DNA (cfDNA) using droplet digital PCR (ddPCR) or next-generation sequencing methods. In this study, we investigated gene mutations in tumor DNA and cfDNA collected from 43 melanoma patients and evaluate their potential as biomarkers. ddPCR and CAncer Personalized Profiling by deep Sequencing (CAPP-Seq) techniques were performed to detect gene mutations in plasma cfDNA obtained from patients with metastatic melanoma. Gene variants, including BRAF, NRAS, TP53, GNAS, and MET, were detectable in the plasma cfDNA, and the results were partially consistent with the results of those identified in the tissues. Among the variants examined, copy numbers of MET mutations were consistent with the disease status in a melanoma patient treated with a BRAF/MEK inhibitor. In conclusion, liquid biopsy using CAPP-Seq and ddPCR has the potential to detect tumor presence and mutations, especially when tissue biopsies are unavailable. MET mutations in cfDNA may be a potential biomarker in patients with metastatic melanoma.

P12-08[O11-09]

NUMB inhibits melanoma migration, invasion, and metastasis

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NUMB is a tumor suppressor in various types of cancers. However, the role of NUMB in melanoma remains unclear. We investigated the role and regulation of NUMB in melanoma. Our results showed that NUMB suppressed invasion and metastasis in melanoma. Namely, NUMB-depleted melanoma cells significantly increased the invasion activity in a 3D collagen matrix. Moreover, the number of metastatic lung nodules formed by NUMB-depleted melanoma cells in mice were more than those formed by control cells. Consistently, high NUMB expression clinically correlates with the improved survival of patients with melanoma. Importantly, GSK-3 inhibition increased NUMB expression in melanoma cells. Furthermore, a GSK-3 inhibitor reduced the invasion of melanoma cells in a NUMB-dependent manner. These results suggest that target-specific inhibitors that can upregulate NUMB such as GSK-3 inhibitor may exert therapeutic effects for melanoma.

P12-09[O11-10]

Nucleosome assembly protein 1-like 4, a new therapeutic target for melanoma

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Melanoma is one of the deadliest skin cancers. The treatment of advanced melanoma has been dramatically improved by immune checkpoint inhibitors and targeted therapies. However, many patients still do not respond to these therapies. A previous study showed that the nucleosome assembly protein 1-like 4 (NAP1L4) is one of the molecules that control neural stem cells. To our knowledge, no study has examined the role of NAP1L4 in melanoma so far. Thus, we investigated whether NAP1L4 could be a potential therapeutic target for melanoma. NAP1L4 was overexpressed in melanoma tissues compared to the nevus tissue. NAP1L4 knockdown reduced melanoma cell migration and invasion. NAP1L4 knockdown upregulated p21 and downregulated Slug expression in melanoma cells. NAP1L4 knockdown decreased the active levels of MMP-2 in the supernatant from melanoma cells. Although NAP1 L4 knockdown inhibited apoptosis in camptothecin-induced DNA damage, it induced cell cycle arrest at the G1/S phase and inhibited cell proliferation. Therefore, NAP1L4 may play a role in cell migration and invasion in melanoma cells.

P12-10[O11-11]

Investigation the mechanism of novel lncRNAs, LncRNA00094, involved in metformin-inducing inhibition of melanoma cells

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Background and Objectives: Metformin has been known as potential therapy for several cancers. The mechanism of the regulation of lncRNAs on metformin-induced suppression on melanoma cells growth needs more investigation. Methods and Results: RNA expression profiles of melanoma cell lines (A2058 and A375) treated with/without 5 mM metformin were examined by next-generation sequencing approach (NGS). The NGS data revealed that 416 lncRNAs were significantly differentially expressed in melanoma cell after metformin treatment. LINC 00094 was among the top 10 downregulated LncRNAs filtered in terms of fold change>1.5 in NGS and TCGA database. In TCGA database, 468 melanoma patients showed the overall survival rate of the group with higher expression level (>4.43) of LINC00094 was significantly lower than the group with lower expression (AHR=1.38, p=0.04) using Cox's regression, and the cut-point (4.43) was determined by ROC method. The expression levels of LINC00094 in A2058 with 2-day 10mM metformin treatment were decreased significantly than those with PBS. In biological function assays, LINC00094-knockdown melanoma cells showed significantly decreased cell proliferation, colony formation, migration, and invasion ability. By using image-flow cytometric analysis, LINC 00094 knockdown significantly induce increasing numbers of sub-G1 cells and apoptotic cells. The expression levels of cell cycle-related proteins were examined by Western blot assay. LINC00094 knockdown melanoma cells revealed lower expression level of CCND1, CDK4, E2F1, CCNA1 and CCNB1, and increased P27. It means LINC00094 knockdown impair cell cycle progression by regulating cell cycle-related genes. Conclusion: LINC00094 play an important role on metformin-suppressed melanoma cell growth and motility.

P12-11[O11-12]

Increased expression of SPARC and TIMP3 in epidermotropic melanoma metastasis

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Primary cutaneous melanoma generally occurs in the epidermis, followed by invasion to the dermis. Opposingly, invasive melanoma cells infrequently migrate to intraepidermal area and form epidermotropic melanoma metastasis (EMM). In this study, we focused on this unique metastatic manner. To identify the key molecules which affect EMM, gene expression in EMM was compared with that in common skin metastasis (CSM). PCR analysis was performed for gene affecting extracellular matrix, cell-adhesion and tumor metastasis on three EMM and three CSM as an initial screening. For molecules showing different expression in the EMM, the expression levels were further verified using real-time qPCR and immunohistochemistry. Five molecules showed a difference in expression by the initial screening. Among them, SPARC was preferentially expressed in EMM (p=0.01) by real-time qPCR. Another candidate molecule, TIMP3, was even not statistically significant (p=0.07) but showed the tendency of higher expression. These results correlated negatively to expression of N-cadherin and β-catenin. The upregulation of SPARC and TIMP3 may disrupt the continuity of canonical Wnt pathway, which regulates adhesion activity of melanoma cells to localize in the dermis, and consequently provoke EMM. Our study highlights the potential role of SPARC and TIMP3 as key molecules in EMM, and analysis of EMM may contribute for understanding melanoma invasion between the epidermis and the dermis.

P12-12[O03-06]

Attenuation of melanocyte reoccupation in long-lasting rhododendrol-induced guinea pig model of vitiligo

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Rhododendrol (RD) is a phenolic compound first developed as a skin lightning material showing tyrosinase-dependent melanocyte toxicity and occasionally induces a vitiligo-like skin depigmentation. While the majority of patients showed improvement after discontinuing the use of RD-containing cosmetics, some patients did not show spontaneous recovery. It is important to study this refractory RD-induced leukoderma in animal models to elucidate its pathogenesis and pathophysiology and establish evidence-based treatments. Several animal models of RD-induced leukoderma showed a rapid recovery of skin lesions after discontinuing RD application. This study aimed to develop an animal model with RD-induced leukoderma without spontaneous recovery for a long time. In black guinea pig (JY-4) possessing epidermal melanocytes in the epidermal basal layer, 30% RD was topically applied to the back skin thrice per day on weekdays for 98 days. On day 14, RD induced obvious skin depigmentation and decreased the epidermal melanin and TRP1+ melanocytes in the basal layer. The L* value of RD-applied skin gradually increased and reached a plateau on days 28-98. After discontinuing RD application, the depigmented skin gradually repigmented. However, some of the RD-applied skin remained depigmented for over 140 days. This long-lasting depigmented lesion had no melanin and TRP1+ melanocytes in the basal layer, whereas repigmented lesions had both. Moreover, the long-lasting depigmented lesion had melanocytes in the hair follicle. Hence, we hypothesized that melanocyte migration to the epidermis was inhibited in this lesion. This model can provide new insights into the pathogenesis of refractory RD-induced leukoderma and vitiligo.

P12-13[O03-07]

Methyl-CpG binding domain protein 3 is a new diagnostic marker and potential therapeutic target of melanoma

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Methyl-CpG binding domain protein 3 (MBD3) belongs to the methyl-CpG binding protein family. MBD3 facilitates the initiation of neural stem cell reprogramming. Melanoma originates in melanocytes derived from neural crest stem cells; therefore, we investigated the role of MBD3 in melanoma. MBD3 was overexpressed in melanoma compared with pigmented nevi. MBD3 knockdown had no effect on the proliferation of melanoma cells (A375 and A2058 cells). Contrarily, it significantly reduced the migration and invasion of A375 cells, but had no significant effect on A2058 cells. Furthermore, MBD3 knockdown reduced N-cadherin protein levels and matrix metalloproteinase-2 (MMP-2) activity in A375 cells, but had no significant effect on A2058 cells. Based on these results, the MBD3 expression level may be a useful biomarker for the diagnosis of melanoma. Thus, MBD3 has potential as a novel therapeutic target for some melanoma patients.

P12-14[O03-08]

NUAK2 is an important factor in acral melanomas development and progression

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The AMPK-related kinase NUAK2 plays a critical role in melanoma development and progression. We previously showed that NUAK2 is a gene that has a prognostic significance in acral melanomas by verifying a public array comparative genomic hybridization (CGH) database and immunohistochemistry of 56 primary acral melanomas (PNAS, 2011) and that pharmacologic inhibition of CDK2 is sufficient to suppress the growth of NUAK2 amplified and PTEN-deficient melanoma cells (Cancer Res, 2015). In order to validate the previous survival data with an increased number of cases, we performed immunohistochemical analyses using specimens of 111 acral melanomas. In addition, we made the new mouse monoclonal antibody against NUAK2, that made us to observe the expression of NUAK2 by immunostaining more specifically than the rabbit polyclonal antibody that was used in our previous study. We performed immunohistochemical analyses by using formalin-fixed, paraffin-embedded tissues from 111 acral melanomas, 18 CSD melanomas, and 39 Non-CSD melanomas. By the percentage of the NUAK2 positive lesion of tumor, we classified all specimens into 4 classes. (0; 0-10% 1+; 10-25%, 2+;25-50%, 3+;50-100%)The Kaplan-Meier curves showed that both the relapse-free survival and the overall survival time of patients with acral melanomas expressing NUAK2 (scored; 3+) were significantly shorter than patients without NUAK2 expression (scored; 0). But in 18 CSD melanomas and 39 Non-CSD melanomas, such a trend wasn't observed. These data demonstrate that over-expression of NUAK2 has a significant impact on the survival of acral melanoma patients. We revalidated the previous data with an increased number of cases with acral melanomas by using the new mouse monoclonal antibody against NUAK2 and a different cohort.

P12-15[O03-09]

Protective efficacy of Sanqi-derived compound K on melanocytes against oxidative stress: in vitro and in vivo evaluation

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Sanqi, a traditional Chinese herb, is widely used for cardiovascular diseases, and its neuroprotective effects against oxidative stress were recently discovered. The purpose of this study was to investigate whether Sanqi-derived Compound K (Sanqi-CK), an active metabolite of Sanqi, could protect melanocytes from oxidative stress. Cultured human primary skin epidermal melanocytes (HEMn-MPs) were treated with hydrogen peroxide (H_2O_2) in the presence or absence of Sanqi-CK. Sanqi-CK exhibited protective effects againstH_2O_2-induced cell death by reducing oxidative stress. In addition, treatment with Sanqi-CK reversed the decreased glutathione reductase activity and decreased ratio of reduced glutathione (GSH)/oxidized glutathione (GSSG) seen in H_2O_2-treated melanocytes. Furthermore, topical application of Sanqi-CK alleviated leukoderma in guinea pigs, a disorder characterized by melanocyte cell death resulting from rhododendrol-induced oxidative stress. Taken together, these data suggest that Sanqi-CK protects melanocytes against oxidative stress, and its protective effects are associated with modulating the redox balance between GSH and GSSG and activating glutathione reductase. Thus, Sanqi-CK may be a good candidate for preventing melanocyte loss in oxidative stress-associated pigmentary disorders.

P12-16[O03-10]

Genipin contained in gardenia fruit enhanced melanogenesis

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Gardenia fruit is widely used in herbal medicine. An ingredient of gardenia fruit is attracting attention as a possible cause of mesenteric phlebosclerosis, which is characterized by fibrotic changes or calcification of the mesenteric vein and the bronze coloration of the colonic membrane. It is suggested that genipin, a metabolite of geniposide (the major ingredient of gardenia fruit) is involved in the bronze coloration. We previously described a patient who had consumed extract of gardenia fruit for seven years and developed skin pigmentation complicated by mesenteric phlebosclerosis (Mizawa M et al. JAMA Dermatol., 2020). Histological examinations of her pigmented skin showed hyperpigmentation of the basal layer and brown pigment granules in the macrophages and spindle cells around the vessels and interstitium in the reticular dermis. The brown pigment was revealed to be melanin on Fontana-Masson staining. The present study investigated whether or not genipin was involved in skin pigmentation through in vitro experiments. Time-of-flight secondary ion mass spectrometry of a skin section was used to detect genipin. This analysis revealed a peak with the molecular weight of genipin. In human melanocytes treated with genipin, an increased melanin production was shown by Fontana-Masson staining and the measurement of absorbance values at 405 nm for detecting intracellular melanin. The exact cause of the skin pigmentation is not known, but we hypothesized that the underlying cause of the hyperpigmentation was melanin deposition that was enhanced by genipin.

P12-17[C05-07]

Genome-scale DNA methylation analysis identifies regulatory region and repeat element alterations that modulate the genomic stability of melanocytic nevi

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Acquired melanocytic nevi grow and persist in a stable form into adulthood. Using genome-wide methylation profiling, we evaluated 32 histopathologically and dermoscopically characterized nevi, to identify key epigenetic regulatory mechanisms involved in nevogenesis. Benign (69% globular and 31% non-specific dermoscopic pattern) and dysplastic (95% reticular/nonspecific dermoscopic pattern) nevi were dissimilar with only two shared differentially methylated (DM) loci. Benign nevi demonstrated an increase in both genome-scale methylation and methylation of Alu/LINE-1 retrotransposable elements, a marker of genomic stability, as well as global methylation. In contrast, dysplastic nevi showed evidence for genomic instability via hypomethylation of Alu/LINE-1 (Alu; P=0.00019 and LINE-1; P=0.000035). Using dermoscopic classifications, reticular/non-specific patterned nevi had 59,572 CpG DM loci (Q<0.05), whereas globular nevi had no significant DM loci. In reticular/non-specific patterned nevi, the tumor suppressor *PTEN* had the greatest proportion of hypermethylated CpG loci in its promoter region compared to all other assayed gene promoters. The relative activity of reticular/non-specific nevi was evidenced by 50,720 hypomethylated loci being enriched for accessible chromatin, and 8,852 hypermethylated loci strongly enriched, for example, marks of active gene promoters, which suggests that gain of DNA methylation observed in these nevus types plays a role in gene regulation.

P13-01[III-3]

Development of molecular atlas of the human nail unit and hair follicle with spatially resolved transcriptomics

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The nail unit and hair follicle are both hard keratin-producing organs that share many biological features. A previously conducted single-cell analysis in polydactyly demonstrated that *MME* and *RSPO4* expression characterized a nail-specific mesenchymal population called onychofibroblasts. Onychofibroblasts and follicular dermal papilla cells showed high expression of *RSPO4*, supporting that onychodermis might be a mesenchymal tissue analogous to the dermal papilla. To build on this, here we used a spatial transcriptomics technology (GeoMx and Visium) and defined a cellular composition and spatially resolved expression profile of the human hair follicle and nail unit. Spatial transcriptomics technology showed a distinct expression profile of human dermal papilla and onychodermis compared with skin dermis. All these two specialized mesenchyme expressed *RSPO4* and were further characterized by the expression of *CRABP1*, *WIF1*, *MSX1*, *MSX2*, and *TRPS1*. Integration of single-cell RNA sequencing and spatially resolved expression data via computational deconvolution methods estimated epithelial and mesenchymal cell abundance in hair and nail-specific architecture and revealed transcriptional similarity between these major skin appendages. We also assessed the potential epithelial-mesenchymal interactions that might engage in the development of hair and nail. In addition, we treated cultured nail matrix keratinocytes (NMKs) with BMP-5, which are highly expressed by onychofibroblasts, and observed an increase of nail-enriched hard keratin expression in a dose-dependent manner, indicating how onychofibroblasts and NMKs coordinate nail plate production. Collectively, our data enable us to provide an important basis for understanding nail and hair biology.

P13-02[C03-02]

Antifibrotic effects and mechanisms of miR-196b-5p of mesenchymal stem cell-derived exosomes in a systemic sclerosis mouse model

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Background: Systemic sclerosis (SSc) is a connective tissue disorder characterized by the development of fibrosis in the skin and internal organs. Increasing evidence suggests that mesenchymal stem cells (MSCs) can be used to a treatment for fibrotic diseases. Recent studies have demonstrated that some of the biological effects of MSCs are due to the secretion of exosomes. However, the precise mechanisms underlying MSCs-derived exosomes in skin fibrosis are not well understood.
Objective: We aimed to elucidate the effect of MSCs-derived exosomes on skin fibrosis in SSc and the mechanism underlying their inhibitory action on fibrosis.
Methods: Exosome was collected from MSCs by ultracentrifugation method. We examined the suppressive effect of MSCs-derived exosome on skin fibrosis in bleomycin-induced SSc mouse model. Skin samples from the injected site were collected for further examination, and micro-RNA analysis of MSCs-derived exosome was performed.
Results: Injection of MSCs-derived exosomes significantly inhibited bleomycin-induced dermal fibrosis in mice. MSCs-derived exosomes significantly reduced the amount of collagen and the number of α-SMA$^+$ myofibroblasts and CD68$^+$ macrophages in lesional skin. They also reduced the expression of type I collagen and TGF-β receptor 1 in fibroblasts *in vitro*. Moreover, micro-RNA analysis revealed that several microRNAs in MSCs-derived exosomes have antifibrotic potential. We confirmed that overexpression of miR-196b-5p in fibroblasts significantly suppressed collagen type I alpha 2 expression.
Conclusion: Inhibition of collagen type I expression by miR-196b-5p in exosomes might be one of the mechanisms by which MSCs suppress skin fibrosis in an SSc mouse model.

P13-03[C03-03]

Obesity accelerates hair thinning by stem cell-centric converging mechanisms

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Obesity is a worldwide epidemic that predisposes individuals to many age associated diseases, but its exact effects on organ dysfunction are largely unknown. Hair follicles, mini epithelial organs that grow hair, are miniaturized by ageing to cause hair loss through the depletion of hair follicle stem cells (HFSCs). Here we report that obesity induced stress, such as that induced by a high-fat diet (HFD), targets HFSCs to accelerate hair thinning. Chronological gene expression analysis revealed that HFD feeding for four consecutive days in young mice directed activated HFSCs towards epidermal keratinization by generating excess reactive oxygen species, but did not reduce the pool of HFSCs. Integrative analysis using stem cell fate tracing, epigenetics and reverse genetics showed that further feeding with an HFD subsequently induced lipid droplets and NFkB activation within HFSCs via autocrine and paracrine IL1R signalling. These integrated factors converge on the profound inhibition of Sonic hedgehog (SHH) signal transduction in HFSCs, thereby further depleting lipid laden HFSCs through their aberrant differentiation and inducing hair follicle miniaturization and eventual hair loss. Conversely, transgenic or pharmacological activation of SHH rescued HFD induced hair loss. These data collectively demonstrate that stem cell inflammatory signals induced by obesity robustly represses organ regeneration signals to accelerate the miniaturization of mini organs, and suggests the importance of daily prevention of organ dysfunction.

P13-04[C03-04]

Therapeutic potential of adipose-derived stem cells for the treatment of recessive dystrophic epidermolysis bullosa

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[Background] Recessive dystrophic epidermolysis bullosa (RDEB) is a severe skin fragility disorder caused by mutations of COL7A1, which encodes type VII collagen (Col7). Adipose-derived stem cells (ADSCs) are of particular utility in regenerative medicine, as they are easily isolable and culturable, and retain the ability to differentiate into various cell types. It was recently reported that ADSCs co-cultured with fibroblasts are able to differentiate into keratinocyte-like cells. In addition, ADSCs promote wound healing in both animal models and clinical studies. [Objective] This present study sought to determine whether intradermally injected human ADSC-derived keratinocyte-like cells increase Col7 deposition and suppress blistering in an murine RDEB model. [Methods] Full-thickness skin harvested from newborn Col7-null mice was engrafted onto the dorsal aspect of immunocompromised nude mice. Keratinocyte-like cells culture-differentiated from human ADSCs were intradermally injected into the area surrounding skin grafts, and this procedure was repeated seven days later. After an additional seven-day interval, skin grafts were harvested for the assessment of human Col7 expression and histological findings. [Results] Intradermal injection of human ADSC-derived keratinocyte-like cells resulted in deposition of human Col7 at dermo-epidermal junction of transplanted mice skin grafts, assessed by immunohistochemistry and real-time PCR. Transmission electron microscopy showed generation of anchoring fibrils at dermal-epidermal junction. [Discussion] ADSC-derived keratinocyte-like cells have therapeutic potential on human subjects with RDEB.

P13-05[C03-05]

Perivascular adipose tissue in dermis induces infiltration of immune cells in the murine imiquimod (IMQ)-induced psoriasis model

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Over a decade, perivascular adipose tissue (PVAT) around large blood vessels such as the aorta, coronary arteries, and mesenteric arteries has emerged as an adipose organ with endocrine and paracrine functions. Significant phenotypical/developmental differences are known to exist between PVAT and other adipose tissues (such as subcutaneous adipose tissue) and among PVATs around different vessels. We previously discovered that PVAT exists around dermal blood vessels in mice; however, its physiological role is still unknown. In this study, we used high-fat diet (HFD)-induced obese mice to investigate PVAT functions in the skin. In these obese mice, adipocytes in PVAT in the ear had enlarged, and macrophages were pronouncedly distributed around PVAT compared to normal diet (ND)-fed control mice. We subjected these mice to the imiquimod (IMQ)-induced psoriasis model and found that pro-inflammatory cytokines such as IL-1beta and IL-17a increased in the skin in the HFD-fed mice compared to the ND-fed controls. We next used the transgenic mice expressing an inducible diphtheria toxin receptor (iDTR) in adipocytes (AdipoqCre;iDTR mice) to examine whether the absence of mature PVAT influences skin inflammation. We intradermally injected diphtheria toxin into the ear of AdipoqCre;iDTR mice to deplete PVAT. We then applied IMQ on the ear and found that the depletion of dermal PVAT decreased the numbers and activities of skin-infiltrating immune cells. These results demonstrate the essential role of dermal PVAT in regulating IMQ-induced psoriatic inflammation.

P13-06[C03-06]

Label-free quality control and identification of human keratinocyte stem cells by deep learning-based automated cell tracking

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The accuracy of disease diagnosis by artificial intelligence (AI) technology using medical images is similar to that by healthcare professionals, which has increased the reliability of AI-based diagnostic assessment. AI technology has also been applied to stem cell research and stem cell therapy. Stem cell-based products have clinical and industrial applications. Thus, there is a need to develop quality control methods to standardize stem cell manufacturing. Here, we report a deep learning-based automated cell tracking (DeepACT) technology for non-invasive quality control and identification of cultured human keratinocyte stem cells. The combination of deep learning-based cascading cell detection and Kalman filter algorithm-based tracking successfully tracked the individual cells within the densely packed human epidermal keratinocyte colonies in the phase-contrast images of the culture. DeepACT rapidly analyzed the motion of individual keratinocytes, which enabled the quantitative evaluation of keratinocyte dynamics in response to changes in culture conditions. Furthermore, DeepACT can distinguish keratinocyte stem cell colonies from non-stem cell-derived colonies by analyzing the spatial and velocity information of cells. This system can be widely applied to stem cell cultures used in regenerative medicine and provides a platform for developing reliable and non-invasive quality control technology.

P13-07[C03-07]

Ahed has crucial roles as a spliceosomal protein for cell proliferation of epidermal keratinocytes

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Ahed is a newly identified gene and having essential roles in hematopoiesis. Epidermis-specific Ahed deficient mice were clearly distinguishable from control littermates by growth retardation, skin thinning at postnatal day 2 (P2) and lethality around P3, likely due to inherent barrier impairment. Tamoxifen-inducible KO (IndEcKO) mice allowed us to explore the postnatal role of Ahed. The topically 4-OH tamoxifen (4OHT) treated skins showed atrophic epidermis and apoptotic cells were found in the epidermis and hair follicles. Primary culture epidermal keratinocytes from the IndEcKO mice showed significant suppression of colony formation by 4OHT treatment *in vitro*. Collectively, the data suggests crucial roles of Ahed in development and maintenance of epidermis, similar to those of hematopoietic cells. To investigate the molecular functions of Ahed, we sought Ahed biding proteins by coimmunoprecipitation - mass spectrometry and found a number of candidates including spliceosomal proteins. Among of them, several proteins were confirmed to generate protein complexes with Ahed by immunoprecipitation - immunoblotting. To find proteins that directly bind with Ahed, *in vitro* transcription/translation - immunoprecipitation - immunoblotting was performed. Next we assessed whether Ahed deficiency affected RNA splicing in the cells and found that Ahed KO keratinocytes harbored altered splicing variants of some genes. The present data suggests that Ahed has a critical role in regulating mRNA splicing of genes, which may be essential for organ development and maintenance, including the epidermis.

P13-08[O08-01]

Dynamic stem cell selection safeguards the genomic integrity of the epidermis

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Maintaining genomic integrity of stem cells is crucial for tissue homeostasis. Epidermal stem cells (EpiSCs), which continuously replenish the stratified layers of keratinocytes, suffer endogenous and exogenous genotoxic stress in daily life. While EpiSCs with severe genomic insults immediately die by apoptosis, some of sublethally damaged cells may go into cellular senescence or initiate cancer by accumulating further genetic and/or epigenetic alterations. However, the exact fates and dynamics of sublethally damaged cells have not been tested *in vivo* because of the lack of a direct lineage tracing technique for DNA-damaged cells. Here, we devised an *in vivo* fate tracing system for EpiSCs with DNA double-strand breaks (DSBs), the most cytotoxic form of DNA damage and demonstrate that almost all (95%) EpiSCs that have acquired DSB exit from the basal layer by the selective differentiation and delamination. Those EpiSCs with DSBs commit to differentiation in the basal layer through upregulation of Notch signaling and downregulation of ITGB1. Further, symmetric cell divisions of surrounding stem cells are concomitantly enhanced, indicating that the selective elimination of those cells from the niche is coupled with the augmented clonal expansion of intact stem cells. These data collectively demonstrate that the dynamic coupling of cell-autonomous and non-cell-autonomous mechanisms coordinately maintains the genomic quality of the epidermis.

P13-09[O08-02]

Impaired holocrine cell rupture of sebocytes in comedo: Revisiting the mechanism of comedo formation in the study with excised human skins

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Comedo, a clogged hair follicle, is a predisposing factor of acne vulgaris. Comedo formation has long been believed to result from obstruction of the follicular orifice by hyperkeratosis, followed by sebum coagulation with corneocytes in the follicle. However, since this process cannot sufficiently explain the formation of open comedo and microcomedo, where the follicular orifice is open, a detailed mechanism of comedo formation remains to be resolved. Western blot of keratotic plug protein from the human nose revealed that only sebaceous gland-specific keratin 7 was clearly detected with an intact molecular weight, but keratins specific to other components of pilosebaceous units, such as an inner root sheath, an outer root sheath and an epidermis, were not detected. Electron microscopy of a clogged follicle in the human breast skin showed that a number of sebocytes including aggregated lipid droplets accumulated in the sebaceous duct, and harbored several autophagosome-like double-membraned vesicles intracellularly. Immunostaining showed that abundant Lamp1, a lysosomal protein, and LC3, an autophagosomal protein, separately existed in sebocytes with shrunk nuclei in sebaceous ducts of clogged follicles. Explant culture of human abdominal skins without comedones stimulated with autophagy inhibitors, bafilomycin a1 or MHY-1485, and 3D confocal imaging of Nile red-stained pilosebaceous units revealed that the diameter of follicular lumen near the junction of sebaceous duct increased. These results suggest the defects in holocrine cell rupture of sebocytes in comedo where autophagy of sebocytes might be impaired. Our findings will provide an important framework to investigate the pathophysiology of acne vulgaris and develop a new strategy for its therapy and prevention.

P13-10[O08-03]

Immunological Properties of Atopic Dermatitis-Associated Alopecia Areata

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Regarding the cytokine balance, alopecia areata has been considered a type 1 inflammatory disease. On the other hand, AA often complicates atopic dermatitis (AD) and AD is regarded as type 2 inflam-matory disease. However, the immunological aspects of AA in relation to AD are still poorly un-derstood. Therefore, we aim to clarify the immunological properties of AD-associated AA. In this study, we performed comparative analysis of the expression of intracytoplasmic cytokines (IFN-γ, IL-4, and IL-13), chemokine receptors (CXCR3 and CCR4) in peripheral blood which were taken from healthy controls, non-atopic AA patients, AA patients with extrinsic AD, and AA patients with intrinsic AD by flowcytometric analysis. We also compared the scalp skin samples taken from AA patients with extrinsic AD before and after treatment with dupilumab. In non-atopic AA patients, the ratios of CD4+IFN-γ+ cells to CD4+IL-4+ cells and CD4+IFN-γ+ cells to CD4+IL-13+ cells were higher than those in AA patients with extrinsic AD. Meanwhile, the ratio of CD8+IFN-γ+ cells to CD8+IL-13+ cells was significantly higher in the non-atopic AA than in the healthy con-trols. In AA patients with extrinsic AD, the skin AA lesion showed dense infiltration of not only CXCR3+ cells but also CCR4+ cells around hair bulb before dupilumab treatment. However, after the treatment, the number of CXCR3+ cells had no remarkable change while the number of CCR4+ cells significantly decreased. Our study provides an important notion that type 2 immunity may participate in the de-velopment of AA in extrinsic AD patients. It may be considered that the immunological state of non-atopic AA is different from that of atopic AA.

P13-11[O08-04]

Time course changes in peripheral blood mononuclear cell subsets during intravenous corticosteroid pulse therapy for severe alopecia areata

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Intravenous corticosteroid pulse therapy (IVPT) has performed to threat rapidly progressive alopecia areata (RP-AA), however, the outcome can only become predictive after a couple of months. Accordingly, identification of early predictors of clinical responses are needed. In this study, time course changes in multiple peripheral blood mononuclear cell (PBMC) subsets were evaluated pre- and post-IVPT for RP-AA to identify those positively corelated with clinical outcomes. Samples collected from twelve-AA cases (responders; n=10, and non-responders; n=2) were subjected to antigen stimulation tests and flowcytometric analysis. In all AA cases, the frequencies of T cells and NK cells were not markedly affected by IVPT. Mean fluorescence intensity levels of IFN-γ production in hair follicle autoantigen (trichohyalin; TCHH) and PHA-P stimulated CD4+ and CD8+ T cells were similarly decreased post-IVPT both in responders and non-responders examined, however the ratio between TCHH- and PH-P reactive subsets was increased at the end of IVPT in a non-responder, while that remained unchanged in responders (n=4). Selective depletion of CD14dimCD16+ proinflammatory monocytes (pMOs) was occurred in all cases after IVPT, resulting in predominance of CD14+CD16- classical monocytes (cMOs). pMOs reappeared one month after IVPT and the recovery rates were not distinct between responders and non-responders. Interestingly, a significant increase in Pam3CSK4 dependent IL-10 producing cMO was noted just after IVPT. Further accumulation of the cases is necessary, however, this preliminary study implied the feasibility of early clinical outcome prediction by PBMC monitoring, represented by the aforementioned potentially pathogenic or immune suppressive subsets.

P13-12[O08-05]

Distinct types of stem cell divisions orchestrate organ regeneration and aging in hair follicles

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Hair follicles, mammalian mini-organs that grow hair, miniaturize during aging, leading to hair thinning and loss. Here we report that hair follicle stem cells (HFSCs) lose their regenerative capabilities during aging owing to the adoption of an atypical cell division program. Cell fate tracing and cell division axis analyses revealed that while HFSCs in young mice undergo typical symmetric and asymmetric cell divisions to regenerate hair follicles, upon aging or stress, they adopt an atypical "stress-responsive" type of asymmetric cell division. This type of division is accompanied by the destabilization of hemidesmosomal protein COL17A1 and cell-polarity-protein aPKCλ and generates aberrantly differentiating epidermal cells instead of regenerating the hair follicle niche. With the repetition of these atypical divisions, HFSCs detach from the basal membrane causing their exhaustion and organ aging. The experimentally-induced stabilization of COL17A1 rescued organ homeostasis through aPKCλ stabilization. These results demonstrate that distinct stem cell division programs may govern tissue and organ aging.

P13-13[O08-06]

Mu-opioid ligand endomorphin induces alloknesis at the periphery

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Mechanical alloknesis is itch hypersensitivity caused by normally innocuous mechanical stimuli. Although a well-known phenomenon, its mechanism has not been fully elucidated. We recently reported the involvement of CD26/dipeptidyl peptidase IV (DPPIV) enzyme in the regulation of psoriatic itch. This enzyme exerts biological activity by processing various substances including neuropeptides. However, the role of CD26/DPPIV in mechanical alloknesis remains unclear. In the present study, we applied innocuous mechanical stimuli using von Frey filaments to the rostral back of CD26KO or wild-type (WT) mice with the number of scratching responses taken as an alloknesis score. The score in CD26KO mice was significantly higher than in WT mice and significantly decreased by either intradermal administration of recombinant DPPIV or naloxone methiodide, a peripheral mu-opioid receptor (MOR) antagonist, whereas that of mutant DPPIV without enzyme activity had no affect. Consequently, we investigated the involvement of endomorphins (EMs; EM-1 and EM-2), which are endogenous ligands for MOR and substrates for the DPPIV enzyme. We observed that EMs were located in keratinocytes, fibroblasts, and peripheral neurons. Behavioral analysis revealed that EMs evoked mechanical alloknesis more than chemical itch, whereas beta-endorphin, another MOR ligand elicited chemical itch more potently than mechanical alloknesis. In addition, DPPIV-digested forms of EMs exerted no mechanical alloknesis. Taken together, our findings revealed EMs-MOR signaling plays a pivotal role in induction of mechanical alloknesis at the periphery under enzymatic control of CD26/DPPIV.

P13-14[O08-07]

Monocytic lineage cells distributed along sweat glands modulate sweat function

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Corticosteroids or immunosuppressants were reported to have a therapeutic effect on patients of hypohidrosis/anhidrosis. They were also known to increase sweating as side effects when administrated on patients of other diseases. The process of sweating involves command from the brain, transmission through the peripheral nerves, and secretion from the sweat glands in the skin. However, it is not clear how corticosteroids or immunosuppressants affect this mechanism. In this study, we report that monocytic lineage cells distributed throughout the sweat glands and can modulate the sweating. We found that monocytic lineage cells spread their processes along the sweat glands under the physiological conditions by using three-dimensional imaging with tissue clearing technique on human and mouse samples. Their processes were often located close to the axon fibers surrounding the glands. Pharmacological activation of the monocytic cells led to decrease of the sweating in mouse footpad. Moreover, immunohistochemical and gene expression analysis indicated the activation of monocytic cells in patients of acquired anhidrosis. These results suggested that monocytic lineage cells could modulate sweating by affecting the neighboring sweat glands and/or the nerves. Corticosteroids or immunosuppressants may increase sweating through the inhibition of the monocytic lineage cells near the sweat glands.

P13-15[O08-08]

The potential of hair-follicle-associated pluripotent (HAP) stem cells to treat Parkinson's disease

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Hair-follicle-associated pluripotent (HAP) stem cells, located in the bulge area of the hair follicle, have previously been shown to differentiate to neurons, glia, keratinocytes, smooth muscle cells, melanocytes and beating cardiac muscle cells in vitro. Subsequently, we demonstrated that HAP stem cells could effect nerve and spinal-cord regeneration in mouse models, differentiating to Schwann cells and neurons in this process. We have now demonstrated that mouse HAP stem cells cultured in neural-induction medium can extensively differentiate to dopaminergic neurons, which express tyrosine hydroxylase, dopamine-transporter, the nuclear receptor Nurr1 and secrete large amounts of dopamine. Furthermore, the gene expression levels of tyrosine hydroxylase and aromatic L-amino acid decarboxylase are increased by neural induction medium. HAP stem cells are the most accessible adult stem cells, and have many advantages over iPS or ES cells for regenerative medicine. HAP stem cells differentiate efficiently to dopaminergic neurons, without genetic manipulations or added growth factors, do not form tumors, and can be cryopreserved without loss of differentiation potential and are thus bankable for each person. Thus HAP stem cells have great potential in the future to improve the symptoms of Parkinson's disease in the clinic.

P13-16[O08-09]

The potential of hair-follicle-associated pluripotent (HAP) stem cells for heart regeneration

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Hair-follicle-associated pluripotent (HAP) stem cells are discovered by us, located above the bulge area of the hair follicle. HAP stem cells have been previously shown to differentiate into neurons, glia, keratinocytes, smooth muscle cells, dopamine-secreting neurons, and beating cardiac muscle cells. HAP stem cells can differentiate into beating cardiac muscle tissue sheets, isoproterenol induces HAP stem cells to differentiate into cardiac muscle cells in large numbers in culture. In the present study, we cultured HAP stem cells from rat vibrissa hair follicles which supplemented with the combination of isoproterenol, activin A, bone morphogenetic protein 4 (BMP4) and basic fibroblast growth factor (bFGF) and induced mature long-myocardial-fiber beating cardiomyocyte sheets. Embryonic stem cells (ESC) and induced pluripotent stem cells (iPSC) have not been shown to differentiated into mature long fiber cardiomyocytes despite great efforts. HAP stem cells thus have important advantages over ESC and iPSC for heart regeneration. In addition, unlike ESC and iPSC, HAP stem cells are readily and non-invasively accessible from everyone, do not form tumors, do not require genetic manipulation to differentiate, can be cryopreserved without loss of pluripotency, banked from each person, and have no ethical issues. HAP stem cells have great clinical potential for heart regeneration.

P13-17[O08-10]

Exploring the impact of ovariectomy on hair growth; Is ovariectomized mouse a model for investigating female pattern hair loss in human?

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Female pattern hair loss is a common hair disease in pre- and postmenopausal women, characterized by thinning of the hair to O-type, mainly at the crown. Although the mice model of this disease has been recently established, detailed investigations of this model mice have to be unveiled. In our research, 3 weeks old C57BL/6 female mice were divided into two groups, a group that underwent ovariectomy (OVX) and a control group that underwent sham surgery (Sham). Dorsal skin was collected at 7 weeks. In addition, 7-8 weeks old mice were also divided into two groups, and skins were collected at 12 and 24 weeks. OVX treatment at 3 weeks after birth had no significant impacts on the hair cycle or significant HF density change between Sham and OVX groups. However, OVX at 3 weeks decreased both the pore size of the HFs and the diameter of the hair shaft of telogen HFs. OVX at 7-8 weeks after birth also had no significant impacts on the hair cycle. However, the pore size of the HFs, the diameter of hair shaft, and HF density were significantly increased by OVX. Notably, OVX significantly increased the thickness of both dermal and subcutis. Here, we found that OVX had opposite impacts on HF structure depending on the period of OVX. Although whether OVX is an ideal mouse model for FPHL needs to be further elucidated, our additional unexpected skin thickness results may be also important for establishing a novel treatment for non-hair related diseases, e.g. obesity.

P14-01[III-2]

CCL5/CCR5 feedforward loop by FLI1 deficiency in microvascular endothelial cells contributes to SSc vasculopathy

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Systemic sclerosis (SSc) consists of three cardinal pathological features, including autoimmune inflammation, vasculopathy and tissue fibrosis. SSc vasculopathy is a critical pathological process bridging between autoimmunity and tissue fibrosis, but the detailed molecular mechanism of SSc vasculopathy remains elusive. Recently, CCL5 has caught much attention as a part of molecules driving angiogenesis. In this study, we focused on the potential role of CCL5 in the development of SSc vasculopathy by using human skin samples, animal models and cultured cells. CCL5 expression was evaluated by immunohistochemistry with the involved skin of SSc patients and bleomycin-treated mice and by quantitative RT-PCR and immunoblotting with FLI1-decificent cultured cells. Vascular permeability was assessed by Evans blue dye injection in bleomycin-treated mice transfected with *Ccl5* siRNA or control siRNA. CCL5 expression was increased in dermal small vessels of SSc-involved skin compared with those of healthy control skin. A similar expression profile of CCL5 was confirmed in the lesional skin of bleomycin-treated mice. *Ccl5* siRNA restored vascular hyperpermeability. *Fli1*$^{+/-}$ peritoneal macrophages expressed CCL5 significantly higher than wild-type counterparts in response to LPS stimulation. *FLI1* siRNA enhanced the expression of CCL5, CCR1, CCR3 and CCR5 in human dermal microvascular endothelial cells. Importantly, the CCL5/CCR5 axis-dependent protein kinase C-δ activation, which promotes FLI1 degradation, and FLI1 deficiency-dependent upregulation of CCL5 and CCR5 form a feedforward loop resulting in vascular destabilization. Altogether, these results indicate that FLI1 deficiency-dependent activation of endothelial CCL5/CCR5 axis may contribute to the development of SSc vasculopathy.

P14-02[C07-04]

Ninjurin-1 contributes to skin wound healing through the formation of functional blood vessels

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Mural cells, which wrap around endothelial cells (ECs) in microvessels, include vascular smooth muscle cells (VSMCs) of the arterioles/venules and pericytes (PCs) of the capillaries. PCs participate in angiogenesis, involving early endothelial sprouting and subsequent vascular maturation. Although there is no specific marker for PCs, NG2 is one of the common markers for PCs in various tissues including skin. Nerve injury-induced protein-1 (Ninjurin-1: Ninj1) was originally identified as a transmembrane homophilic adhesion molecule in Schwann cells and neurons induced in nerve injury. A recent study has shown that Ninj1 in PCs is involved in the maturation of vessels through PC-EC interaction during hindlimb ischemia. Although Ninj1 presumably contributes to the regeneration of various tissues, its role in skin injury remains unclear. We aimed to elucidate the role of Ninj1 in wound healing using an in vivo mouse wound model. First, to examine the Ninj1 expression, we performed immunofluorescence and showed that Ninj1 was expressed in VSMCs/PCs in microvessels of the skin. Quantitative PCR and Western blot analysis showed increased expression of Ninj1 in wound skin. Next, to investigate the function of Ninj1, we assessed wound healing in NG2-specific Ninj1 knockout (KO) mice. Ninj1 KO mice showed delayed wound healing and reduced PC coverage in new microvessels compared with control mice. To analyze the effect of reduced PC coverage in cutaneous angiogenesis, we administered FITC-Lectin to the tail vein of mice and visualized functional vessels with blood flow. Functional vessels were significantly reduced in Ninj1 KO mice. These findings indicate that Ninj1 in PCs is involved in angiogenesis during cutaneous wound healing through vascular maturation.

P14-03[C07-05]

Odorant-dependent Merkel cell chemosensation: implications for wound healing

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Merkel cells (MCs) are found in the skin and release neuromediators through secretory vesicles. Although MCs have been known so far exclusively for being transducers of mechanical pressure applied to the skin, recent observations suggest that their role may extend beyond pure mechanosensation. In the present study, we report that over 70% of epidermal K8+/K18+/K20+ MCs co-expressed OR2AT4, hinting that this olfactory receptor may have an important physiological role in these cells. To explore this, we exposed human skin from healthy subjects to the topical application of the specific OR2AT4 agonist Sandalore ex vivo. Sandalore did not affect K20+ cell numbers or proliferation nor apoptosis. Instead, Sandalore up-regulated the number of K20+ cells expressing Piccolo (presynaptic marker), suggesting increase in neurotransmitter release. In parallel, the intracellular content of nerve growth factor (NGF) in MCs was ablated after exposure to Sandalore, possible due to active release upon Sandalore-mediated cellular depolarization. Corroborating this hypothesis, live-cell imaging showed release of the fluorescent false neurotransmitter, FFN206, from pre-labelled MCs, 5-min after Sandalore treatment of epidermal sheets from healthy donors. Therefore, OR2AT4 activation appears to induce MC depolarization, promoting the secretion of vesicles containing neuromediators such as NGF. Because NGF is known to promote wound healing, our results suggest that MCs may support skin healing response previously observed after Sandalore application. In conclusion, we show that human MCs not only are mechanosensory cells, but also operate as important chemosensory cells in human skin that can identify selected odorants, whose stimulation may alter neuromediators secretion by MCs.

P14-04[C07-06]

Adipose derived stem cells inhibits fibrotic effect of keloid derived dermal fibroblasts

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Background: Keloid results from a dysregulated cutaneous healing response that produces excessive extracellular matrix deposition. Although local inflammation is thought to be involved in keloid development, precise mechanism underlying pathogenesis remains uncertain. In both animal models and clinical studies, mesenchymal stem cells (MSCs) promote wound healing. In addition, MSCs secrete immunomodulatory and anti-inflammatory factors. Among MSCs, adipose-derived stem cells (ADSCs) are the most promising sub-population for use in therapeutic applications, as large volumes of human adipose tissue are readily obtainable without significant donor site trauma. Objective: The present study sought to investigate the potential role of ADSCs in the pathogenesis of keloid formation, and to examine the effect of ADSCs on keloid formation and skin fibrosis. Methods: Keloid-derived dermal fibroblasts were co-cultured with ADSCs. After 48 hours, the cells were harvested and subjected to immunofluorescence, real-time PCR, collagen gel contraction assay, and western blotting. Results: Expressions of transforming growth factor-β, type I collagen, and smooth muscle protein 22-α were decreased in keloid-derived dermal fibroblasts co-cultured with ADSCs. Co-cultureing with ADSCs also inhibited contractile activity of keloid-derived dermal fibroblasts and α smooth muscle actin expression in keloid-derived dermal fibroblasts. Discussion: ADSCs antagonized fibrotic response in keloid-derived dermal fibroblasts. ADSCs may be therapeutically useful for keloid. Clarification of the molecular mechanism underlying the effect of ADSCs should be investigated for elucidation of the mechanism of keloid development.

P14-05[C07-07]

Skin-derived human β-defensin-3 promotes wound healing and angiogenesi

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Background: Wound healing is a dynamic and highly programmed process; its prolongation can lead to delayed wound healing or a non-healing chronic wound. In addition to its antimicrobial activity, human β-defensin-3 (hBD-3) induces activation of keratinocytes, mast cells, neutrophils and macrophages that are involved in wound healing. However, its effects on fibroblasts, which are the major cell type responsible for wound healing, remain unclear. Objectives: To investigate the effects of hBD-3 on fibroblast activation and wound healing. Methods: Full-thickness wounds were created on the back of mice, and hBD-3 was topically applied every 2 days. mRNA expression of angiogenic factors was examined by RT-PCR and the presence of neutrophils, macrophages and fibroblasts in wound tissues was evaluated using immunohistochemistry. Angiogenic factor production by human dermal fibroblasts was examined by ELISA, while activation of FGFR, JAK and STAT pathways was evaluated by Western blot. Cell proliferation was assessed by CCK-8 assay, while the migration was evaluated by chemotaxis chamber and wound scratching assays. Results: Following hBD-3 treatment, the mouse wounds healed faster, showed accumulation of neutrophils and macrophages in the early stage of wound healing, and displayed an increased number of fibroblasts and newly formed vessels compared to those of the control mice. hBD-3 also promoted the production of various angiogenic factors, proliferation and migration of human fibroblasts. We found that hBD-3-mediated fibroblast activation was controlled by FGFR1/JAK2/STAT3 pathway, as evidenced by the inhibitory effects of pathway-specific inhibitors. Conclusion: This study provides evidence regarding the contribution of hBD-3 to wound healing via activation of fibroblasts.

P14-06[O01-03]

Calcitriol, the active form of vitamin D, regulates epidermal tight junction barrier function in diabetes

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Background: Diabetes mellitus is a common disease that affects a variety of organs, including the skin, where hyperglycemia is associated with skin barrier dysfunctions and non-healing wounds. Calcitriol stimulates the production of antimicrobial peptides, including cathelicidin LL-37, which not displays antimicrobial activities but also shows pleiotropic immunomodulatory functions and regulates the skin barrier function. However, it is unclear whether calcitriol has effect on impaired skin barrier and wound healing in high glucose milieu. Objective: To investigate the effect of calcitriol on tight junction (TJ) barrier function in human keratinocytes under high glucose conditions. Methods: Keratinocytes were stimulated with calcitriol in normal and hyperglycemic milieus, and expression of TJ-related proteins was measured by RT-PCR. Immunofluorescence was used to examine the intercellular distribution of TJ-related proteins. The TJ barrier function was assessed by transepithelial electrical resistance (TER) measurement using cellZcope. Results: Following calcitriol stimulation, the mRNA expression levels of TJ-related proteins, including the claudin 4, 7, occludin and ZO-1 significantly increased in both normal and high glucose conditions. Calcitriol enhanced the distribution of TJ-related proteins at cell-cell borders and induced the phosphorylation of pathways involved in regulation of TJ barrier function such as aPKC, Rac1, PI3K and Akt. Indeed, we confirmed that calcitriol enhanced the TER in keratinocyte monolayers. Conclusion: The observation that calcitriol regulates epidermal barrier function in high glucose milieu suggests that calcitriol may be used as a therapeutic agent for treatment of diabetic foot ulcers to restore impaired skin barrier.

P14-07[O01-04]

Trehalose-induced senescence-associated secretory phenotype accelerates organotypic skin culture development

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The living skin equivalent (LSE) is an organotypic coculture containing well-differentiated keratinocytes cultivated on fibroblast-populated dermal substitutes. Various biomaterials have been used as dermal matrix substitutes, but the search continues for an ideal matrix that is accessible and has minimal toxicity. Using human primary fibroblasts and keratinocytes, we demonstrated that fibroblasts treated with trehalose, which is a nonreducing disaccharide, significantly accelerated rapid and extensive spread of the keratinocyte layer without any deleterious effects. Histological and flow cytometric evaluation showed significantly more Ki67 positive and G2 phase fibroblasts in trehalose-containing LSEs. The trehalose treatment increased the ERK1/2 and Akt phosphorylation in fibroblasts. To examine the dynamic nature of the response, we comprehensively examined the transient gene expressions in the trehalose-pretreated fibroblasts using RNA-sequence and Ingenuity pathway analysis, which revealed that trehalose significantly increased the expression of cell cycle inhibitors, various growth factors, and other beneficial factors associated with wound healing, such as CDKN1A, EREG, FGF2, DPT, and VEGFA. In contrast, the expressions of AURKA, AURKB, UBE2, PLK1, MYBL2, and LMNB1, the loss of which is a robust hallmark of senescence, were significantly downregulated. Furthermore, the trehalose-treated fibroblasts were positive for senescence-associated beta-galactosidase. Considered together, our data revealed that fibroblasts treated with trehalose accelerated the development of advanced organotypic skin culture, which indicated that targeting transient senescence-associated secretory phenotype could be therapeutically useful for regenerative medicine.

P14-08[O01-05]

Antioxidant protein Peroxiredoxin 4 uniquely improved aging-related delayed wound healing in mice

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Accumulation of excessive oxidative stress delays wound healing by inducing dysfunction of tissue-repairing cells. Aging significantly increases oxidative stress in the wound, which is one of the causes of delayed wound healing in the elderly. Several antioxidative enzymes have crucial roles in aging-related delayed wound healing. Peroxiredoxin 4 (PRDX4), an enzyme catalyzing the detoxification of hydrogen peroxide, is a unique secreted member of the antioxidative protein PRDX family and widely expressed in various organs. In the previous reports, it has shown that PRDX4 is present in the skin and is upregulated after injury, but its roles in wound healing remain unknown. In this study, we subjected young (4-week-old), adult (12-week-old) and aged (1-year-old) of three ages C57BL/6J (WT) or human PRDX4 transgenic (Tg) mice to skin wound formation. The overexpression of PRDX4 accelerated wound healing in adult, especially aged mice. Cell-richer granulation tissue was found in adult and aged Tg mice, compared to matched WT mice. In aged group, reduced oxidative stress and inflammation, increased angiogenesis and basic FGF and more macrophages infiltration and less neutrophils infiltration and apoptotic fibroblasts were observed in Tg mice. In contrast, severely impaired wound healing and high wound-related mortality were observed in the adult and aged PRDX4-knockout mice. In vitro, the overexpression of PRDX4 promoted the proliferation and migration of fibroblasts derived from adult or aged mice and made fibroblasts more resistant to the cytotoxicity of hydrogen peroxide. Our data are suggesting that PRDX4 is essential for wound healing and can improve the healing process of the elderly from various aspects.

P14-09[O01-06]

AMP-IBP5, an antimicrobial peptide derived from insulin-like growth factor-binding protein 5, promotes diabetic wound healing

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Impairment of keratinocyte functions is responsible for the delayed wound healing in diabetic patients. In addition to its antimicrobial activity, the antimicrobial peptide derived from insulin-like growth factor-binding protein 5 (AMP-IBP5) activates keratinocytes, fibroblats and mast cells, which are involved in wound healing; however, it remains unclear whether AMP-IBP5 promotes wound healing. The aim of this study was to examine the effects of AMP-IBP5 on diabetic wound healing and clarify the underlying molecular mechanisms. Using human primary keratinocytes cultured in high glucose conditions, we observed that AMP-IBP5 rescued the high glucose-induced attenuation of keratincyte proliferation, migration and production of angiogenic growth factors such as angiogenin and vascular endothelial growth factor. AMP-IBP5-induced activation of keratinocytes was mediated by the epidermal growth factor receptor, signal transducer and activator of transcription 1 and 3, and mitogen-activated protein kinase pathways, as evidenced by the inhibitory effects of pathway-specific inhibitors. Indeed, we confirmed that AMP-IBP5 induced activation of these pathways. In vivo, AMP-IBP5 markedly accelerated wound healing, increased the expression of angiogenic factors and promoted vessel formation in both normal and diabetic mice. Overall, the finding that AMP-IBP5 accelerated diabetic wound healing by protecting against glucotoxicity and promoting angiogenesis suggests that AMP-IBP5 might be a potential therapeutic target for treating chronic diabetic wounds.

P14-10[O01-07]

Determination of host defense peptide inducers for their therapeutic use in diabetic foot ulcers

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Chronic wounds like diabetic foot ulcer (DFU) are a health problem in patients with diabetes mellitus, which it is one of the most common disease in the world. Several studies have determined that 10 to 15% of these patients have the risk develop a foot ulcer in their lifetime. The main problem regarding wound healing in this sort of ulcers is that cellular mechanisms are deregulated by hyperglycemia conditions and that these ulcers are often related with infections by multidrug resistant bacteria, thus increasing the amputation risk considerably. Although several potential therapeutic drugs have been developed for the treatment of DFUs, most of them are unaffordable in low-income countries, furthermore the growing of multidrug resistant bacteria has worsened the landscape. Recently, the use of host defense peptides such as LL-37 has been proposed as an alternative to promote an effective wound healing whereas the infection is controlled. Nonetheless the high production cost of this peptide makes it an unfeasible alternative. Nonetheless, several LL-37 inducers have been proposed such as the Histone Deacetylase inhibitors (HDACi). The signaling mechanisms induced are involved with the transcription factor Signal Transducer and Activator of Transcription 3 (STAT3) and Hypoxia-inducible factor 1 (HIF-1 alpha) which promote LL-37 expression and are responsible of several angiogenesis and proliferative process. Entinostat is one of the main host defense peptide inducers through the HDACi. The repositioning of this drug can lead to several compounds that can be used as prospects in the diabetic foot ulcer treatment by the enhancing of host defense peptides expression and the activation of the STAT3 and HIF-1 aplha pathway.

P14-11[O01-08]

Effects of antimicrobial peptide human β-defensins on the expression of angiogenin in human dermal fibroblasts

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Background: The skin produces a plethora of antimicrobial peptides (AMPs) that not only show antimicrobial activities against pathogens but also display various immunomodulatory functions. Human β-defensins (hBDs) are the most well characterized skin-derived AMPs that contribute to diverse biological processes, including the production of cytokines, and the migration, proliferation and differentiation of host cells. In addition, we recently reported that hBD-3 promoted wound healing and angiogenesis through induction of angiogenic factor expression, migration and proliferation of fibroblasts. Angiogenin is one of the most potent angiogenic factors; however, the effects of hBDs on the expression of angiogenin in dermal fibroblasts remain unclear.
Objectives: To investigate the effects of hBDs on the secretion of angiogenin on dermal fibroblasts.
Methods: Cultured normal human dermal fibroblasts were incubated with hBD-1 to hBD-4 and the cell-free culture supernatants were harvested for assessment of angiogenin production by ELISA. The phosphorylation of mitogen-activated protein kinases and nuclear translocation of nuclear factor-kappa B (NF-κB) was assessed by Western blot.
Results: The production of angiogenin was dose-dependently increased by hBD-1 to hBD-4. All hBDs enhanced the phosphorylation of Jun-N-terminal kinase (JNK) and p38, and promoted the nuclear translocation of NF-κB. We observed that JNK, p38 and NF-κB were necessary for the hBD-mediated production of angiogenin, as evidenced the inhibitory effects of JNK- and p38- and NF-κB-specific inhibitors.
Conclusion: We provide novel evidence of the role of hBDs in the cutaneous immunity through the production of angiogenin, in addition to their antimicrobial activities and other immunomodulatory properties.

P15-01[O01-09]

Spinal cholecystokinin 2 receptor is involved in induction of alloknesis

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Mechanisms of chemical induced itch have been clarified, but those of the pathogenesis of alloknesis remain unclear. In this study of genetically modified mice and cholecystokinin (CCK) conjugated saporin-treated mice, we investigated whether cholecystokinin 2 receptors (CCK2R) expressed in the spinal cord are involved in alloknesis. Histologically, in situ hybridization revealed CCK2R mRNA expressed in dorsal horn neurons but CCK1R mRNA expression only slightly detectable. We administered CCK8S into the intrathecal cavity (which has been shown to induce alloknesis) of wild-type, CCK1R, and CCK2R knockout mouse; applied innocuous mechanical stimulation with von Frey filaments; and performed an alloknesis assay of immediate scratching behavior as a single point. In the assay, CCK8S-induced alloknesis was markedly reduced in CCK2R knockout compared to wild-type and CCK1R knockout mice. CCK8S-induced alloknesis was inhibited by intrathecal injection of CCK2R antagonist L-365, 260 but not CCK1R antagonist SR 27897. Ablation of spinal CCK receptor-expressing cells by intrathecal injection of CCK-saporin attenuated CCK8S-induced alloknesis. Notably, dry skin-induced alloknesis was inhibited by oral administration of CCK2R antagonist L-365,260, with no effect on locomotion. These findings suggest spinal CCK2R play a role in induction of alloknesis. Spinal CCK2R may be a promising candidate for alloknesis treatment.

P15-02[C03-01]

Early-onset female pattern hair loss: a case-control study for analyzing clinical features and genetic variants

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Background: Female pattern hair loss (FPHL) is the most common cause of alopecia in adult women. Based on the onset age, FPHL is classified into two subtypes: early-onset FPHL and late-onset FPHL To date, most clinical and genetic studies on FPHL have been conducted without classifying these two subtypes, which limits attaining the clinical features and genetic characteristics of early-onset FPHL.
Objective:To investigate the clinical features and genetic characteristics of early-onset FPHL.
Method: Early-onset FPHL cases and controls without FPHL were prospectively recruited in Department of Dermatology at Seoul National University Hospital. The demographics and clinical features were collected from the participants. For the genetic variants analysis, DNA was isolated from blood and genotyped for evaluating allele frequency of single nucleotide polymorphisms (SNPs) in candidate genes.
Results: Early-onset FPHL patients manifested a decreased hair shaft density and cross-section area of shaft, in vertex area, frontal and parieto-temporal area. Early-onset FPHL is associated with androgen dependent features including scalp greasiness, folliculitis, hirsutism, and polycystic ovary syndrome. Scalp pain and itching were reported more frequently in early-onset FPHL. Genotyping analysis resulted significant SNPs around *PPARGC 1A, ABCC4, CYP17A1, CYP19A1*, and *TACR1* in early-onset FPHL cases.
Conclusions: Focusing only on early-onset FPHL for the first time, this study reported clinical features and genetic loci for early-onset FPHL, which could provide an intuition for excavating the underlying pathologic etiology of early-onset FPHL.

P15-03[C09-01]

A deep learning framework enables prompt and objective scoring of Nail Psoriasis Severity Index

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Nail psoriasis occurs in 10% to 80% of psoriasis patients, which causes functional and cosmetic impairment. Nail Psoriasis Severity Index (NAPSI) was proposed as an objective standardized score to evaluate disease activity of nail psoriasis. Although NAPSI has been widely used in clinical trials, it has not been used in clinics, due to the clinicians' time-consuming burden and limited opportunities to examine nail psoriasis. For the same reason, it has a potential interobserver variability. The purpose of this study is to develop a quick and stable NAPSI scoring system with deep learning. Our system consists of two models; 1) detection of nail regions within an image, 2) NAPSI scoring of the detected nail regions. For training of the "nail region detector", we collected 1054 nail images using web scraping on Google search. Then, we annotated the coordinates of rectangles that surround the nails in each image. For the "NAPSI scorer", nine dermatologists who are clinically experienced in nail practice scored NAPSI of 2940 images taken at our hospital. As a result, our "nail region detector" distinguished the nails with an average precision of 72.6%. It also detected nails very well on almost all images for "NAPSI scorer", but to a lesser extent on the images that were taken from farther distance. Our "NAPSI scorer" scored NAPSI of the detected nails within 1 point error with 82.3% accuracy. Although this research has some limitations due to a single-center study, we proposed that our deep learning model could acquire the skills of recognizing nails and scoring NAPSI, which overcomes the time-consuming manual task and interobserver variability. It is expected to become a valuable tool for diagnosis and treatment standardization of nail psoriasis.

P15-04[O01-10]

The effectivity of metformin solution as a melanogeneis inhibitor: A chromameter analysis on human

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Introduction: Chronic sun exposure induces skin hyperpigmentation through stimulation of melanogenesis with clinical manifestations such as melasma and lentigo. Hydroquinone is currently the gold standard therapy for hyperpigmentation disorder but its long-term use has been linked with various side effects. Metformin, a biguanide agent that is traditionally used as an anti-hyperglycemic drug, has been shown to possess melanogenesis inhibitory activityObjective: To examine the effectiveness of the topical metformin solution in inhibiting melanogenesis in ultraviolet B (UVB)-induced patientsMethods: This randomized controlled trial was done on healthy subjects aged 20-45 years with Fitzpatrick skin types 4 and 5. After the minimum erythematous dose (MED) of each subject was determined, Daavlin MED DosePatch was applied to the inner right upper arm with five open holes. A chroma meter analysis was carried out on each hole to obtain the baseline L* (black-and-white spectrum) and individual typology angle (ITA, indicator of skin color) followed by UVB induction at a dose of 2 MED. Hole 1, 2, and 3 were then randomly applied with 15%, 30% metformin, and placebo solution, respectively. Hole 4 was only given UVB irradiation and hole 5 was given Kligman's formula (positive control). The treatment was continued for seven days and the L* score and ITA were assessed and comparedResult: A total of 35 subjects (mean age 32.3 years) participated in this study. The Kligman and 30% groups showed higher L* scores than the negative control $p<0.05$. Furthermore, the ITA score of Kligman and 30% groups were the highest among all groups, despite not being statistically significantConclusion: metformin 30% solution is a potential alternative agent for inhibiting UVB-induced melanogenesis.

P15-05[O01-11]

Predicting regional Eczema Area and Severity Index from the images of atopic dermatitis using deep convolutional networks

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Atopic dermatitis (AD) is one of the most common inflammatory skin diseases characterized by chronic and recurrent eczema on the skin. Eczema Area and Severity Index (EASI) is a widely used scoring tool for assessment of disease activity of AD. However, scoring EASI is a time-consuming and burdensome task for dermatologists in the clinics. The purpose of this research is constructing a deep learning framework which scores EASI rapidly and stably. We created a dataset that consisted of approximately 5000 clinical images of AD patients, and EASI corresponding to these images. The clinical images were taken at our hospital and nine dermatologists who were trained for examination of AD annotated EASI. In this study, one skin image included one of the three body regions based on the rule of EASI, such as trunk, upper limbs, and lower limbs. Images of head and neck were excluded to protect the personal information. As a result, our deep learning model could predict EASI with an accuracy of 60%, but it also showed an overfitting problem which might have been caused by a shortage of data of severe cases or little changes in temporal transition of EASI in each patient. We also suspected that this model leaned inappropriate features such as each patient's body shape or hairiness instead of the pattern of eczema. We are trying to improve the versality of our model to utilize it as an objective tool in a clinical situation, which may lead to appropriate evaluations and treatments for each patient with AD.

P15-06[O01-12]

Serum biomarkers correlate with disease response in Moderate to Severe Atopic Dermatitis patients treated with baricitinib

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Baricitinib (bari), a selective Janus kinase (JAK)1/JAK2 inhibitor, is approved in several countries for the treatment of moderate-to-severe atopic dermatitis (AD) in adults who are candidates for systemic therapy. To correlate the clinical efficacy of bari with AD-associated signature biomarkers, we analyzed blood samples taken at baseline and week 4 from patients in a monotherapy trial BREEZE-AD1 as well as in the topical steroid combination trial BREEZE-AD7, Here, we investigated whether bari changes severity-associated biomarkers downstream of its target profile and addresses inflammation and the chronic itch mediators, in correlation to changes in clinical response of moderate-to-severe AD patients. Thirty biomarkers were assessed in serum samples from patients at baseline and week 4 using a multiplex MSD (Mesoscale Discovery #K 15054D) proteomic platform. Log fold change modelling was used to assess biomarker expression relative to baseline and biomarker association to clinical response was evaluated using the Kruskal-Wallis test. Our data revealed that biomarkers such as TARC, eotaxin-3, MCP-4, IP-10, IL-15, all of which are classically relevant in the pathophysiology of AD, were significantly altered in the responder groups (Proportion of patients achieving IGA of 0 or 1 with a ≥2-point improvement at Week 16) by bari at week 4 when compared to baseline levels. Our data suggest that certain subsets of disease associated biomarkers are regulated as early as 4 weeks with bari and associate with clinical response. Collectively, our ability to identify biomarkers that associate with clinical response in AD patients may assist in effective therapeutic guidance for treatment of this heterogenous disease.

Late Abstract Submission

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L-01

Histone deacetylase 4 reverses cellular senescence via DDIT4 in dermal fibroblasts

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Histone deacetylases (HDACs) remove acetyl groups from lysine chains on histones and other proteins and play a crucial role in epigenetic regulation and aging. Previously, we demonstrated that HDAC4 is consistently downregulated in aged and ultraviolet (UV)-irradiated human skin in vivo. Cellular senescence is a permanent cell cycle arrest induced by various stressors. To elucidate the potential role of HDAC4 in the regulation of cellular senescence and skin aging, we established oxidative stress- and UV-induced cellular senescence models using primary human dermal fibroblasts (HDFs). RNA sequencing after overexpression or knockdown of HDAC4 in primary HDFs identified candidate molecular targets of HDAC4. Integrative analyses of our current and public mRNA expression profiles identified DNA damage-inducible transcript 4 (DDIT 4) as a critical senescence-associated factor regulated by HDAC4. Indeed, DDIT4 and HDAC4 expressions were downregulated during oxidative stress- and UV-induced senescence. HDAC4 overexpression rescued the senescence-induced decrease in DDIT4 and senescence phenotype, which were prevented by DDIT4 knockdown. In addition, DDIT4 overexpression reversed changes in senescence-associated secretory phenotypes and aging-related genes, suggesting that DDIT4 mediates the reversal of cellular senescence via HDAC4. Collectively, our results identify DDIT4 as a promising target regulated by HDAC4 associated with cellular senescence and epigenetic skin aging.

L-02

Metabolic reprogramming defines myeloid cell function in skin repair

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Skin injury induces a complex, dynamic cellular program proceeding in sequential stages of inflammation, tissue growth and differentiation. Cells of the monocyte/macrophage lineage sense a variety of environmental cues of injured tissue and integrate those into a host protective healing response. The molecular determinants that precisely control the dynamics of macrophage functional plasticity during healing progression are largely unknown and are just beginning to emerge. Here we demonstrate that skin injury induces different metabolic programs in wound macrophages by profiling their early versus late stages at both the transcriptional and functional levels. We show that glycolytic metabolism in early phase wound macrophages is not sufficient to ensure a productive repair response. Instead, combining conditional disruption of the electron transport chain in myeloid cells by deletion of mitochondrial aspartyl-tRNA synthetase (DARS2) with single cell sequencing analysis of wound macrophages, we found that at early stage a defined subpopulation of macrophages repurposes mitochondrial activity to initiate a cascade of mtROS production, HIF1alpha stabilization, ultimately driving an effective pro-angiogenic program essential for timely healing. In contrast, to convey late phase wound macrophages into repair mode they depend on IL-4Ralpha-mediated mitochondrial respiration and so far unknown regulation of mitohormesis. In future studies it will be important to understand how type 2-mediated mitochondrial stress and type 2 macrophage effector functions are connected. From the translational perspective the question rises whether modulating mitochondrial stress provides a target for therapeutic benefit in pathological wound healing scenarios.

L-03

Application of microdissection-based spatial transcriptomics for mechanistic and biomarker investigations in dermatology

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The skin acts as the first barrier to our body, and its structure is closely associated with the expression of various skin phenotypes. The three layers and the appendages of skin vary significantly in their anatomy and function. Therefore, understanding the spatial landscape of the skin should be essential for mechanistic investigation and biomarker discovery in dermatology. To address this issue, here, we have established a spatial transcriptome (ST) system by using 100 μm-diameter punch microdissection (md) in frozen skin sections (hereafter 'mdRNA-seq'). The advantages of this system are, namely:
1. High resolution: this system can detect the expression profile of more than 10,000 genes in ϕ100 μm spot, which provides much better resolution than the conventional ST method. Hence it allows the detection of genes with a low expression.
2. Native detection: no enzymatic digestion step is required.
3. Targeted sampling and low cost: this enables collection of the regions of interest, such as skin appendages.
We confirmed the accuracy of the mdRNA-seq method by comparing the distribution of the cell type-specific genes using single-cell RNA-seq data. We next applied the mdRNA-seq method to analyze skin specimens from atopic dermatitis (AD) patients and AD-model mice. The dermal transcriptional profiles exhibited species differences; however, the epidermal gene signature showed common changes between humans and mice along with the progression of AD. Taking advantage of this technique, we finally identified a set of epidermal biomarkers that reflects the local inflammatory status. In summary, mdRNA-seq provides a powerful tool for elucidating complex skin pathologies by revealing site-specific gene expressions undetectable by ordinary methods.

L-04

Anti-staphylococcus aureus effect of the hot spring water via metal accumulation

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Hot spring water (HSW) has long been used to treat inflammatory skin diseases, including atopic dermatitis (AD). AD is characterized by an abundance of *Staphylococcus aureus* (SA) colonized on the affected skin, and the density of SA is associated with disease severity. Previous studies demonstrated that HSW improves AD skin condition mainly by inhibiting SA growth with acidic pH, while the contribution of ionic substances in HSW remains to be systematically explored.
In this study, we first evaluated the growth activity of SA strains in the neutral pH HSW, which was obtained from the myoken-44 hot spring from the Kirishima area in Japan. We observed the HSW significantly inhibits two standard SA strains and ten strains isolated from AD skin by tracking the growth curve. To evaluate the contribution of ionic substances in HSW to SA growth, we then tested eight SA stains with complete genomics sequencing data. The growth activity of two out of eight strains was not inhibited by HSW (non-inhibited strains). Subsequently, we analyzed the membrane transporters-coding genes and aligned them to the KEGG database, and we found the non-inhibited strains had more iron-sulfur cluster proteins that work for uptake of sulfur-containing organic compounds. Moreover, enrichment of SmtB/ArsR family transcriptional regulator targeting lead/cadmium/zinc/bismuth-responsive transcriptional repressor was observed in non-inhibited strains. These results suggest that the HSW inhibited SA growth by accumulating heavy metals such as iron, sulfur, lead, and cadmium.
In conclusion, anti-SA mechanisms of the HSW link to heavy metal accumulation, and the uncovered mechanism may support the development and use of hot spring physiotherapy.

L-05

Particulate matter triggers Th17 polarization in atopic dermatitis in association with increased pregnane X receptor signaling

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Background: Epidemiological studies have demonstrated that particulate matter (PM) exposure can cause the development and exacerbation of atopic dermatitis (AD). However, the mechanisms of how PM affects atopic dermatitis are still unclear. Recently, pregnane X receptor (PXR), one of xenobiotic receptors, has been suggested as a potential mechanism eliciting dermatitis after repeated skin exposure to pollutants.
Objective: This study aimed to investigate PM-induced effects on atopic dermatitis and the role of PXR.
Methods: Standard reference material of fine PM (SRM 2786) was applied on BALB/C mice of 2, 4-dinitrochlorobenzene (DNCB)-induced atopic dermatitis model. The mRNA and protein expression levels of inflammatory markers and PXR were evaluated.
Results: PM significantly increased epidermal and dermal thickness and inflammatory cell infiltration. Serum immunoglobulin E (IgE) and Th2 cytokines (IL-4 and IL-13) increased in DNCB-induced atopic dermatitis mice, yet they did not increase further by additional PM treatment. Expressions of IL-17A and IL-17-related cytokines including IL-1β, IL-6, and CXCL5 increased by DNCB treatment and increased further by additional PM treatment. Similarly, DNCB and PM increased expressions of PXR and its downstream targets (CYP1A1, CYP1B1, and CYP3A11). Plus, PM of high concentration (100μg/cm^2) increased PXR expression much more compared to low concentration (20μg/cm^2). Effects of PM were ameliorated by resveratrol treatment, an antioxidant.
Conclusions: PM induced Th17 polarization and increased PXR expression in DNCB-induced atopic dermatitis mice. These results suggest that PM triggers AD progression to chronic disease and PXR might be involved in this process.

L-06

Bird's-eye viewing of dermatologists' research trends using a natural language processing approach: the contribution of Japanese researchers

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With the growing acceptance of evidence-based policy making, visualization, quantification, and evaluation of R&D activities in any scientific fields are becoming increasingly important as they may provide objective basis for future policy directions. Although many efforts have been made to analyze Japanese R&D activities, the activity of Japanese dermatology community is only scarcely observed. This gives us the question about how they are performing and how their activities can be evaluated.
As a first step in answering this question we created a landscape of dermatologists' research activities worldwide. To this end, we performed a literature analysis combined with natural language processing. Bibliographic records that were published from dermatology or related departments during 2016 to 2020 were collected from database SCOPUS. We selected 58,000 papers that had any record of citation. Among them 42,589 records had digital object identifier and abstract information in PubMed dataset and were used for later analysis. To develop a 2D-mapped view, the titles and abstract texts were extracted from the literatures to be embedded by the SPECTER model that was developed and made openly usable by Allen Institute for AI. The vectorized papers were dimensionality reduced by UMAP and plotted in 2D. We set out to employ Gaussian mixture models to generate subpopulations of the publications. By manually assessing the wordclouds and the literature lists, each subpopulation was labeled with brief titles expressing their nature. Author affiliation information was collected from SCOPUS, and heatmap analyses revealed the categories where Japanese researchers strongly or weakly contributed compared to other countries. Analyses were performed for international comparison.

L-07

Expression of TAM receptors in melanoma of Korean patients

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Receptor tyrosine kinases (RTKs) are expressed, ectopically, overexpressed, or hyperactivated in tumor cells and are therefore attractive targets for cancer therapy. Overexpression of TAM (TYRO3, AXL, MER) family of RTKs has been observed in human cancers.
This study was performed to investigate the expression of TAM receptors in melanoma of Korean patients.
A total of 46 melanoma cases were analyzed for TAM expression, consisting of 32 cases of acral lentiginous melanoma (ALM), 9 cases of superficial spreading melanoma (SSM), and 5 cases of nodular melanoma (NM). Forty six primary melanomas and eight metastatic melanomas were immunohistochemically stained for TYRO3, AXL, and MER. In addition, BRAF mutation status was assessed by immunohistochemical analysis with BRAF^{V600E}.
Among 46 primary melanomas, AXL, TYRO3, and MER expression was observed in 95.7%, 87.0%, and 37.0% of melanomas, respectively. In metastatic tumors, all 8 cases expressed AXL and TYRO3 and 5 cases showed MER expression. MER expression was found more frequently in SSM and NM than in ALM (55.6%, 60.0%, and 28.1%, respectively). MER expression was observed more frequently in > 1 mm thick melanomas than in ≤ 1mm thin melanomas of the T1 stage (41.1% vs. 25.0%). MER expression was also detected more frequently in BRAF^{V600E} expressing melanomas than in BRAF^{V600E} negative melanomas (53.3% vs. 31.0%).
We observed that AXL and TYRO3 were commonly expressed in melanoma, whereas MER was expressed in advanced melanoma. Therefore, TAM receptors can be considered therapeutic targets in Korean melanoma patients, especially MER in cases of advanced tumor.

L-08

Autophagy is a defense mechanism rescuing hair loss against particulate matter exposure

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Autophagy is an essential catabolic pathway induced under various types of cellular stress. Accumulating evidence suggests that autophagic flux is induced by ambient particulate matter (PM), a major environmental cause of diseases. Given that small diameter PMs can penetrate into hair follicles (HFs), we hypothesized that autophagy could be induced to serve as a protective role in hair growth against PM exposure. To identify whether PM exposure affects hair growth, *ex vivo* individualized HFs and outer root sheath (ORS) cells were cultured in the presence of PM. We found that PM promoted anagen to catagen entry and inhibited HF growth *ex vivo*. PM also adversely affected cell viability in a dose- and time- dependent manner. We also found that PM induced autophagic flux in ORS cells and HFs. Conversely, inhibition of autophagy by knocking down the autophagy-related gene 5 with siRNA increased susceptibility to PM-induced cell death and catagen progression. Using the C57BL/6 mouse model, we observed that PM-exposed mouse hair follicles exhibited early catagen transition, which was rescued by rapamycin, the well-known autophagy inducer. In conclusion, our data shows that PM has a detrimental effect causing hair loss. Moreover, we propose autophagy as a novel mechanism to protect hair growth from PM exposure.

L-09

Skin Microbiome Analysis using Postally-Delivered Tape-Stripped Material for General Consumers

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The demand for skin microbiome analysis is constantly increasing for both patients and general public. Recently, the tape-stripping kit for self-sampling, which tolerate outdoor-temperature postal service, was developed. To evaluate the skin microbiome of our existing customers of cosmetic products, we analyzed their facial microbiome using this kit.
Following the ethical approval, written informed consents were obtained from 76 customers (females aged 20-49, 56 with and 20 without acne). Samples were taken from the face by using tape-stripping kits, posted by regular mail, and their DNA extracted in the laboratory. After the PCR amplifications of bacterial 16S rRNA gene and fungal ITS1 region, metagenomic analysis was performed by using MiSeq sequencer. In addition, qPCR was performed to quantify *C. acnes*, *Corynebacterium* sp., *S. epidermidis*, and *Malassezia* sp.
All samples passed the routine quality checks and yielded microbial profiles. The hierarchical clustering revealed the bacterial biomes to compose three groups, which are *C. acnes*-dominated, *Neisseriaceae*-abundant, and others. In the same manner, the fungal biomes composed four groups, *M. restricta*-abundant, *M. globosa*-abundant, and two others. Acneic or oily skin harboured larger number of *C. acnes* and *M. restricta* compared with non-acneic or dry skin. Our results indicate that the postally received samples were fully competent with microbiome analysis.

Keywords: skin microbiome, tape-stripping, postal, bacteria, *Cutibacterium acnes*, fungus, *Malassezia*

L-10

Comprehensive morphological observation of epidermal Merkel cells in human skin

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Merkel cells (MCs) are one of the mechano-receptors present in skin. They are known to receive gentle touch and they form the MC-neurite complex that conveys touch sensations to the brain. Recent studies have shown the involvement of MCs in the conversion of touch to itch. They demonstrated that alloknesis in aging and dry skin is associated with a loss of MCs in mice. In humans, age-related changes in MCs have been reported in digital skin, but not in hairy skin. Since the face is one of the main parts of body to receive touch or physical contact, we aimed to clarify how the density and distribution of MCs and connected nerve fibers in the cheek skin change with age.
Since only a few MCs were observable in vertical cross-sections of skin, we prepared epithelial sheets. Human cheek samples were obtained from 7 donors (27 - 91 yo). Those samples were stained with antibodies against K8 and K20 and observed using confocal laser scanning microscopy. PGP 9.5 and NF200 immunostaining was also performed in the cross-sections from the same subjects and quantified. Finally, we investigated the MC-neurite complex in whole human skin using multi-photon microscopy.
As a result, MCs were found around the hairs, glands, and ridged parts of the skin in accordance with previous reports. MCs were basically scattered in cheek skin. MC density showed a dramatic reduction with age in a positive correlation with A-fiber. These results suggest MCs decrease as part of a MC-neurite complex. Finally, we demonstrated for the first time 3D images of the MC-neurite complex in human skin. NF 200 positive fibers were found to be connected with several MCs.
In conclusion, our results show a scattered distribution of MCs and a decrease in MC and A-fiber density with age in human cheek skin.

L-11

Withdrawn

L-12

Evaluation of anti-pigmentation cassette to other anti-pigmentation ingredients

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Human skin color is a multi-faceted process, resulting in the range of skins we see. Melanin is generated in melanocytes and released in cellular vesicles called melanosomes into keratinocytes. Intrinsic and extrinsic factors (e.g. UV, POMC and α-MSH) contribute to the production of melanin. Melanin biosynthesis can be inhibited by targeting the rate-limiting enzyme tyrosinase, melansome transfer, cell turnover or melanin degradation. Tranexamic acid (TXA), has been suggested to inhibit pigmentation by blocking inflammation that triggers melanogenesis. Vitamin B3 is known for its anti-inflammatory and antioxidant properties, and interference in melanosome transfer. We compared these materials to a proprietary cassette that includes (1-(2,4-dihydroxyphenyl) -3- (2,4-dimethoxy-3-methylphenyl) propane) , a synthetic derivative of an extract of Dianella ensifolia, which has been separately shown to effectively inhibit tyrosinase in vitro.
We assessed changes in intrinsic pigmentation induction in melanocyte-containing reconstructed skin models via spectrophotometric analysis, macroscopic images and melanin content. We analyzed reflectance at 470nm, a wavelength attributed to melanin, and derived ITA (individual topology angle) from L* and b*, a value to determine overall skin color. After 14 days, a significant increase in ITA was observed in skins treated with the cassette at 2%, indicative of a lighter overall color. An increase in reflectance was also found, indicating the presence of less melanin. There was no change in overall melanin content, but a perceivable change in color and distribution of melanin was observed in images. These data suggest that the cassette decreases the production of pigmentation to a greater degree than TXA and Vitamin B3 at comparable levels.

L-13

Unmet educational needs and clinical practice gaps in the management of generalized pustular psoriasis: Global insights from the front line

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Generalized pustular psoriasis (GPP) is a rare, neutrophilic skin disease with recurrent flares of sterile pustules and systemic features. Varying diagnostic criteria and a lack of approved therapies pose serious challenges to GPP management. On 24 July 2020, 13 dermatologists from 10 countries attended a workshop to share experiences in managing GPP. Educational and clinical practice gaps, grouped by healthcare system level, were discussed and ranked. Lack of GPP experience among healthcare professionals (HCPs) was identified as the highest priority individual-level practice gap, and a challenging aspect of GPP management was prompt, effective treatment to ensure rapid control of cutaneous and systemic features. Limited understanding of GPP among non-specialists means misdiagnosis is common, delaying referral and treatment start. In countries where patients may present to general practitioners or emergency departments, GPP is often mistaken for an infection. At the organisational level, educating emergency department HCPs to recognise GPP as an autoinflammatory disease was seen as a high priority, along with improved communication, cooperation and definitions of roles and responsibilities within multidisciplinary teams. At the regulatory level, the need for robust clinical trial data was identified as the highest priority, followed by the need for clear, consistent treatment guidelines and approved therapies. The most important educational imperatives are for HCPs to understand that GPP can be life threatening if correct treatment initiation is delayed and to recognise when to refer cases to a dermatologist experienced in GPP management. Robust clinical trial data, consensus diagnostic criteria and guidelines for the treatment and prevention of GPP flares are needed.

Author Index

The 46th Annual Meeting of the Japanese Society for Investigative Dermatology

Author Index

TML: Tanioku Kihei Memorial Lecture, **JAL:** JSID Award Lecture, **JKA:** JSID Kisaragi Award,
WS: World Showcase of Investigative Dermatology, **SAS:** State-of-the-Art Symposium of Skin Research,
JDS: JDS Symposium, **JAOF:** JSID-Asia-Oceania-Forum,
MRA: The 22nd Maruho Research Award Presentations by award winners and award ceremony,
SRA: Sun Pharma RISING SUN AWARD 2021,
MS: Morning Seminar, **LS:** Luncheon Seminar, **ES:** Evening Seminar,
I〜III: Plenary Session, **C:** Concurrent Oral Session, **O:** 3 minutes presentation and discussion,
P: Poster Presentation, **L:** Late abstract submission, **SE:** 2020 JSID's Fellowship Shiseido Research Grant

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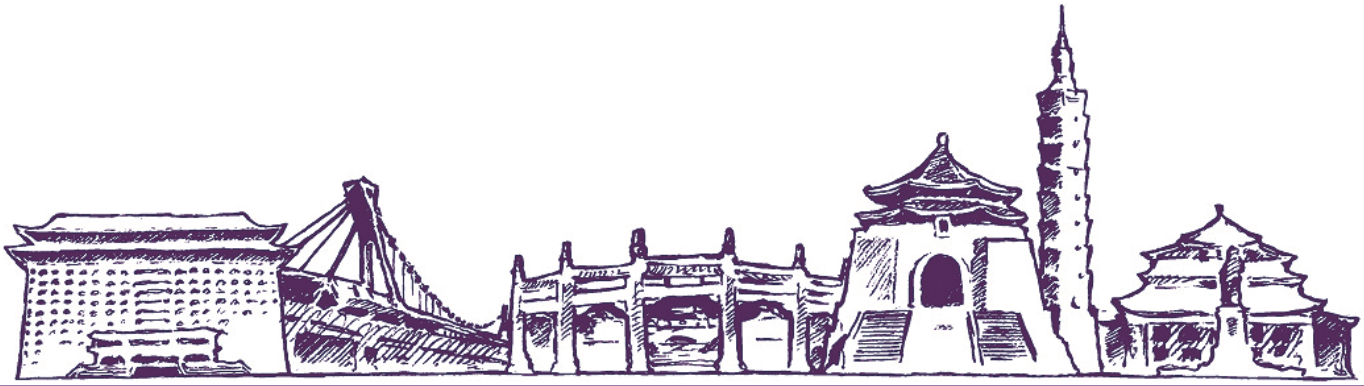

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