第3回CIBoGリトリート

第14回NAGOYAグローバルリトリート

名古屋大学医学系研究科
CIBoG卓越大学院

【プログラム・抄録集】

令和4年2月19日(土)

名古屋大学　リトリート実行委員会
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第3回CIBoGリトリートの開催にあたって
（第14回NAGOYAグローバルリトリート）

名古屋大学大学院医学系研究科長　門松　健治

常に進歩し続ける生命医科学の分野において次代を担う若手研究者の育成は、私たちが属する研究機関の重要な責務であります。この10年で生命医科学は劇的な進歩を遂げてきました。生命医科学ビッグデータを解析して、病気の理解や新たな治療法の開発、さらには病気の発症を未然に防ぐような個別化予防の創成が社会的にも求められ、傑出した研究を行うためには情報科学をはじめとする多様な分野間の連携が必須となっております。

NAGOYAグローバルリトリートは、東海圏の若手研究者が研究分野や所属機関を超えて、幅広く交流し、お互いの研究活動を理解する、またとない機会であり、お互いに探究心を刺激し合う貴重なイベントです。企画から運営まで全て若手研究者自身が行っている点もその特徴と言えます。

本リトリートは、平成20年度にグローバルCOEプログラム「機能分子医学への神経疾患・腫瘍の融合拠点」を基盤として初めて開催され、今回が14回目です。回数を重ねる中で、神経疾患・腫瘍分野にとどまらず、生物医学領域全体を対象とした会として発展し、現在に至っています。さらに、令和元年度に卓越大学院プログラムとして採用された「情報・生命医科学コンボリューション on グローカルアライアンス卓越大学院（CIBoG卓越大学院）プログラム」の枠組みの中で開催されました。名古屋大学大学院医学系研究科、国立長寿医療研究センター、愛知県がんセンター、生理学研究所、愛知県医療療育総合センター　発達障害研究所および名古屋大学環境医学研究所に、名古屋大学創薬科学研究科、名古屋大学情報学研究科、名古屋大学生命農学研究科、岐阜大学などを加えた、多くの施設からご参加いただきます。様々なバックグラウンドを持つ若手研究者の参加のもと、活発な議論が行われ、多分野研究の交流の場となることを期待します。

第14回を迎えるにあたり、特別講演において大阪大学　茂呂和世先生にご講演頂くことは、誠に光栄であります。一昨年までであれば「あいち健康プラザ」にて2日間の合宿形式の開催でありましたが、今年は新型コロナウイルス感染症（COVID-19）の感染状況より、オンライン形式での1日開催となりました。1日開催ではございますが、今回のリトリートも、特別講演に加え、CIBoG大学院生を含む大学院生・若手研究者による口頭発表や、一般講演、医学奨励賞受賞講演が設けられ、各施設から推薦された若手研究者による講演も行われます。ご多忙の中、快くご協力頂きました諸先生方に心より御礼を申し上げます。

このリトリートが、若手研究者の皆さんにとって、よい刺激となり、新しい交流がうまれることを願ってやみません。

第3回CIBoGリトリートの開催にあたって
（第14回NAGOYAグローバルリトリート）
～ 実行委員会より ～

実行委員会代表　名古屋大学大学院医学系研究科　分子生物学　尾崎　智也

I would like to thank all the participants for taking time out of your busy schedules of research, clinical work, and education to join us. Although there may be some shortcomings in the management of the retreat, I believe that the retreat will provide many opportunities for you to participate in cutting-edge research, including special lectures, presentations by colleagues in other fields, and new encounters through discussions. It will be a great pleasure for us, the planning committee, if we can be of any help to you in your research life. Let's enjoy the retreat.

この度、第3回CIBoGリトリート（第14回NAGOYAグローバルリトリート）を開催させて頂くこととなりました。本リトリートは、毎年2月に若手研究者育成や東海地区の研究機関の連携などを目的とした学術交流会であり、従来「NAGOYAグローバルリトリート」という名称で2009年から開催しておりました。2019年度より、名古屋大学大学院医学系研究科では卓越大学院プログラムに採択されたことを受け、本プログラムの通称であるCIBoG（Convolution of Informatics and Biomedical Sciences on Glocal Alliances）が本学術交流会を主催しております。また、名古屋大学大学院医学系研究科が共催となり、周辺の研究機関（国立長寿医療研究センター、愛知県がんセンター、愛知県医療療育総合センター発達障害研究所、生理学研究所）に加え、名古屋大学環境医学研究所、名古屋大学大学院生命農学研究科、創薬科学研究科、情報学研究科、さらに岐阜大学も参画しております。

一昨年までは大府市のあいち健康プラザにて2日間の合宿形式で開催されておりましたが、今年は、新型コロナウイルス感染症の拡大に伴い、昨年同様Webでの1日開催となりました。1日開催ではございますが、CIBoG大学院生を含む大学院生・若手研究者による口頭発表や一般講演、医学奨励賞受賞講演、そして特別講演もプログラムに入っており、このリトリートを通じて、この地域で実施されている多くの医学系研究に触れられる内容の濃いプログラムとなっております。

参加者の皆様におかれましては、研究、臨床、教育にお忙しい合間をぬって、ご参加いただきありがとうございます。運営に至らない点があるかとは思いますが、特別講演をはじめとする最先端の研究、他分野の同世代研究者の発表、そしてディスカッションを通して皆様の研究が益々発展しますことを実行委員一同お祈り申し上げます。

スケジュール

2022.2.19

9:00～ 9:10	開会の辞
9:10～10:25	口頭発表 Session A （3部屋，各7演題，各10分（7分発表＋3分質疑応答））
10:25～10:30	休憩
10:30～11:45	口頭発表 Session B （3部屋，各7演題，各10分（7分発表＋3分質疑応答））
11:45～11:50	休憩
11:50～13:15	口頭発表 Session C （3部屋，各7～8演題，各10分（7分発表＋3分質疑応答））
13:15～14:00	休憩
14:00～15:00	一般講演（3演題，各18分（発表14分＋質疑応答4分））
15:00～15:10	休憩
15:10～16:10	特別講演　茂呂和世先生
16:10～16:20	休憩
16:20～17:35	医学奨励賞受賞講演（4演題，各18分（発表14分＋質疑応答4分））
17:35～17:55	表彰・閉会式

Schedule

2022.2.19

9:00～ 9:10	Opening Remarks
9:10～10:25	Oral Presentations Session A: 3 rooms, 7 titles, 10-min each (7-min presentation & 3-min Q&A)
10:25～10:30	Break
10:30～11:45	Oral Presentations Session B: 3 rooms, 7 titles, 10-min each (7-min presentation & 3-min Q&A)
11:45～11:50	Break
11:50～13:15	Oral Presentations Session C: 3 rooms, 7 or 8 titles, 10-min each (7-min presentation & 3-min Q&A)
13:15～14:00	Break
14:00～15:00	General Lectures: 3 titles, 18-min each (14-min lecture & 4-min Q&A)
15:00～15:10	Break
15:10～16:10	Special Lecture: Dr. Kazuyo Moro (Osaka University)
16:10～16:20	Break
16:20～17:35	The Medical Research Award-Wining Lecture: 4 titles, 18-min each (14-min lecture & 4-min Q&A)
17:35～17:55	Award Ceremony & Closing Remarks

講演者一覧

2022.2.19

司会・進行（午前）：羽根　正弥（名古屋大学生命農学研究科　糖鎖生命コア研究所）

9:00～ 9:10	開会の辞

9:10～10:25	口頭発表 Session A（3部屋，各7演題，各10分（7分発表＋3分質疑応答））

Room 1　座長：日比野絵美（名古屋大学創薬科学研究科　構造分子薬理学）
河谷　昌泰（名古屋大学環境医学研究所　神経系分野Ⅱ）

Room 2　座長：宇野　光平（名古屋大学医学系研究科　総合保健）
藤巻加於梨（名古屋大学医学系研究科　分子細胞免疫学）

Room 3　座長：河村奈緒子（岐阜大学　糖鎖生命コア研究所）
植松　高史（名古屋大学医学系研究科　神経内科学）

10:25～10:30	休　　憩

10:30～11:45	口頭発表 Session B（3部屋，各7演題，各10分（7分発表＋3分質疑応答））

Room 1　座長：羽根　正弥（名古屋大学生命農学研究科　糖鎖生命コア研究所）
髙橋　秀和（名古屋大学医学系研究科　消化器内科学）

Room 2　座長：濵口　知成（名古屋大学医学系研究科　神経遺伝情報学）
伊佐次光莉（名古屋大学医学系研究科（保健）リハビリテーション療法学）

Room 3　座長：祖父江　顕（名古屋大学環境医学研究所　病態神経科学）
畑中　理菜（名古屋大学生命農学研究科　糖鎖生命科学）

11:45～11:50	休　　憩

11:50〜13:15　口頭発表 Session C（3部屋，各7〜8演題，各10分（7分発表＋3分質疑応答））

Room 1　座長：永田　健一（名古屋大学医学系研究科　機能組織学）
神田　　容（名古屋大学環境医学研究所　分子代謝医学）

Room 2　座長：横井　　聡（名古屋大学医学系研究科　神経内科学）
鈴木　佑治（名古屋大学医学系研究科　分子生物学）

Room 3　座長：尾崎　智也（名古屋大学医学系研究科　分子生物学）
酒井　昭平（名古屋大学環境医学研究所　病態神経科学）

13:15〜14:00　休　　憩

司会・進行（午後）：宇野　光平（名古屋大学医学系研究科　総合保健）

14:00〜15:00　一般講演（3演題，各18分（発表14分＋質疑応答4分））

座長：小林　憲太（生理学研究所　ウィルスベクター開発室）
岩間信太郎（名古屋大学医学系研究科　糖尿病・内分泌内科学）
篠原　　充（国立長寿医療研究センター　分子基盤研究部）

Rejuvenation of aged T cells for effective adoptive cancer immunotherapy

籠谷　勇紀（愛知県がんセンター　腫瘍免疫応答研究分野）

Development of sialic acid chemistry and its application to glycan syntheses

河村奈緒子（岐阜大学　糖鎖生命コア研究所）

Properties of 2'–5'–linked oligonucleotides with a conformationally locked sugar conformation in an N–form.

定池　雅司（名古屋大学創薬科学研究科　基盤創薬学専攻）

15:00〜15:10　休　　憩

15:10〜16:10　特別講演（1演題）

座長：坪田　庄真（名古屋大学医学系研究科　分子生物学）
足立　雄太（愛知県がんセンター　がん標的治療TR分野）

The identification of ILC2 has changed the concept of type 2 immune diseases

茂呂　和世（大阪大学大学院　医学系研究科 生体防御学教室／大阪大学 免疫学フロンティア研究センター　免疫・アレルギー／理化学研究所　生命医科学研究センター　自然免疫システム研究チーム）

16:10～16:20	休　　憩

16:20～17:35	医学奨励賞受賞講演（4演題，各18分（発表14分＋質疑応答4分））

座長：吉崎　嘉一（発達障害研究所　障害モデル研究部門）
　　小西　博之（名古屋大学医学系研究科　機能組織学）
　　阪本　考司（名古屋大学医学系研究科　呼吸器内科学）

Splicing regulation of large exons secures phase-separation of transcription factors in vertebrates

河地　利彦（名古屋大学医学系研究科　神経遺伝情報学）

CD4+ T cells are essential for the development of destructive thyroiditis induced by anti–PD–1 antibody in thyroglobulin–immunized mice

安田　康紀（名古屋大学医学部附属病院　糖尿病・内分泌内科）

Neutrophil/lymphocyte ratio as a predictor of lymph node metastasis in extramammary Paget's disease

江畑　　葵（名古屋大学医学系研究科　皮膚科学）

Embryonal erythropoiesis and aging exploit ferroptosis/Lysosomal nitric oxide determines transition from autophagy to ferroptosis after exposure to plasma-activated Ringer's lactate

Hao Zheng（名古屋大学医学系研究科　生体反応病理学）

17:35～17:55	表彰、閉会式

List of speakers

2022.2.19

Moderators：Masaya Hane（Glyco-Life Science, Nagoya University Institute for Glyco-core Research（iGCORE））

9:00～ 9:10	Opening Remarks

9:10～10:25	Oral Presentations Session A: 3 rooms, 7 titles, 10-min each （7-min presentation & 3-min Q&A）

Room 1 Chairs：Emi Hibino（Structural Molecular Pharmacology, Nagoya University Graduate School of Pharmaceutical Sciences）

Masahiro Kawatani（Neuroscience II, Nagoya University Research Institute of Environmental Medicine（RIEM））

Room 2 Chairs：Kohei Uno（Nagoya University Graduate School of Medicine (Health Sciences)）

Kaori Fujimaki（Immunology, Nagoya University Graduate School of Medicine）

Room 3 Chairs：Naoko Komura（Gifu University Institute for Glyco-core Research（iGCORE））

Takashi Uematsu（Neurology, Nagoya University Graduate School of Medicine）

10:25～10:30	Break

10:30～11:45	Oral Presentations Session B: 3 rooms, 7 titles, 10-min each （7-min presentation & 3-min Q&A）

Room 1 Chairs：Masaya Hane（Glyco-Life Science, Nagoya University Institute for Glyco-core Research（iGCORE））

Hidekazu Takahashi（Gastroenterology, Nagoya University Graduate School of Medicine）

Room 2 Chairs：Tomonari Hamaguchi（Neurogenetics, Nagoya University Graduate School of Medicine）

Hikari Isaji（Occupational Therapy, Nagoya University Graduate School of Medicine (Health Sciences)）

Room 3 Chairs：Akira Sobue（Neuroscience and Pathobiology, Nagoya University Research Institute of Environmental Medicine (RIEM)）

Rina Hatanaka（Glyco-Life Science, Nagoya University Graduate School of Bioagricultural Sciences）

11:45～11:50	Break

11:50～13:15	Oral Presentations Session C: 3 rooms, 7 or 8 titles, 10-min each (7-min presentation & 3-min Q&A)

Room 1 Chairs：Kenichi Nagata (Functional Anatomy and Neuroscience, Nagoya University Graduate School of Medicine)

Hiro Kohda (Molecular Medicine and Metabolism, Nagoya University Research Institute of Environmental Medicine (RIEM))

Room 2 Chairs：Satoshi Yokoi (Neurology, Nagoya University Graduate School of Medicine)

Yuji Suzuki (Molecular Biology, Nagoya University Research Institute of Environmental Medicine (RIEM))

Room 3 Chairs：Tomoya Ozaki (Molecular Biology, Nagoya University Graduate School of Medicine)

Shohei Sakai (Neuroscience and Pathobiology, Nagoya University Research Institute of Environmental Medicine (RIEM))

13:15～14:00	Break

Moderators：Kohei Uno (Nagoya University Graduate School of Medicine (Health Sciences))

14:00～15:00	General Lectures: 3 titles, 18-min each (14-min lecture & 4-min Q&A)

Chairs：Kenta Kobayashi (Viral Vector Development, National Institute for Physiological Sciences (NIPS))

Shintaro Iwama (Endocrinology and Diabetes, Nagoya University Graduate School of Medicine)

Mitsuru Shinohara (Aging Neurobiology, National Center for Geriatrics and Gerontology)

Rejuvenation of aged T cells for effective adoptive cancer immunotherapy

Yuki Kagoya (Division of Immune Response, Aichi Cancer Center Research Institute
Division of Cellular Oncology, Department of Cancer Diagnostics and Therapeutics, Nagoya University Graduate School of Medicine)

Development of sialic acid chemistry and its application to glycan syntheses

Naoko Komura (Gifu University Institute for Glyco-core Research (iGCORE))

Properties of 2'-5'-linked oligonucleotides with a conformationally locked sugar conformation in an N-form.

Masashi Sadaike (Division of Structural Molecular Pharmacology, Nagoya University Graduate School of Pharmaceutical Sciences)

15:00～15:10	Break

15:10～16:10	Special Lecture: 1 title

Chairs：Shoma Tsubota（Molecular Biology, Nagoya University Graduate School of Medicine）
Yuta Adachi（Molecular Therapeutics, Aichi Cancer Center）

The identification of ILC2 has changed the concept of type 2 immune diseases

Kazuyo Moro （Professor, Laboratory for Innate Immune Systems, Department of Microbiology and Immunology, Graduate School of Medicine, Osaka University
Laboratory for Innate Immune Systems, RIKEN Center for Integrative Medical Sciences（IMS））

16:10～16:20	Break

16:20～17:35	The Medical Research Award-Wining Lecture: 4 titles, 18-min each （14-min lecture & 4-min Q&A）

Chairs：Kaichi Yoshizaki (Disease Model, Institute for Developmental Research)
Hiroyuki Konishi (Functional Anatomy and Neuroscience, Nagoya University Graduate School of Medicine)
Koji Sakamoto (Respiratory Medicine, Nagoya University Graduate School of Medicine)

Splicing regulation of large exons secures phase-separation of transcription factors in vertebrates

Toshihiko Kawachi （Neurogenetics, Nagoya University Graduate School of Medicine）

CD4^{+} T cells are essential for the development of destructive thyroiditis induced by anti–PD-1 antibody in thyroglobulin-immunized mice

Yoshinori Yasuda （Endocrinology and Diabetes, Nagoya University Hospital）

Neutrophil/lymphocyte ratio as a predictor of lymph node metastasis in extramammary Paget's disease

Aoi Ebata （Dermatology, Nagoya University Graduate School of Medicine）

Embryonal erythropoiesis and aging exploit ferroptosis/Lysosomal nitric oxide determines transition from autophagy to ferroptosis after exposure to plasma-activated Ringer's lactate

Hao Zheng （Pathology and Biological Responses, Nagoya University Graduate School of Medicine）

17:35～17:55	Award Ceremony & Closing Remarks

List of Oral Presenters

＊Please note that the time may change slightly due to the extension and replacement of presentations.

Session No/Time	Room No	Presentation Time/No		Name	Department or Division	Institute	Title
Session A 9:10–10:25	Room 1	9:10～9:20	1	Yumiko Kasugai	Cancer Epidemiology and Prevention	Aichi Cancer Center	Association between germline pathogenic variants and breast cancer risk in Japanese women: the HERPACC study.
		9:20～9:30	2	Hinano Komura	Glyco-Life Science	Nagoya University Graduate School of Bioagricultural Sciences, iGCORE	Carbohydrate-binding properties of a novel sialic acid binding site on Siglec-9
		9:30～9:40	3	Yoko Tanaka	Psychiatry	Nagoya University Graduate School of Medicine	Relationship between driving and gaze indices using a driving simulator
		9:40～9:50	4	Katsunori Yogo	Medical Quantum Science	Nagoya University Graduate School of Medicine (Health Sciences)	Radiosensitization effect of gold nanoparticles on plasmid DNA damage induced by therapeutic MV X-rays
		9:50～10:00	5	Hiroto Ito	Neuroscience II	Nagoya University Research Institute of Environmental Medicine (RIEM)	Deficiency of orexin signaling during sleep is involved in abnormal REM sleep architecture in narcolepsy
		10:00～10:10	6	Dong Yutao	Neuropsychopharmacology and Hospital Pharmacy	Nagoya University Graduate School of Medicine	Dynamic changes and functions of orexin neurons activities in motivative behavior
		10:10～10:20	7	Paniz Farshadyeganeh	Neurogenetics	Nagoya University Graduate School of Medicine	Elucidation of the functional significance of skeletal muscle-specific splicing variant of glucosamine-fructose-6-phosphate aminotransferase isomerizing 1 (GFPT1)
	Room 2	9:10～9:20	1	Ting Wang	Neuroscience and Pathobiology	Nagoya University Research Institute of Environmental Medicine (RIEM)	Beneficial effects of Dimethyl Fumarate on the neuroinflammation in Alzheimer's disease mice
		9:20～9:30	2	Kaichi Yoshizaki	Disease Model	Aichi Developmental Disability Center Institute for Developmental Research	Voluntary exercise of C57BL/6J male mice was enhanced in the presence of both conspecific C57BL/6J and heterospecific BALB/cCrSlc male mice.
		9:30～9:40	3	Norihiko Yokoi	Membrane Physiology	National Institute for Physiological Sciences (NIPS)	LGI1-ADAM22 levels to regulate seizure thresholds in mice
		9:40～9:50	4	Hiro Kohda	Molecular Medicine and Metabolism	Nagoya University Research Institute of Environmental Medicine (RIEM)	Molecular mechanism underlying cell death-triggered adipose tissue fibrosis during the development of obesity
		9:50～10:00	5	Miki Umeda	Virology	Nagoya University Graduate School of Medicine	Molecular mechanisms of HCoV-229E coronavirus entry
		10:00～10:10	6	Wenda Li	Mori Lab	Nagoya University Graduate School of Informatics	Spatially Variant Biases Considered Self-supervised Depth Estimation Based on Laparoscopic Videos
		10:10～10:20	7	Koyo Tsujikawa	Neurology	Nagoya University Graduate School of Medicine	Actin-binding protein filamin-A drives tau aggregation and contributes to progressive supranuclear palsy pathology

Session No/Time	Room No	Presentation Time/No		Name	Department or Division	Institute	Title
Session A 9:10–10:25	Room 3	9:10～9:20	1	Mika Takai	Hematology and Oncology	Nagoya University Graduate School of Medicine	Screening with in-vitro spheroids cultures identified the efficacy of ibrutinib for IVLBCL
		9:20～9:30	2	Yuya Hara	Virology	Nagoya University Graduate School of Medicine	Identification of BLRF2 as a tegument network hub via comprehensive analyses of intraviral Epstein-Barr virus protein-protein interactions
		9:30～9:40	3	Shohei Sakai	Neuroscience and Pathobiology	Nagoya University Research Institute of Environmental Medicine (RIEM)	TBK selectively eliminates pathogenic monomeric TDP-43 via humoral factors
		9:40～9:50	4	Rinako Tanaka	Neuropsychopharmacology and Hospital Pharmacy	Nagoya University Graduate School of Medicine	Effect of a Rho-kinase inhibitor, fasudil, on cognitive impairments induced by methamphetamine administration in mice carrying mutations of the Arhgap10 gene
		9:50～10:00	5	Yuji Suzuki	Molecular Biology	Nagoya University Graduate School of Medicine	Regulation of phosphorylation on a neuronal adaptor protein by enzyme-linked receptors for glycosaminoglycans
		10:00～10:10	6	Yujun Zhou	Bio-organic Chemistry	Gifu University Graduate School of Natural Science and Technology, iGCORE	Synthesis and Evaluation of (S)-5'-C-Aminopropyl and (S)-5'-C-Aminopropyl-2'-arabinofluoro-modified antisense oligonucleotides
		10:10～10:20	7	Yoshiyuki Kishimoto	Neurology	Nagoya University Graduate School of Medicine	A novel device to evaluate upper limb ataxia quantitatively
Session B 10:30–11:45	Room 1	10:30～10:40	1	Mai Horiuchi	Neuroscience and Pathobiology	Nagoya University Research Institute of Environmental Medicine (RIEM)	Sigma 1 receptor prevents ATAD3A dimerization to maintain normal mitochondrial function
		10:40～10:50	2	Takumi Kagawa	Occupational and Environmental Health	Nagoya University Graduate School of Medicine	Intranasal levels of lead as an exacerbation factor for allergic rhinitis in humans and mice
		10:50～11:00	3	Yusuke Yamaga	Hematology and Oncology	Nagoya University Graduate School of Medicine	The effects of Cancer-associated fibroblasts as components of the malignant lymphoma microenvironment to Anti-CD20 antibody therapy
		11:00～11:10	4	Yoshinori Oda	Structural Biology	Nagoya University Graduate School of Pharmaceutical Sciences	Structural basis of local anesthetics binding to voltage-gated sodium channels
		11:10～11:20	5	Mona Alhussein Aboalela	Cancer Immune Therapy Research Center	Nagoya University Graduate School of Medicine	Expression of CAR Targets on Solid Tumors by Armed Oncolytic virus has synergetic effect on CAR T cell therapy
		11:20～11:30	6	Yohei Tsukamoto	Molecular and Cellular Biology	Nagoya University Graduate School of Medicine	3'-Sialyllactose on Notch: Notch1 functions as a scaffold of O-linked, 3'-sialyllactosylated glycans
		11:30～11:40	7	Ayuka Murakami	Neurology	Nagoya University Graduate School of Medicine	Metabolome and transcriptome analysis on muscle of sporadic inclusion body myositis
	Room 2	10:30～10:40	1	Kazuhiro Kumagai	Immunology	Nagoya University Graduate School of Medicine	Tumor-specific glutamine metabolism inhibition may promote CD8+ TILs activation and enhance the efficacy of immunotherapy
		10:40～10:50	2	Kasumi Maekawa	Neuroscience and Pathobiology	Nagoya University Research Institute of Environmental Medicine (RIEM)	Testosterone regulates the neuroinflammation through glial androgen receptor in Alzheimer's disease mice

Session No/Time	Room No	Presentation Time/No		Name	Department or Division	Institute	Title
Session B 10:30–11:45	Room 2	10:50～11:00	3	Seita Tomida	Glyco-biochemistry	Gifu University Graduate School of Natural Science and Technology, iGCORE	Functions of FUT8 stem region
		11:00～11:10	4	Monami Kihara	Molecular Biotechnology	Nagoya University Graduate School of Bioagricultural Sciences	Acquisition of Anti-SARS-CoV-2 Spike Human Monoclonal Antibody from Single B Cells of COVID-19 Infected Patients Using Cell-free Protein Synthesis System
		11:10～11:20	5	Masataka Kusano	Molecular Microbiology	Nagoya University Graduate School of Pharmaceutical Sciences	Analysis of bst1+ that regulates lifespan in fission yeast
		11:20～11:30	6	Nawarat Rattanajearakul	Endocrinology and Metabolism	National Institute for Physiological Sciences (NIPS)	Role of NPY-CRH neural axis in the PVH in carbohydrate selection in mice
		11:30～11:40	7	Hiromi Tamada	Functional Anatomy and Neuroscience	Nagoya University Graduate School of Medicine	FIB/SEM analyses for mitochondrial in the axon initial segments (AIS) and microglial activation around AIS after nerve injury
	Room 3	10:30～10:40	1	Hirotake Misu	Endocrinology and Metabolism	National Institute for Physiological Sciences (NIPS)	Exercise-induced changes in the hypothalamic neural circuits controlling energy metabolism
		10:40～10:50	2	Shurui Chen	Immunology	Nagoya University Graduate School of Medicine	Comprehensive Analysis of Pathways Involved in Liposomal Gene Transfer
		10:50～11:00	3	Fumie Mitani	Cancer Cell Regulation	Aichi Cancer Center	Asteltoxin suppresses extaracellular vesicle secretion though AMPK/mTOR-mediated activation of lysosome function
		11:00～11:10	4	Takeru Shiina	Mori Lab	Nagoya University Graduate School of Informatics	Graphical Extraction of Intra-acinar Airways from Micro-CT Volumes of Resected Human Lungs
		11:10～11:20	5	Yudai Tamada	Preventive Medicine	Nagoya University Graduate School of Medicine	Secondhand aerosol exposure from heated tobacco products and its socioeconomic inequalities in Japan: The JASTIS study 2017-2020
		11:20～11:30	6	Kei Hashimoto	Neuroscience and Pathobiology	Nagoya University Research Institute of Environmental Medicine (RIEM)	A hydrophobic residue is critical for species-specific aggregation of canine SOD1 with E40K mutation in canine degenerative myelopathy
		11:30～11:40	7	He Zhang	Immunology	Nagoya University Graduate School of Medicine	A Novel Antibody Drug Conjugate Targeting CCR8+ Tumor-infiltrating Regulatory T Cells Induces a Strong Antitumor Immunity
Session C 11:50–13:15	Room 1	11:50～12:00	1	Yoshitaka Adachi	Hematology and Oncology	Nagoya University Graduate School of Medicine	Genome-wide CRISPR screen in human CAR-T cells identifies CUL5 as negative regulator of CAR-T cells effector function
		12:00～12:10	2	Yohei Sugimoto	Genome Dynamics	Nagoya University Research Institute of Environmental Medicine (RIEM)	Biochemical analysis of molecular mechanisms dealing with AP site-HMCES cross-link
		12:10～12:20	3	Yuki Aoyama	Molecular Cell Biology	Nagoya University Graduate School of Medicine	Elucidation of the pathogenesis of Alzheimer's disease focusing on the white matter function
		12:20～12:30	4	Emi Hibino	Structural Molecular Pharmacology	Nagoya University Graduate School of Pharmaceutical Sciences	Structure of glycyrrhizin binding to the scaffolding protein ZO1-PDZ1 domain of tight junctions and its function

Session No/Time	Room No	Presentation Time/No		Name	Department or Division	Institute	Title
Session C 11:50–13:15	Room 1	12:30～12:40	5	Shaochuan Zhang	Neurogenetics	Nagoya University Graduate School of Medicine	Characterization of compound heterozygous mutation derived from DOK7-related-CMS patient
		12:40～12:50	6	Kenji Sakakibara	Neurology	Nagoya University Graduate School of Medicine	AI-based live-cell-image analysis for spinal and bulbar muscular atrophy pathology
		12:50～13:00	7	Atefeh Joudaki	Neurogenetics	Nagoya University Graduate School of Medicine	Prediction of the Splicing Effects of Single-Nucleotide Variants (SNVs) at 1st nucleotide of an exon
	Room 2	11:50～12:00	1	Ritsuko Shimogawa	Neuroscience and Pathobiology	Nagoya University Research Institute of Environmental Medicine (RIEM)	Neuroinflammation in Toll-like receptor 7 agonist-induced mouse model for systemic lupus erythematosus
		12:00～12:10	2	Md. Kamal Uddin	Virology	Nagoya University Graduate School of Medicine	Epstein-Barr Virus BBLF1 is Involved in Efficient Virus Egress
		12:10～12:20	3	Masahiro Nishimura	Creative Physical Therapy	Nagoya University Graduate School of of Medicine (Health Sciences)	Analysis of Dynamic Postural Control Related to Trunk-Lower Extremity Coordination on Gait Initiation
		12:20～12:30	4	Masahiro Kawatani	Neuroscience II	Nagoya University Research Institute of Environmental Medicine (RIEM)	Synaptic inputs from motor cortex do not have a role in motor-related membrane potential dynamics in mouse somatosensory cortex
		12:30～12:40	5	Ryosuke Ichihara	Tumor Pathology	Nagoya University Graduate School of Medicine	Matrix remodeling-associated protein 8 is a marker of a subset of cancer-associated fibroblasts in pancreatic cancer
		12:40～12:50	6	Bushra Samira	Neurogenetics	Nagoya University Graduate School of Medicine	The downregulation of PTBP1 promotes alternative splicing of AGRN mRNA essential for AChR clustering
		12:50～13:00	7	Akihiro Fukushima	Integrative Physiology	Nagoya University Graduate School of Medicine	A central oxytocin neural pathway that regulates metabolism
		13:00～13:10	8	Tomoki Hirunagi	Neurology	Nagoya University Graduate School of Medicine	Exercise-induced Ampk activation ameliorates polyglutamine-mediated neuromuscular degeneration in SBMA mice
	Room 3	11:50～12:00	1	Yuko Tashima	Molecular and Cellular Biology	Nagoya University Graduate School of Medicine	Analysis of mechanism to control the expression of NOTCH receptors by detecting abnormal O-glycosylation
		12:00～12:10	2	Midori Shibushita	Molecular Cell Biology	Nagoya University Graduate School of Medicine	Visualizing neuronal circuit activity underling sensory abnormalities of ASD
		12:10～12:20	3	Yutaro Nagasawa	Center for Brain Research	National Institute for Physiological Sciences (NIPS)	Exploring RhoGEFs involved in Cdc42 activation in excitatory synapses
		12:20～12:30	4	Takahiro Nakagawa	Animal Cell Function	Nagoya University Graduate School of Bioagricultural Sciences, iGCORE	Effects of sialic acid synthesis and degradation deficiency on medaka development
		12:30～12:40	5	Zhiwen Wu	Immune Response	Aichi Cancer Center	CD83 marks progenitor exhausted T cell population
		12:40～12:50	6	Shin-ichiro Horigane	Neuroscience I	Nagoya University Research Institute of Environmental Medicine (RIEM)	Calcium transients control a morphogenetic cycle underlying neuronal migratory movement
		12:50～13:00	7	Kaori Fujimaki	Immunology	Nagoya University Graduate School of Medicine	Elucidation of the mechanism of reduced ICB treatment efficacy in advanced-stage cancer

発表規定

1 口頭発表

① スライドは英語で表記して下さい。

② 1ページ目には必ず氏名、講座名等を英語で記載してください。

③ スライドのサイズ、枚数の指定はありません。

④ 持ち時間約7分とし、英語でご発表下さい（質疑応答は3分）。

⑤ 当日までに接続テストを行って下さい。

⑥ 発表者は10分程度の余裕を持って待機して下さい。

⑦ 時間厳守でご協力お願いいたします。

2 注意事項

Web開催ですので、ポスターや発表内容のダウンロードや写真撮影は厳禁とご理解ください。

特別講演抄録

Special Lecture

The identification of ILC2 has changed the concept of type 2 immune diseases

Speaker Kazuyo Moro

Affiliation Professor, Laboratory for Innate Immune Systems, Department of Microbiology and Immunology, Graduate School of Medicine, Osaka University
Laboratory for Innate Immune Systems, RIKEN Center for Integrative Medical Sciences (IMS)

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Group 2 innate lymphoid cells (ILC2s), which we identified in 2010, play an important role in type 2 immune system such as allergies, parasitic infections, and fibrosis. ILC2 are tissue-resident cells, and derived from common lymphoid progenitor, similar to other lymphocytes such as T cells and B cells. While T cells are activated by antigen, ILC2s are activated by cytokines, lipids, and hormones, and produce variety of type 2 cytokines. IL-5 and Eotaxin production from ILC2s induces eosinophilia and production of IL-13 induces secretion of mucin as well as airway hyperreactivity. GM-CSF from ILC2s involves in bone homeostasis, and IL-4 induces unique IgE production from B1 cells and increases allergic sensitivity. Over the past ten years, many research groups have joined this research field and identified new immune responses that are regulated by ILC2s. In particular, the importance of ILC2s in allergic diseases has received a fair amount of attention and new evidence indicates that allergic disorders occur not only from allergen-specific pathways but are also induced by allergen non-specific pathways due to ILC2 activation. Since it has become clear that ILC2s cause various type 2 immune diseases, research to suppress ILC2s and development of drugs targeting ILC2s have been actively conducted. In this talk, I would like to introduce the latest research on ILC2 and also talk about how we identified ILC2s.

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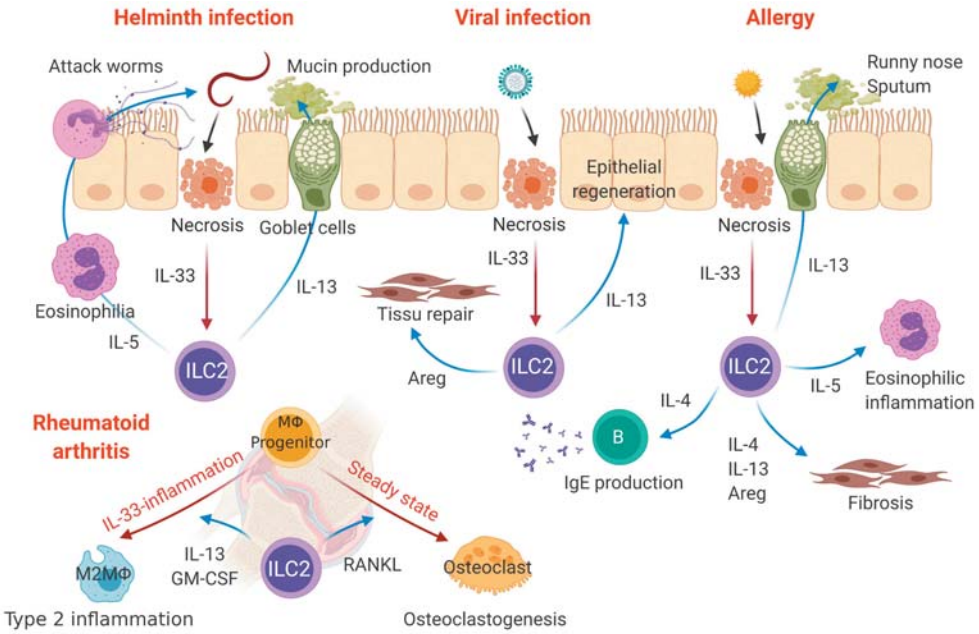

医学奨励賞　受賞講演抄録

Splicing regulation of large exons secures phase-separation of transcription factors in vertebrates

Speaker Toshihiko Kawachi

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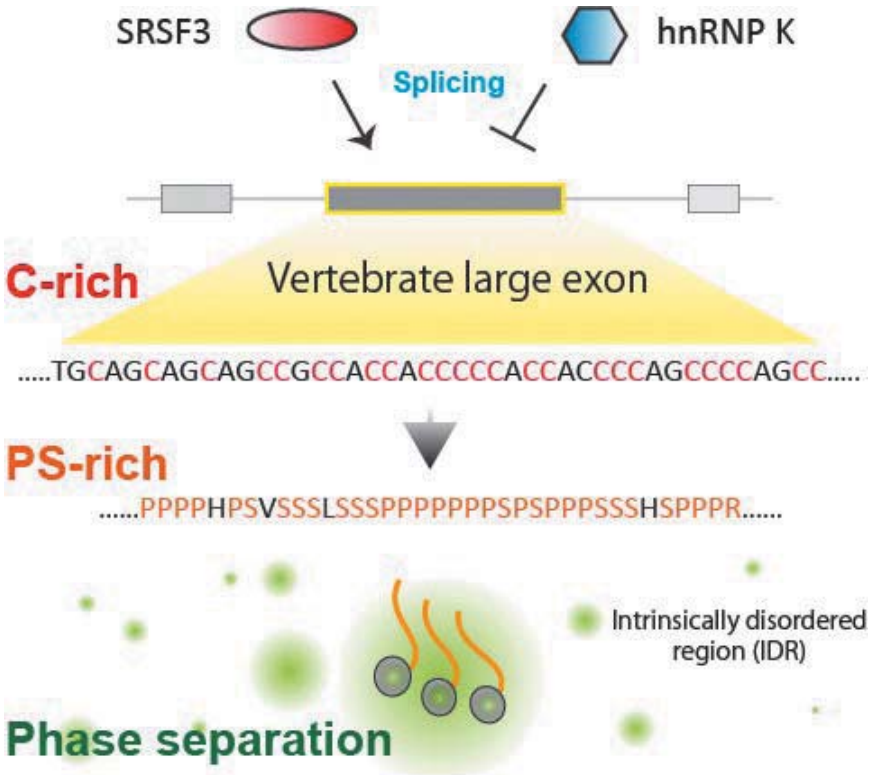
Large exons cannot be readily recognized by the spliceosome. Nevertheless, many large exons are evolutionarily conserved and constitutively spliced. Furthermore, the proteomic significance of large exons remains elusive. In this study, we identified a set of ~3,000 SRSF3-dependent large constitutive exons (S3-LCEs). The enriched C-nucleotides in S3-LCEs recruit two splicing factors, hnRNP K and SRSF3. hnRNP K induces the splicing suppression of S3-LCEs, which is mitigated by SRSF3 to achieve constitutive splicing of S3-LCEs. SRSF3 depletion deletes intrinsically disordered regions (IDRs) of transcription factors by skipping S3-LCEs and disrupts their phase-separated assemblies. Enrichment of C-nucleotides in large exons to code for proline and serine in intrinsically disordered regions of transcription factors was evolutionarily acquired in vertebrates. Layered splicing regulation by hnRNP K and SRSF3 secures their proper phase separation of transcription factors in vertebrates.

References

Toshihiko Kawachi*, Akio Masuda* et.al. Regulated splicing of large exons is linked to phase separation of vertebrate transcription factors. The EMBO Journal, 40:e107485 (2021).

*These authors contributed equally.



CD4+ T cells are essential for the development of destructive thyroiditis induced by anti–PD-1 antibody in thyroglobulin-immunized mice

Speaker Yoshinori Yasuda

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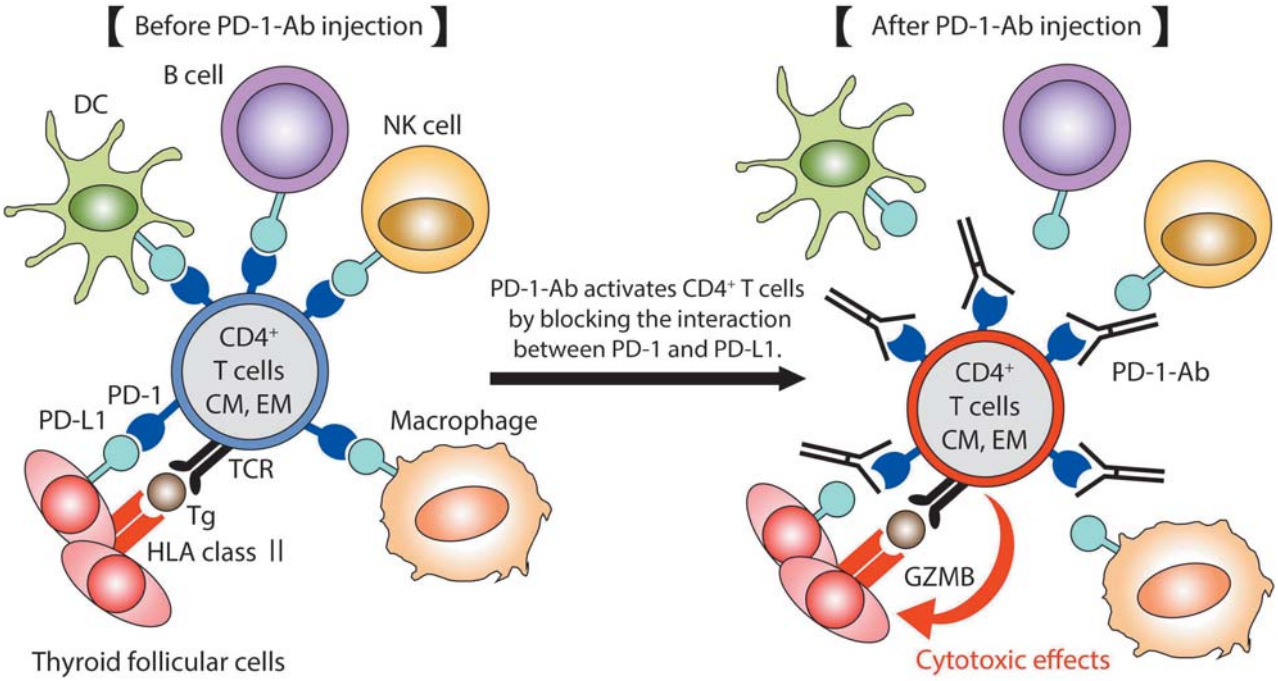
Immune-related adverse events induced by anti–programmed cell death–1 antibodies (PD-1-Ab), including destructive thyroiditis (thyroid-irAE), are thought to be caused by activated T cells. However, the T cell subsets that are directly responsible for damaging self-organs remain unclear. To clarify which T cell subsets are involved in the development of thyroid-irAE, a mouse model of thyroid-irAE was analyzed. PD-1-Ab administration 2.5 months after immunization with thyroglobulin caused destructive thyroiditis. Thyroiditis was completely prevented by previous depletion of $CD4^+$ T cells and partially prevented by depleting $CD8^+$ T cells. The frequencies of central and effector memory $CD4^+$ T cell subsets and the secretion of interferon-γ after stimulation with thyroglobulin were increased in the cervical lymph nodes of mice with thyroid-irAE compared with controls. Histopathological analysis revealed infiltration of $CD4^+$ T cells expressing granzyme B in thyroid glands and major histocompatibility complex class II expression on thyrocytes in mice with thyroid-irAE. Adoptive transfer of $CD4^+$ T cells from cervical lymph nodes in mice with thyroid-irAE caused destruction of thyroid follicular architecture in the irradiated recipient mice. Flow cytometric analyses showed that the frequencies of central and effector memory $CD4^+$ T cells expressing the cytotoxic marker CD27 were higher in peripheral blood mononuclear cells collected from patients with thyroid-irAE induced by PD-1-Ab versus those without. These data suggest a critical role for cytotoxic memory $CD4^+$ T cells activated by PD-1-Ab in the pathogenesis of thyroid-irAE.



Neutrophil/lymphocyte ratio as a predictor of lymph node metastasis in extramammary Paget's disease

Speaker Aoi Ebata

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To prevent further development of extramammary Paget's disease (EMPD), it is critical to detect lymph node metastasis at an early stage. Therefore, biomarkers that predict the risk of lymph node metastasis are required. In the present retrospective study, we evaluated the potential of neutrophil-to-lymphocyte ratio (NLR) in peripheral blood samples as a biomarker for the risk of lymph node metastasis in EMPD. This study involved 137 EMPD patients who underwent sentinel lymph node biopsy (SLNB) at our hospital from March 2003 to March 2020. We analyzed the correlations between NLR or SLNB positivity and clinical features/ laboratory findings. Receiver-operator curves were constructed using the DeLong model and the NLR cutoff value was defined as 3.0. The high NLR group had 30 patients whose NLRs exceeded 3 and the low NLR group had 107 patients whose NLRs were no more than 3, and 23% and 8% each of them showed sentinel lymph node metastasis (SLNM).
The rate of SLNM was significantly higher in the high NLR group. The odds ratio of SLNM for patients with NLR greater than 3 was 3.311. Then, we classified the patients into 2 groups by SLNB results. Sixteen patients (11.7%) showed SLNM. In the logistic regression analysis of 5 variables in 137 patients (Table II) and six variables including carcinoembryonic antigen in 55 patients for SLNB positivity, only NLR was found to be significantly associated with SLNB positivity. Here we reported NLR might be a significant predictor for LNM in EMPD patients.

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Figure. Extramammary Paget's Disease occurred in the inguinal region

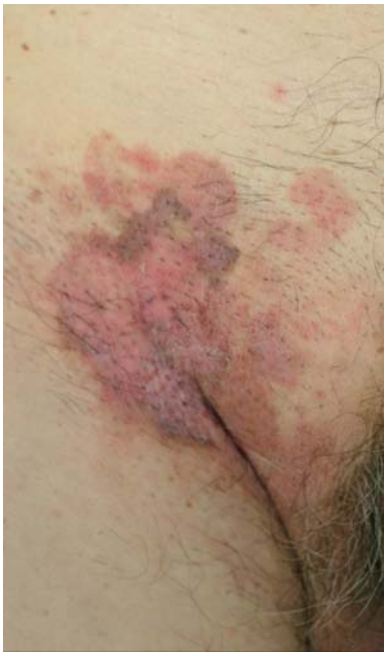

Table II. Characteristics of extramammary Paget disease patients with versus without sentinel LN metastasis, and a logistic regression analysis for SLNB positivity in 137 patients with respect to the 5 variables of age, sex, tumor depth, tumor site, and serum NLR level

	Patients (%)			Multivariate analysis	
Characteristic	Positive SLNs	Negative SLNs	*P* value	Odds (95% CI)	*P* value
Patients (%)	16 (11.7)	121 (88.3)			
Age of diagnosis			.612		
Median (IQR)	71.5 (64-75.25)	72.0 (66-79)		1.01 (0.93-1.10)	.830
Min-max	58-89	49-89			
Sex			.203		
Male	14 (87.5)	88 (72.7)		1.43 (0.20-10.6)	.723
Female	2 (12.5)	33 (27.3)		1.00	
Site of primary lesion			.920		
Axillae	0 (0)	0 (0)		1.00	
Genitalia	15 (93.8)	111 (91.7)			
Lower abdomen	0 (0)	1 (0.8)			
Perianal region	1 (6.3)	9 (7.4)		0.58 (0.05-6.37)	.652
Peripheral blood cell count, median (IQR)					
WBC/μL	5800 (4300-6625)	6200 (5300-7200)	.294		
ANC/μL	3850 (2825-4600)	3800 (3100-4600)	.843		
ALC/μL	1250 (1075-2150)	1700 (1400-2200)	.135		
Invasive level (%)					
IE	0 (0)	44 (36.4)	.000000185*	1.00	
MDI	4 (25)	61 (50.4)		1.95×10^{7} (0.00-Inf)	.991
DI	12 (75)	16 (13.2)		3.08×10^{8} (0.00-Inf)	.990
Serum concentration					
LDH U/L			.548		
≦222	14 (87.5)	96 (79.3)			
>222	2 (12.5)	22 (18.2)			
unknown	0 (0.0)	3 (2.5)			
Fibrinogen mg/dL			.116		
<200	1 (6.3)	1 (0.8)			
≧200, <400	13 (81.3)	96 (79.3)			
≧400	1 (6.3)	23 (19.0)			
Unknown	1 (6.3)	1 (0.8)			
CEA ng/mL			.464		
≦5	10 (62.5)	49 (40.5)			
>5	4 (25.0)	12 (9.9)			
Unknown	2 (12.5)	60 (49.6)			
NLR			.0245*		
≦3	9 (56.3)	98 (81.0)		1.00	
>3	7 (43.8)	23 (19.0)		6.48 (1.46-28.8)	.0141*
Odds ratio	3.311 (95% CI 1.117 to 9.804)		.038*		

ALC, Absolute lymphocyte count; *ANC*, absolute neutrophil count; *CEA*, carcinoembryonic antigen; *DI*, deep invasion into/beyond the reticular dermis; *IE*, intraepidermis; *LDH*, lactate dehydrogenase; *MDI*, microinvasion into the papillary dermis; *SLN*, sentinel lymph node; *WBC*, white blood cell count.
*Statistically significant ($P < .05$).

Embryonal erythropoiesis and aging exploit ferroptosis/Lysosomal nitric oxide determines transition from autophagy to ferroptosis after exposure to plasma-activated Ringer's lactate

Speaker Hao Zheng

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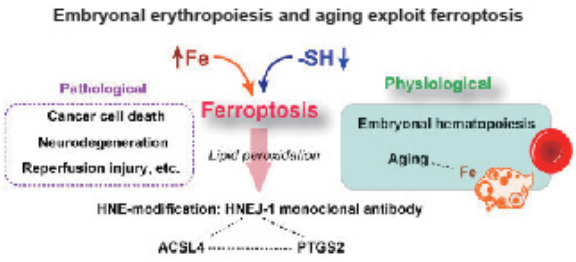
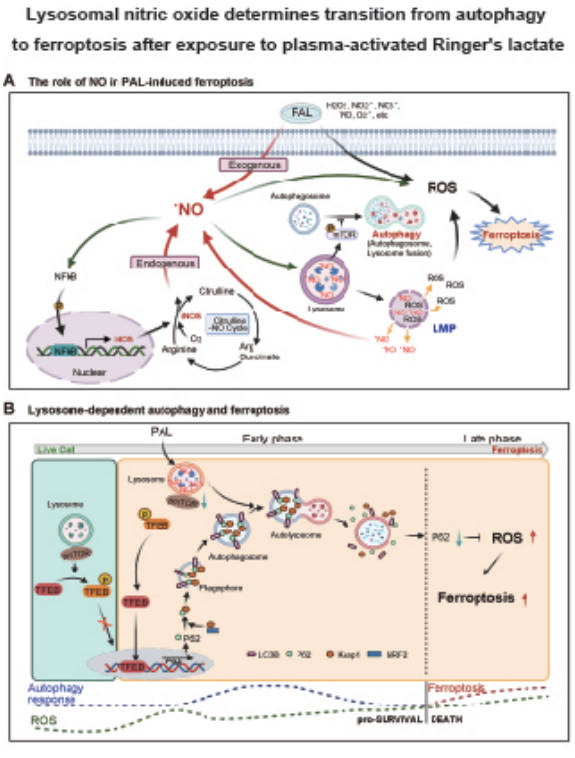
Ferroptosis is a form of regulated cell necrosis, as a consequence of Fe(II)-dependent lipid peroxidation. Here, we show that 4-hydroxy-2-nonenal (HNE)-modified proteins detected by a HNEJ-1 mouse monoclonal antibody is a robust immunohistochemical technology to locate ferroptosis in tissues in combination with morphological nuclear information, based on various models of ferroptosis. We observed a significant age-dependent increase in ferroptosis in various organs, which was accompanied by iron accumulation. Epidermal ferroptosis in ageing SAMP8 mice was significantly promoted by high-fat or carbohydrate-restricted diets. During embryogenesis of Fischer-344 rats, we found ferroptosis in nucleated erythrocytes at E13.5, which disappeared in enucleated erythrocytes at E18.5. Administration of a ferroptosis inhibitor significantly delayed erythrocyte enucleation. Our results demonstrate the involvement of ferroptosis in physiological processes. Non-thermal plasma (NTP), an engineered technology to generate reactive species, induces ferroptosis and/or apoptosis specifically in various-type cancer cells. NTP-activated Ringer's lactate (PAL) is another modality for cancer therapy at preclinical stage. Here we found that PAL induces selective ferroptosis of malignant mesothelioma cells, where metabolome screening identified upregulated citrulline-nitric oxide (.NO) cycle as a PAL target. .NO probe detected biphasic peaks transiently at PAL exposure with time-dependent increase, which was responsible for inducible .NO synthase (iNOS) overexpression. .NO and lipid peroxidation occupied lysosomes as a major compartment. Not only ferrostatin-1 but inhibitors for .NO and/or iNOS could suppress this ferroptosis. PAL-induced ferroptosis accompanied autophagic process in the early phase transforming into the later phase with boosted lipid peroxidation. Therefore, .NO-mediated lysosomal impairment is central in PAL-induced ferroptosis.





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一般講演抄録

Rejuvenation of aged T cells for effective adoptive cancer immunotherapy

Speaker Yuki Kagoya

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Division of Cellular Oncology, Department of Cancer Diagnostics and Therapeutics, Nagoya University Graduate School of Medicine

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Adoptive cancer immunotherapy, in which antitumor T cells are prepared *in vitro* and infused back into the patient, is a promising therapeutic option for patients with advanced cancer. Especially, CD19-directed chimeric antigen receptor (CAR)-engineered T cells have shown unprecedented efficacy against relapsed or refractory B cell malignancies. However, adoptive immunotherapy against sold tumors has yet to be successful in most of the patients.

Antitumor T cells undergo terminal differentiation upon repeated antigen exposure in the tumor microenvironment, resulting in the loss of long-term survival capacity. These dysfunctional T cells possess epigenetic and transcriptional signature distinct from conventional naive and memory T cells. We hypothesized that modulation of key epigenetic/transcriptional regulators associated with T cell differentiation may help to enhance long-lived potential of T cells. We have identified that genetic ablation of PRDM1, which encodes Blimp1, efficiently supports the maintenance of an early memory phenotype as well as cytokine polyfunctionality in repeatedly stimulated CAR-T cells. PRDM1-knockout CAR-T cells displayed superior *in vivo* persistence and long-term antitumor response compared to the control CAR-T cells in multiple adoptive immunotherapy models. Mechanistically, PRDM1 knockout globally altered epigenetic and transcriptomic profiles of CAR-T cells towards those of early memory T cells. Intriguingly, PRDM1 knockout was also effective for tumor-infiltrating lymphocytes (TIL) with a terminally differentiated phenotype to partially restore memory T cell properties. In this talk, I will summarize these findings and discuss future directions to further improve antitumor T cell functions.

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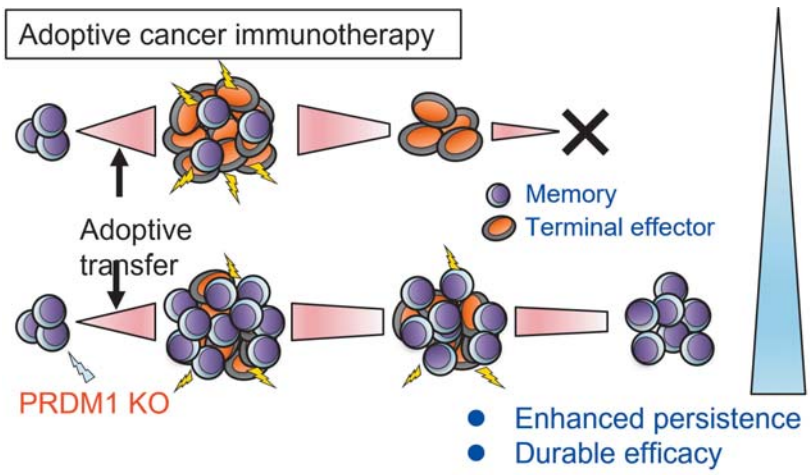

Development of sialic acid chemistry and its application to glycan syntheses

Speaker Naoko Komura

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Sialic acid is biologically and therapeutically the most important sugar residue in glycoproteins and glycolipids. However, chemical synthesis of sialic acid–containing glycans remains very challenging mainly due to the difficulty in the formation of α-glycoside linkages of sialic acids.

To overcome the difficulty of chemical sialylation, we have developed a fully α-selective sialylation method using a macro-bicyclic sialic acid donor, wherein the C1 and C5 positions were tethered with an alkyl linker.[1)] In the sialylation reactions of the macro-bicyclic sialic acid donor, the macrocyclic tether moiety sterically blocks the β-face, thereby ensuring completely α-selective sialoside formations. We have demonstrated that the sialylation method enabled the formation of O-glycosides and C-glycosides in excellent yields in a fully stereoselective manner. Importantly, the bicyclic sialoside moiety could be converted into the C5-amino derivative via chemoselective cleavage of the 2,2-dichololoethoxycarbamoyl moiety of the tether, which enabled C5-diversification after sialylations. Taking these advantages, we have successfully synthesized C5-diversified sialic acid–containing glycolipids (gangliosides).[1, 2)] Furthermore, the sialylation method has been successfully applied for the synthesis of sialic acid oligomer.

In conclusion, we have developed a reliable and powerful method for the stereoselective synthesis of diverse sialic acid–containing compounds.

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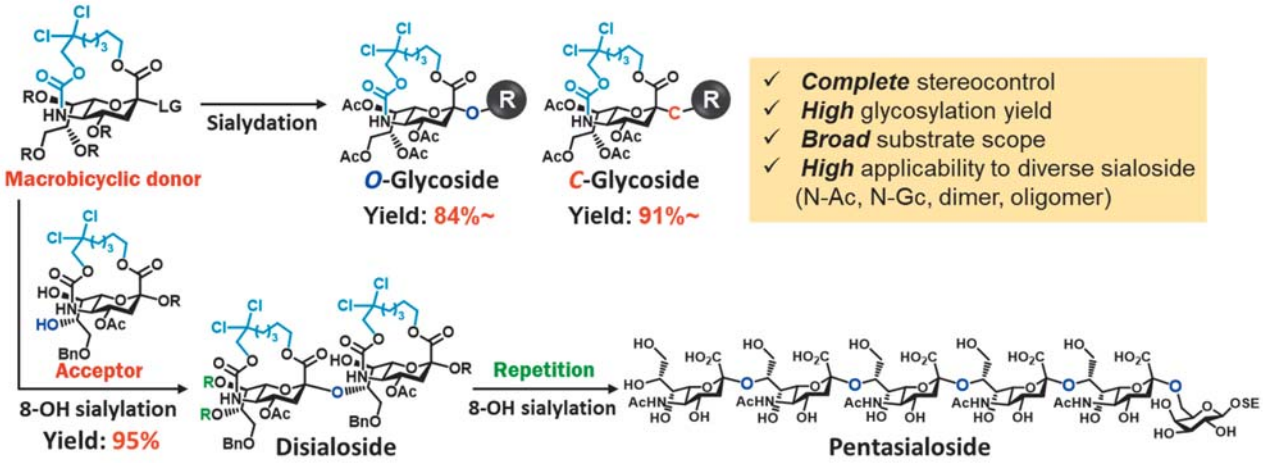

Properties of 2'-5'-linked oligonucleotides with a conformationally locked sugar conformation in an N-form.

Speaker Masashi Sadaike

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Recently, nucleic acid medicine has been attracting attention as a new pharmaceutical modality. We thought that 2'-5'-linked nucleic acids, which are relatively resistant to exonuclease that digest 3'-5'-linked nucleic acids such as DNA/RNA, would be a promising drug discovery modality. However, there are few examples of research on 2'-5'-linked nucleic acids, and their properties are not well understood. In particular, 2'-5'-linked nucleic acids with N-type sugar conformation have not been found in nature, and their properties are not known at all, so we have been conducting research to elucidate their properties.

So far, we have designed and synthesized a 2'-5'-linked artificial nucleoside with an N-type sugar puckering, and have successfully introduced it into 3'-5'-linked DNA sequences. Therefore, in this study, we planned to introduce the 2'-5'-linked artificial nucleoside into a 2'-5'-sequence (3'-DNA) and elucidate their properties.

The introduction of the artificial nucleoside with an N-type sugar puckering into 3'-DNA was achieved by using the corresponding phosphoramidite blocks with a levulinyl group as the protecting group of the 5'-hydroxy group. A single base modification with the artificial nucleoside of a 3'-DNA sequence was found to slightly improve the thermal stability of the duplex structure with DNA/RNA. It is noteworthy that this modification could afford a very high resistance to enzymatic digestion, comparable to the phosphorothioate modification. In addition, RNA digestion was induced by RNaseH-dependent activity even with a single base modification to the DNA sequence. These results suggest that this modifier has a potential as a nucleic acid drug discovery modality, including antisense technology, and I would like to use this knowledge to develop better nucleic acid materials.

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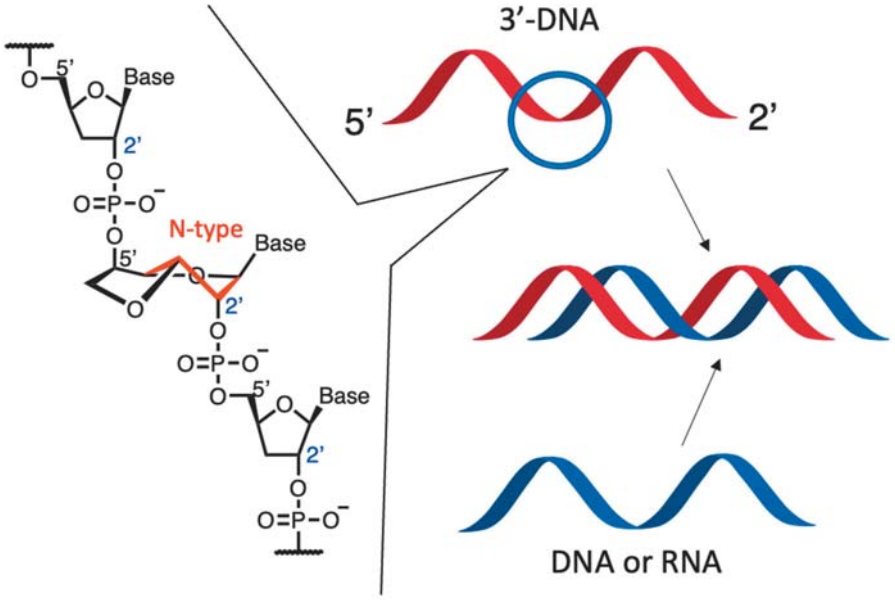

口頭発表抄録

Session A Room 1-1

Association between germline pathogenic variants and breast cancer risk in Japanese women: the HERPACC study.

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Approximately 5-10% of breast cancers are hereditary, caused by germline pathogenic variants (GPVs) in breast cancer predisposition genes. Most studies of the prevalence of GPVs and risk of breast cancer for each gene based on cases and non-cancer controls have been conducted in Western countries, and little information from Japanese populations is available. Furthermore, no studies considered confounding by established environmental factors and single nucleotide polymorphisms (SNPs) together in GPV evaluation. To evaluate the association between GPVs in nine established breast cancer predisposition genes including BRCA1/2 and breast cancer risk in Japanese women comprehensively, we conducted a case-control study within the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (629 cases and 1153 controls). The associations between GPVs and the risk of breast cancer were assessed by odds ratios (OR) and 95% confidence intervals (CI) using logistic regression models adjusted for potential confounders. A total of 25 GPVs were detected among all cases (4.0%: 95%CI:2.6-5.9), whereas four individuals carried GPVs in all controls (0.4%). OR for breast cancer by all GPVs including BRCA1/2 was 12.2 (4.4-34.0, P = 1.74E-06). In conclusion, GPVs increase the risk of breast cancer in Japanese women regardless of environmental factors and SNPs.

Session A Room 1-2

Carbohydrate-binding properties of a novel sialic acid binding site on Siglec-9

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Sialic acid-binding immunoglobulin-like lectins (Siglecs) are predominantly expressed on immune cells and recognize sialic acid-terminated glycolipids and glycoproteins. Recognition of glycans by Siglecs are complex and precise binding properties for Siglecs have not been fully elucidated. Previously, we reported a novel sialic acid-binding region (site2) in addition to the well-known primary ligand-binding region (site1) on Siglec-7 based on in silico analysis and site-directed mutagenesis1,2. Here, we report that Siglec-9, which has 74 % sequence identity with Siglec-7, also has site2 and possibly uses two different binding sites depending on the glycan structure of the epitope. Siglec-9 is thought to suppress inflammatory responses by binding to ligands, and it is important to clarify the mechanism, including ligand binding, for its medical application. This report gives us new insights into the ligand-binding properties of Siglec.

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Session A Room 1-3

Relationship between driving and gaze indices using a driving simulator

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The urgent solution to prevent traffic accidents requires understanding drivers' driving skill problems causing the accidents. Furthermore, as drivers must visually recognize pedestrians and surrounding vehicles for driving safety, it is necessary to consider the driver's gaze characteristics. Thus, we measured healthy subjects' driving performance by a driving simulator and gaze to clarify their relationship. Three driving tasks (road-tracking, car-following, and harsh-braking) were conducted, and three gaze tasks (free-viewing, fixation, and pursuit) were performed in 36 healthy subjects. This study was approved by the Nagoya University Hospital Bioethics Review Committee, and written informed consent was obtained from all study participants. As a result, the correlation analysis between driving and gaze showed that the index of the standard deviation of lateral position in the road-tracking task was related to the number of fixations, the number of saccades, and the total distance of gaze in the free-viewing task of the gaze analysis, and it was also significantly correlated with the vertical direction and speed gain and saccade-related indicators in the smooth pursuit task. These results indicate that gaze function may predict driving ability.

Session A Room 1-4

Radiosensitization effect of gold nanoparticles on plasmid DNA damage induced by therapeutic MV X-rays

【Presenter】 Katsunori Yogo
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Gold nanoparticles (AuNPs) can be used with megavolt (MV) X-rays to exert radiosensitization effects, as demonstrated in cell survival assays and mice treatments. However, the detailed mechanisms are unclear; in addition to physical dose enhancement, several chemical and biological processes have been proposed. Reducing the AuNP concentration while providing sufficient enhancement is necessary for the clinical application of AuNPs. Here, we used positively charged (+) AuNPs to determine the radiosensitization effects of AuNPs combined with MV X-rays on DNA damage in vitro (1). We examined the effect of low concentrations of AuNPs on DNA damage and reactive oxygen species (ROS) generation. DNA damage was promoted by 1.4-nm +AuNP with dose enhancement factors of 1.4 ± 0.2 for single-stranded breaks and 1.2 ± 0.1 for double-stranded breaks. +AuNPs combined with MV X-rays induced radiosensitization at the DNA level, indicating that the effects were physical and/or chemical rather than biological. Although -AuNPs induced similar ROS levels, they did not cause considerable DNA damage. Thus, dose enhancement by low concentrations of +AuNPs may have occurred by increasing the local +AuNP concentration around DNA or via DNA binding. Further studies using cancer cell with +AuNPs should be performed to expand their applications for radiation therapy in MV ranges.

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Session A Room 1-5

Deficiency of orexin signaling during sleep is involved in abnormal REM sleep architecture in narcolepsy

【Presenter】 Hiroto Ito
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【Affiliation】 Nagoya University Research Institute of Environmental Medicine (RIEM)
【Favorite Technique】 In vivo Ca imaging (nVista, fiberphotometry), in vivo optogenetic experiment, EEG EMG measurement, plasmid construction, AAV production. injection surgery.
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Narcolepsy (Type I) is caused by the loss of orexin neurons (Orx-neurons) considered as "wake-active and wake-promoting neurons". However, the neural mechanism is still unknown through which the loss of orexin signaling cause the characteristic symptoms of narcolepsy; abnormal rapid eye movement (REM) sleep architecture, such as cataplexy. Here, we elucidated the activity dynamics of orexin neurons during sleep regulate REM sleep architecture and suppress cataplexy. Orexin neurons were highly active during wake, showed intermittent synchronous activity during non-REM (NREM) sleep, and became silent during the transition from NREM to REM sleep. During REM sleep, there was weak activity by a subpopulation of orexin neurons. Interestingly, orexin neurons that lacked orexin peptides were less active in REM sleep. Optogenetic inhibition of orexin neurons promoted NREM-REM sleep transitions in NREM sleep. REM sleep dependent inhibition of orexin neurons increased subsequent REM sleep. Interestingly, cataplexy increased subsequent to REM sleep-dependent inhibition of orexin neurons that lacked orexin peptides. Taken together, deficiency of orexin signaling during sleep is directly involved in the abnormal REM sleep architecture of narcolepsy.

Session A Room 1-6

Dynamic changes and functions of orexin neurons activities in motivative behavior

【Presenter】 Dong Yutao
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Orexin neurons in the hypothalamus regulate physiological functions, including energy homeostasis and wakefulness, and are also related to motivation and decision making. In this study, we investigated whether the activities of orexin neurons are related to motivated behavior under the fixed ratio (FR) schedule of a touchscreen-based operant task using fiber photometry. We found that chemogenetic activation of orexin neurons induced an increase of breaking point in a progressive ratio test. Under FR5 conditions in which rats were able to obtain a food pellet by touching the screen consecutively five times, we also found the orexin activities were increased after the fifth screen touch (after which food would be delivered). The activity peaked before rats obtained reward, and then decreased after food intake. In addition, under FR20 conditions the orexin activities were higher than those in FR5 conditions. This suggested that orexin activities were depended on degree of effort to obtain a reward. Together, these observations indicate that the orexin activities change in motivative behaviors, and that orexin neurons may be involved in reward prediction and expectation in taking behaviors.

Session A Room 1-7

Elucidation of the functional significance of skeletal muscle-specific splicing variant of glucosamine-fructose-6-phosphate aminotransferase isomerizing 1 (GFPT1)

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Glutamine fructose-6-phosphate transferase 1 (GFPT1) is a rate-limiting enzyme of the hexosamine biosynthesis pathway (HBP) to control the formation of hexosamine products and the availability of precursors for N- and O-linked glycosylation of proteins and lipid. A novel GFPT1 splice variant (GFPT1-L), containing a 54-bp or 48-bp insertion of exon 9 in human and mouse, respectively, is predominantly expressed in the skeletal muscle and weakly expressed in the heart. The addition of 18 or 16 amino acids at position 229 of the protein causes less enzymatic activity for GFPT1-L. However, why skeletal muscles highly express this splicing variant is not well understood. Here, we generated a knock-out mouse model for Gfpt1 exon-9 to investigate the role of the GFPT1-L variant in skeletal muscle.

Session A Room 2-1

Beneficial effects of Dimethyl Fumarate on the neuroinflammation in Alzheimer's disease mice

【Presenter】 Ting Wang
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Neuroinflammation, mediated by the activation of glial cells and subsequent production of proinflammatory molecules, plays a significant role in the pathologies of Alzheimer's disease (AD). Previous studies reported nuclear factor erythroid 2-related factor 2 (Nfe2l2 or Nrf2) attenuated inflammation in neurodegenerative diseases, however, the detailed mechanism remains unclear. Here, we identified deregulation of the Nrf2-regulated genes and neuroinflammation in astrocytes isolated from cortices of AppNL-G-F/NL-G-F (App-KI) mice by RNA sequencing. To elucidate the mechanism of Nrf2-mediated neuroprotection in AD, we examined the role of Nrf2 by using Dimethyl Fumarate (DMF), a clinically available drug to activate Nrf2 pathway. We measured the mRNA expressions in Nrf2 pathway and activated (A1) astrocyte genes. DMF significantly decreased expressions of A1 genes such as H2-d, H2-t23 and Gbp2, and enhanced expressions of Nrf2 and its downstream genes in primary astrocytes. Moreover, chronic oral administration of DMF significantly ameliorated the cognitive impairment of App-KI mice. DMF-treated App-KI mice also showed significant decrease of H2-d and C3, and increase of Osgin1 expression in isolated astrocytes. DMF treatment also reduced amyloid-β deposition in the cortice of App-KI mice. These results suggest that DMF ameliorates neuroinflammation by suppressing reactive astrocytes in App-KI mice through activating Nrf2 pathway.

【References】

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Session A Room 2-2

Voluntary exercise of C57BL/6J male mice was enhanced in the presence of both conspecific C57BL/6J and heterospecific BALB/cCrSlc male mice.

【Presenter】 Kaichi Yoshizaki
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Social facilitation is a psychological phenomenon that an individual's performance improves in frequency and intensity due to mere presence of other individuals, and affects behaviors. We previously reported that voluntary exercise of more social C57BL/6J, but not less social BALB/cCrSlc male mice, was enhanced in the presence of conspecific observer mice, implicating functional deficiency in either or both of self-presentation and perception of others in BALB/cCrSlc male mice. To clarify which is the functional deficiency, we examined voluntary exercise in the presence of heterospecific observer male mice, and found that voluntary exercise of more social C57BL/6J male mice was enhanced in the presence of both conspecific C57BL/6J and heterospecific BALB/cCrSlc observer male mice. Diurnal variation analysis revealed that enhanced voluntary exercise by conspecific C57BL/6J observer male mice was observed during the dark period, while that by heterospecific BALB/cCrSlc observer male mice was observed during the light and dark periods. These results suggest that each conspecific C57BL/6J and heterospecific BALB/cCrSlc observer male mice affect social facilitation, that is, self-presentation of BALB/cCrSlc male mice is not disabled. In the future, we examine perception of others in less social BALB/cCrSlc male mice.

Session A Room 2-3

LGI1-ADAM22 levels to regulate seizure thresholds in mice

【Presenter】 Norihiko Yokoi
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【Favorite Technique】 Biochemical analysis of brain tissues to reveal and quantify physiological protein complexes
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What percentage of the protein function is required to prevent disease symptoms is a fundamental question in genetic disorders. Decreased transsynaptic LGI1-ADAM22 protein complexes, because of their mutations or autoantibodies, cause epilepsy and amnesia. However, it remains unclear how LGI1-ADAM22 levels are regulated and how much LGI1-ADAM22 function is required. Here, we found that ADAM22 is stoichiometrically phosphorylated in the mouse brain. In ADAM22 phosphorylation-deficient knock-in mice, the amounts of the ADAM22 and LGI1 proteins in the brain were decreased to about 40% and 55%, respectively, compared to that in the wild-type mouse brain without seizures. Phosphorylation-deficient ADAM22 abolished the phosphorylation-dependent interaction with 14-3-3 adaptor proteins, and subjected to AP2-mediated endocytosis for degradation. We demonstrated that quantitative dual phosphorylation of ADAM22 by protein kinase A (PKA) mediates high-affinity binding of ADAM22 to dimerized 14-3-3 and forskolin-induced PKA activation increases ADAM22 levels. Leveraging a series of ADAM22 and LGI1 hypomorphic mice, we found that ~50% of LGI1 and ~10% of ADAM22 levels are sufficient to prevent lethal epilepsy. Furthermore, ADAM22 function is required in excitatory and inhibitory neurons. These results suggest strategies to increase LGI1-ADAM22 complexes over the required levels by targeting PKA or 14-3-3 for epilepsy treatment.

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Session A Room 2-4

Molecular mechanism underlying cell death-triggered adipose tissue fibrosis during the development of obesity

【Presenter】 Hiro Kohda
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Obesity is considered as a state of chronic and low-grade inflammation. We have provided evidence on the molecular mechanisms of obesity-induced adipose tissue inflammation and adipose tissue dysfunction, especially focusing on the crosstalk between adipocytes and macrophages. We previously showed that expression of Macrophage-inducible C-type lectin (Mincle), a pathogen sensor for Mycobacterium tuberculosis, is induced in adipose tissue macrophages during the development of obesity. Mincle accelerates adipose tissue inflammation and fibrosis, thereby exacerbating ectopic lipid accumulation and insulin resistance in the liver (ref.1). However, how Mincle-expressing macrophages activate fibroblasts still remains to be elucidated. In this study, we performed single-cell RNA sequencing analysis of the stromal vascular fraction (SVF) in visceral adipose tissue from diet-induced obese mice to analyze the cell-cell interaction between Mincle-expressing macrophages and activated fibroblasts. We identified 11 macrophage and 7 fibroblast subclusters. Contrary to our expectation, there was no specific macrophage cluster, in which Mincle was exclusively expressed. Indeed, Mincle expression was increased in several distinct macrophage clusters during the development of obesity. We performed CellChat analysis, which allows easy exploration of the cell-cell communications, between Mincle-expressing macrophages and obesity-related fibroblasts. We are currently verifying the predicted interaction pathway in in vitro and in vivo experiments.

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Session A Room 2-5

Molecular mechanisms of HCoV-229E coronavirus entry

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【Favorite Technique】 Ultracentrifugal virus purification
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Coronaviruses are RNA viruses that cause respiratory infections in humans and infect cells via fusion with the host cell membrane or via endocytosis. However, the mechanistic details of this infection pathway are still unknown, especially those involved in viral uncoating. In this study, we try to analyse the molecular mechanisms of coronavirus entry into host cells using the coronavirus strain, HCoV-229E. Initially, we established a HCoV-229E purification method by infecting human hepatoma Huh-7 cells to obtain a high titre virus. Using the purified HCoV-229E virus, we synchronised viral infection to early endosomes via ammonium chloride treatment, and then chased endosome maturation by exchanging medium. As a result, this clarified that the virus taken up into the endosomes co-localised with the early endosome marker, EEA1, and VCP (p97). It is reported that VCP interacts with HDAC6, and has been established to be involved in ubiquitin metabolism. Therefore, these results may suggest that ubiquitin chains are involved in the uncoating step of HCoV-229E, similar to Influenza A virus (IAV) uncoating. However, the ubiquitin signal pattern of HCoV-229E is different to that of IAV, suggesting that the uncoating of HCoV-229E may use a new mechanism that differs from that of other RNA viruses.

Session A Room 2-6

Spatially Variant Biases Considered Self-supervised Depth Estimation Based on Laparoscopic Videos

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【Favorite Technique】 Depth estimation from laparoscopic images
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Depth estimation is an essential tool in obtaining depth information for robotic surgery and augmented reality technology in the current laparoscopic surgery robot system. Since there is a lack of ground-truth for depth values and laparoscope motions during operation, depth estimation networks have difficulties in predicting depth maps from laparoscopic images under the supervised strategy. It is challenging to generate the correct depth maps for the different environments from abdominal images. To tackle these problems, we propose a novel monocular self-supervised depth estimation network with sparse nest architecture. We design a non-local block to capture broader and deeper context features that can further enhance the scene-variant generalization capacity of the network for the differences in datasets. Moreover, we introduce an improved multi-mask feature in the loss function to tackle the classical occlusion problem based on the time-series information from stereo videos. We also use heteroscedastic aleatoric uncertainty to reduce the effect of noisy data for depth estimation. We compared our proposed method with other existing methods for different scenes in datasets. The experimental results show that the proposed model outperformed the state-of-the-art models qualitatively and quantitatively.

Session A Room 2-7

Actin-binding protein filamin-A drives tau aggregation and contributes to progressive supranuclear palsy pathology

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While amyloid-β lies upstream of tau pathology in Alzheimer's disease, key drivers for other tauopathies, including progressive supranuclear palsy (PSP), are largely unknown. Various tau mutations are known to facilitate tau aggregation, but how the nonmutated tau, which most cases with PSP share, increases its propensity to aggregate in neurons and glial cells has remained elusive. Here, we identified genetic variations and protein abundance of filamin-A in the PSP brains without tau mutations. We provided in vivo biochemical evidence that increased filamin-A levels enhance the phosphorylation and insolubility of tau through interacting actin filaments. Also, reduction of filamin-A corrected aberrant tau levels in the culture cells from PSP cases. Moreover, transgenic mice carrying human filamin-A recapitulated tau pathology in the neurons. Our data highlight that filamin-A promotes tau aggregation, providing a potential mechanism by which filamin-A contributes to PSP pathology.

Session A Room 3-1

Screening with in-vitro spheroids cultures identified the efficacy of ibrutinib for IVLBCL

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Intravascular large B-cell lymphoma (IVLBCL) is a rare disease form of malignant lymphoma characterized by the lack of lymphadenopathy and the selective proliferation of tumor cells within vessels of systemic organs. The limited number of tumor cells from diagnostic specimens hinders the elucidation of underlying biology of IVLBCL. Although recent prospective trial revealed that immunochemotherapy combined with central nervous system oriented therapy improves clinical outcomes of IVLBCL, a certain number of patients who develops the relapsed or refractory disease still exists, and no treatment has been established for these patients. To overcome intractable diseases, pre-clinical evaluations using appropriate systems in-vitro and in-vivo are indispensable. To address these issues, we developed an in-vitro spheroid culture system of IVLBCL tumor cells in addition to patient-derived xenograft (PDX) models. Using it, the screening of 49 FDA-approved compounds identified ibrutinib, Bruton's kinase inhibitor, as a potential therapeutic agent. The effect of ibrutinib was also validated in PDX model established from a patient who developed relapsed disease after the current active treatment and it showed significant anti-tumor activity. Our data demonstrates that spheroid culture can be a useful tool in understanding the biology of IVLBCL.

Session A Room 3-2

Identification of BLRF2 as a tegument network hub via comprehensive analyses of intraviral Epstein-Barr virus protein-protein interactions

【Presenter】 Yuya Hara
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【Favorite Technique】 Fluorescent immunostaining, FACS, WB, qPCR, virus titer measurement
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Protein-protein interactions (PPIs) are crucial for various biological processes. Epstein-Barr virus (EBV) proteins typically form complexes, regulating the replication and persistence of the viral genome in human cells. However, the role of EBV protein complexes under physiological conditions remains unclear. In this study, we performed comprehensive analyses of EBV PPIs in living cells using the NanoBiT system. We identified 195 PPIs, many of which have not previously been reported. Computational analyses of these PPIs revealed that BLRF2, which is only found in gammaherpesviruses, is a central protein in the structural network of EBV tegument proteins. To characterize the role of BLRF2, we generated two BLRF2 knockout EBV clones using CRISPR/Cas9. BLRF2 knockout significantly decreased the production of infectious virus particles, which was restored by exogenous BLRF2 expression. Our data suggest that BLRF2 is a tegument network hub that plays essential roles in progeny virion maturation.

Session A　Room 3-3

TBK selectively eliminates pathogenic monomeric TDP-43 via humoral factors

【Presenter】 Shohei Sakai
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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by the selective death of motor neurons. TDP-43 pathology, which consists of cytosolic mislocalization, aggregation, and hyperphosphorylation of TDP-43 protein in motor neurons, is a common pathological feature in both sporadic and inherited cases of ALS. TBK1 is one of notable ALS-causative genes to study the molecular basis of TDP-43 pathology, because it is closely related to proteostasis. However, the molecular link between TBK1 and TDP-43 mostly remains unknown due to difficulty in reproducing TDP-43 pathology in experimental models. Recently, our group discovered expression of monomeric form of TDP-43 reproduces TDP-43 pathology-like features in cells (Oiwa et al., submitted). Here, we examined the effect of TBK1 on TDP-43 protein level using its monomeric TDP-43 mutant cell model. Intriguingly, suppression of endogenous TBK1 increased not wild-type (WT) but pathogenic monomeric TDP-43 and its phosphorylated form. On the other hand, overexpression of TBK1 predominantly reduced monomeric TDP-43 compared to WT. These data suggested that TBK1 selectively eliminates pathogenic TDP-43. Moreover, we identified humoral factors secreted by TBK1 overexpression has a potential that selectively eliminates monomeric TDP-43. Elucidation of detailed molecular mechanism of TBK1-mediated protein clearance is underway.

Session A　Room 3-4

Effect of a Rho-kinase inhibitor, fasudil, on cognitive impairments induced by methamphetamine administration in mice carrying mutations of the Arhgap10 gene

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Our group has recently identified Arhgap10 gene mutations in Japanese schizophrenia patients by the genome-wide CNV analysis. ARHGAP10 belongs to the RhoGAP superfamily and regulates RhoA signaling. We also found Arhgap10 S490P/NHEJ mice which were generated to mimic the patient case showed a significant decrease in spine density of pyramidal neurons in the medial prefrontal cortex (mPFC) (layer 2/3) and a higher sensitivity to methamphetamine (METH) in the visual discrimination (VD) task. In this research, to clarify a potential role of Rho-kinase (ROCK) as a new therapeutic target for schizophrenia, we investigated whether fasudil, a ROCK inhibitor, was effective in the neuropathological changes in spine density of cortical neurons and a higher sensitivity to METH in the VD task in Arhgap10 S490P/NHEJ mice. We measured spine density in the mPFC after fasudil treatment using Golgi staining. Mice were administered METH (0.3 mg/kg, i.p.) 30 min before and fasudil (20 mg/kg, i.p.) 5 min before the VD task. Fasudil ameliorated the decrease in spine density of cortical neurons in the mPFC and restored impairment of VD induced by METH in Arhgap10 S490P/NHEJ mice. These observations suggest that ROCK is a potential therapeutic target in schizophrenia.

Session A　Room 3-5

Regulation of phosphorylation on a neuronal adaptor protein by enzyme-linked receptors for glycosaminoglycans

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【Background】 The damaged central nervous system does not regenerate again. Our group revealed that chondroitin sulfate (CS) accumulated in the lesion, activates PTPσ (receptor-type protein tyrosine phosphatase), which dephosphorylates cortactin and disrupts autophagy flux, resulted in axonal regeneration failure1. Considering that the phosphorylation level of intracellular substrates seems important for axon growth, kinase is necessary. Interestingly, recent study revealed that heparan sulfate, which has a similar structure to CS, activates ALK (receptor-type protein tyrosine kinase)2. Our following work identified some substrate candidates for PTPσ and ALK including APBB1, which is known as an adaptor protein enriched in the brain.
【Results/Conclusion】 APBB1 gene knockdown in cultured neurons inhibited axon regeneration. APBB1 was a substrate for ALK/PTPσ in vitro (both in cells and in tube). ALK affected the interaction of APBB1 with other proteins especially in the nucleus, and PTPσ diminished this effect. In the early postnatal mouse brain, Alk expression was concentrated in the hypothalamus, while the expression of Ptprs and Apbb1 were observed in the wide region. These observations suggest that the regulation of phosphorylation on APBB1 by ALK and PTPσ might be involved in the development of hypothalamus, probably by modifying its adaptor capacity in the nucleus.

【References】

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2. B. Phillip et al., Sci. Signal., 360, ra6 (2015).

Session A　Room 3-6

Synthesis and Evaluation of (S)-5'-C-Aminopropyl and (S)-5'-C-Aminopropyl-2'-arabinofluoro-modified antisense oligonucleotides

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Abstract: In our previous studies, inserting an aminoalkyl side chain into the 5'-site of nucleosides could significantly increase the nuclease resistance of the resulting oligonucleotides. Meanwhile, the siRNAs with (S)-5'-C-aminopropyl-2'-O-methyl-modification showed better thermal stability than (R)-5'-C-aminopropyl-2'-O-methyl-modified ones. Here, (S)-5'-C-aminopropyl-thymidine (5'AP-T) and (S)-5'-C-aminopropyl-2'-arabinofluoro-thymidine (5'AP-2'araF-T) were synthesized to unravel their effect in DNAs for antisense approach. Compared with the natural ones, it was revealed that DNA/RNA duplexes containing 5'AP-2'araF-T were sufficiently thermally stable, while those containing 5'AP-T featured thermal destabilization. Depending on the thermodynamic parameter, the thermal destabilization was related to the unfavorable entropy. Meanwhile, the incorporation of these analogs significantly enhanced the nuclease resistance of the DNA oligomers. Moreover, the 5'AP-2'araF-modified DNA/RNA duplexes showed a superior ability to activate RNase H-mediated cleavage compared to the 5'AP-modified DNA/RNA duplexes. Hence, the (S)-5'-C-aminopropyl-2'-arabinofluoro-modified nucleoside analogs might be potential candidates for the application of RNase H-dependent antisense oligonucleotides as therapeutics, although the introduction position should be optimized in further studies.

【References】

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2. Zhou Y. et al., RSC Adv., 10, 41901-41914 (2020).

Session A Room 3-7

A novel device to evaluate upper limb ataxia quantitatively

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【Objective】The aim of our study is to develop a novel device to assess upper limb ataxia quantitatively in the patients with spinocerebellar ataxia (SCA) and to assess its validity, reliability, and sensitivity to disease progression.【Methods】We recruited subjects with SCA and healthy controls (HCs). Upper limb ataxia was evaluated using a device that measures the three-dimensional position every 10 ms. Participants were instructed to move a pen-like part of the device iteratively between two buttons. The trajectory length, time, velocity, and variation coefficient of the stroke, and calculated the distortion index using the mean squared error. Subjects were followed 12 months after the baseline evaluation.【Results】A total of 42 subjects with SCA and 33 HCs were assessed. Distortion index was well correlated with the disease duration and the total score of the Scale for the Assessment and Rating of Ataxia ($r = 0.428$, $p = 0.005$ and $r = 0.630$, $p < 0.001$, respectively) and showed the largest standardized response mean (SRM) in the longitudinal analysis (SRM = 0.57).【Conclusion】This new device can assess the upper limb ataxia quantitatively in the patients with SCA and distortion index showed a high sensitivity to disease progression.

Session B Room 1-1

Sigma 1 receptor prevents ATAD3A dimerization to maintain normal mitochondrial function

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by selective death of motor neurons. Dominant or recessive mutations in SOD1 or SIGMAR1 are causative for inherited ALS, respectively. We have previously demonstrated that the collapse of mitochondria-associated membranes (MAM), a contacting site of endoplasmic reticulum (ER) with mitochondria, is a common mechanism of ALS and that sigma 1 receptor (SigR1), a gene product of SIGMAR1, is essential for MAM integrity. Here, we identified a mitochondrial membrane protein, AAA ATPase domain-containing protein 3A (ATAD3A), as a novel interactor of SigR1. Overexpression of ATAD3A significantly increased MAM formation. Using ATAD3A domain deletion mutants, we revealed that two coiled-coil domains (CC1/2) were crucial for interaction with SigR1 and the MAM induction by ATAD3A. Intriguingly, depletion of SigR1 induced homo-dimerization of ATAD3A accompanied by mitochondrial fragmentation. The ATAD3A dimerization was also observed in SOD1G93A ALS model mice, in which SigR1 lost its physiological function. Combined with the previous study that the ATAD3A dimer induces mitochondrial fission, these findings suggest that SigR1 suppresses the ATAD3A dimerization to prevent mitochondrial fragmentation. Thus, our study implies that MAM impairment through SigR1 dysfunction in ALS may compromise mitochondrial function via ATAD3A-induced mitochondrial fragmentation.

Session B Room 1-2

Intranasal levels of lead as an exacerbation factor for allergic rhinitis in humans and mice

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【Background】Allergic rhinitis (AR) has become a global health problem because of its high worldwide prevalence. Health disturbances caused by exposure to various elements including heavy metals have been recognized worldwide. However, there has been no clinical study showing the effects of heavy metals on allergic reaction in the nasal cavity of patients with seasonal AR before the season (preseason) and during the season (season). Moreover, there has been no experimental study showing effects of intranasal exposure to heavy metals on pathological conditions of allergic rhinitis.【Result】Pb levels in epithelial lining fluid (ELF) from patients were >40% higher than those from control subjects during the pollen season. Pb level in ELF was positively associated with pollen counts for the latest 4 days before visiting a hospital as well as severity of subjective symptoms. Intranasal exposure to Pb exacerbated symptoms in allergic mice, suggesting Pb as an exacerbation factor. Pb levels in ELF and nasal mucosa in Pb-exposed allergic mice were higher than those in Pb-exposed non-allergic mice, despite intranasally challenging the same amount of Pb.【Conclusion】Increased nasal Pb level could exacerbate subjective symptoms of AR, indicating Pb as a novel hazardous air pollutant for AR.

【References】

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2. Xu H et al. JACI,. 148(1), 139-147.e10 (2021).

Session B Room 1-3

The effects of Cancer-associated fibroblasts as components of the malignant lymphoma microenvironment to Anti-CD20 antibody therapy

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Rituximab, an anti-CD20 antibody, has improved the outcome of B-cell lymphoma treatment. Recently, Obinutuzumab has been introduced, and has enhanced antibody-dependent cytotoxic (ADCC)[1]. On the other hand, cancer-associated fibroblasts (CAFs) are representative cells that establish the tumor microenvironment, and their effects on immunocompetent cells have attracted attention. We aimed to compare the therapeutic effects of rituximab and obinutuzumab using clinical samples and to evaluate the effects of CAFs. ADCC was evaluated by CytoTox-Glo™ assay kit using NK cells collected from healthy donor peripheral blood. The test was evaluated in monoculture and in co-culture with CAFs. We evaluated 30 patients who underwent lymph node biopsy. The median CD20 expression was 81.5%, and ADCC of rituximab and obinutuzumab was 21.2% vs 52.5% (P=<0.005). The data also correlated with clinical outcomes. The other, ADCC of NK cells monocultured or co-cultured with CAFs was 27.3% vs 45% (P=0.26) for rituximab and 36.8% vs 61.7%(P=<0.005) for obinutuzumab. Clinical therapeutic efficacy for each antibody and influence of CAFs on NK cells was confirmed. The effects of TGFβ released by CAFs on cytokine signaling, inflammation, and immune cell regulation have been reported[2] and may contribute to our study.

【References】

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2. Grauel LA et al. Nat Commun.,11, 6315 (2020).

Session B　Room 1-4

Structural basis of local anesthetics binding to voltage-gated sodium channels

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The nerve system is responsible for various actions such as sensing, memory, moving. Voltage-gated sodium channels (Navs) are essential for electrical signal transmission in axons. They sense membrane potential depolarization and open the ion gate. With the function, Navs lining up in axon membrane are activated one by one. Finally, the electrical signal reaches the synapse. Due to the responsibility on signal transmission, Navs are the target of some drugs such as local anesthetic and antiarrhythmic agents. Local anesthetic drugs which target Navs block the sodium current and shut the pain signal out. While some drugs targeting Navs are in use, the detailed interactions are unclear. Gamal El-Din T.M. et al. PNAS, 115, 13111-13116 (2018) revealed the crystal structures of a prokaryotic Nav (NavAb) with some drugs, but detailed interactions between NavAb and drugs are still unclear because of NavAb's fourfold structure and the characteristic of crystal structure. Therefore we are trying to solve them with cryo-EM single particle analysis. We are now facing an issue that NavAb particles on the cryo-EM grid are very likely to be disordered, so we are searching for good conditions to make a better cryo-EM grid for large-scale data collection.

Session B　Room 1-5

Expression of CAR Targets on Solid Tumors by Armed Oncolytic virus has synergetic effect on CAR T cell therapy

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Chimeric antigen receptor (CAR) T cell therapy showed limitation in solid tumors compared to hematological malignancies due to the heterogeneous surface antigen expression patterns in solid tumors, which reduce the effective antitumor response of CAR-T cell therapy. Furthermore, tumor cells may escape from CAR-T by partial or complete loss of target antigen expression. To overcome the limitation of CAR-T therapy for solid cancer, we developed a combination therapy of CAR-T and an oncolytic virus that induces the expression of antigens in tumors. Here we engineered an attenuated oncolytic herpes simplex virus-1 (HSV-1) by deletion of the neurovirulence viral genes ICP 34.5 and replacing it by insertion of mesothelin (MSLN) gene (HSV-MSLN) to selectively deliver MSLN to malignant cells. Our virus showed in vivo safety even after using a high dose (1 X 107 pfu) in tumor-bearing mice and a strong antitumor effect. In vitro, HSV-MSLN induced cell cytotoxicity and expressed MSLN in the Pan02 tumor cell line in a MOI-dependent manner. HSV-MSLN-infected Pan02 cell line induced activation and expression of IFNγ in MSLN-CAR T cell. Our findings may reveal a mechanism that allows the combination of OVs and CAR-T to trigger and improve CAR-T cell antitumor response in solid tumors in vivo.

【Reference】

1. Fesnak A et al. Nat. Rev. Cancer, 16, 566-581 (2016).

Session B　Room 1-6

3'-Sialyllactose on Notch: Notch1 functions as a scaffold of O-linked, 3'-sialyllactosylated glycans

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Notch signaling is important for the development and homeostasis of multicellular organisms. Dysregulation of Notch signaling leads to various human diseases. Genetic and biochemical studies have revealed that O-linked glycosylation on Notch receptors is essential for the transduction of Notch signaling. However, it is not fully understood how O-linked glycans regulate the activity of Notch signaling. To pursue this, we need to know the sites and structures of O-linked glycans on Notch receptors. Our mass spectrometric analysis of proteolytic digests derived from mouse NOTCH1 and 2 overexpressed in HEK293T cells revealed that many of the epidermal growth factor-like (EGF) repeats of NOTCH1 and 2 are modified with O-glucose (Glc), O-fucose (Fuc), and O-GlcNAc glycans at different stoichiometries. Surprisingly, we discovered sialylated, hexosylated O-Glc glycans specifically attached to the O-Glc site of EGF10 within the ligand-binding region of NOTCH1. Further chemical analyses on ?-elimination-released glycans indicated that the structure of the novel O-Glc glycans appeared to be Neu5Ac?2-3Gal?1-4Glc-O. Genetic deletion of both GXYLT1 and GXYLT2 in HEK293T cells increased the ratio of the novel glycans on EGF10 in NOTCH1, suggesting the competition between xylosyl-extension and galactosyl-extension for O-Glc glycans. The novel glycans may confer a previously unknown function specifically on NOTCH1.

Session B　Room 1-7

Metabolome and transcriptome analysis on muscle of sporadic inclusion body myositis

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【Objective】 Sporadic inclusion body myositis (sIBM) is the most common acquired myopathy in patients older than 50 years of age. sIBM is often steroid-resistant, and its pathophysiology remains elusive. This study aims to explore pathogenic pathways underlying sIBM and identify novel therapeutic targets using metabolomic and transcriptomic analyses.【Methods】 In this retrospective observational study, we analyzed biopsied muscle samples from 14 sIBM patients and six healthy control subjects to identify metabolic profiles. Frozen muscle samples were used to measure metabolites with cation and anion modes of capillary electrophoresis time of flight mass spectrometry (CE-TOFMS). We validated the metabolic pathway altered in muscles of sIBM patients through RNA sequencing and histopathological studies.【Results】 A total of 198 metabolites were identified. Metabolomic and transcriptomic analyses identified specific metabolite changes in sIBM muscle samples. The pathways of histamine biosynthesis and certain glycosaminoglycan biosynthesis were upregulated in sIBM patients, whereas those of carnitine metabolism and creatine metabolism were downregulated. Histopathological examination showed infiltration of mast cells and deposition of chondroitin sulfate in skeletal muscle samples, supporting the results of metabolomic and transcriptomic analyses.【Conclusions】 This study suggest that mast cells, chondroitin sulfate biosynthesis, carnitine, and creatine play roles in sIBM pathophysiology.

Session B Room 2-1

Tumor-specific glutamine metabolism inhibition may promote CD8+ TILs activation and enhance the efficacy of immunotherapy

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Cancer immunotherapy by targeting to PD-1/PD-L1 and CTLA-4 has been approved for several cancer types, and its clinical application is actively performed. However, the therapeutic effect and response rate are limited. Various factors are associated with this limitation, one of which is cancer immune escape. Recently, many researchers reported that the reprogramming of tumor-metabolism derived from gene mutation and copy number variations (CNVs) build immune-suppressive environment in tumor. Here, we show that Notch1 signaling in cancer cells is a key regulator of immunotherapy sensitivity and tumor oxidative phosphorylation (OXPHOS)/glutamine metabolism. Notch1-deficient cancer cells appeared to reinforce mitochondrial function and caused metabolic reprogramming by glutamine addiction. As a result, glutamine concentration was decreased in tumor. In turn, the glutamine-depleted conditions limited the proliferation/activation of CD8+ TILs by inhibiting glycolytic metabolism through mTORC1 signaling, which inhibited the effector function of TILs. Tumor-specific glutamine metabolism inhibition using glutamine transporter targeting shRNA may improve CD8+ TILs metabolic condition and promote proliferation/activation, leading to increasing efficacy of immunotherapy.

Session B Room 2-2

Testosterone regulates the neuroinflammation through glial androgen receptor in Alzheimer's disease mice

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Neuroinflammation, mediated by the activation of microglia and astrocytes with secreted humoral factors, is deeply involved in the pathomechanism of Alzheimer's disease (AD). Our result of RNA sequencing has shown that the expression of androgen receptor (AR) was decreased in the human precuneus with early AD pathology and isolated microglia and astrocytes from AppNL-G-F/NL-G-F (App-KI) mice, the new generation AD model. Previous studies have demonstrated that testosterone is associated with AD pathologies, but the details of correlation between glial AR and AD pathology are still unclear. Therefore, we investigated the effect of testosterone through glial AR on AD pathology using castrated-App-KI male mice. In isolated-microglia of aged castrated-App-KI mice, mRNA levels of pro-inflammatory molecules (Cxcl10 and Ccl5) tended to be increased. Meanwhile, mRNA level of Socs3, critical for cytokine secretion linked to neuroinflammation, was significantly decreased in isolated astrocytes. Moreover, in Barnes maze test for evaluating spatial learning and memory, aged wild-type mice exhibited the tendency of increase in the number of errors by castration, but this worsening effect by castration was slight in aged App-KI mice. These results suggested that testosterone may regulate pro-/anti-inflammatory molecules through glial AR and affect neuroinflammation and perhaps cognitive dysfunction.

Session B Room 2-3

Functions of FUT8 stem region

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FUT8 (α1,6-fucosyltransferase) transfers fucose to the innermost GlcNAc residues in N-glycans and is a type-II membrane protein having a stem region between an N-terminal cytosolic region and a large C-terminal catalytic domain. In general, it is considered that the stem region of glycosyltransferases is involved in the regulation of Golgi localization, however, the functions of the FUT8 stem region are still unclear. Here, we revealed that the FUT8 stem region is essential for the enzyme oligomerization. FUT8ΔStem mutants in which the stem region was replaced with glycine/serine linkers were expressed in HEK293 FUT8 KO cells, and the western blotting, lectin blotting and HPLC analysis showed that the enzymatic activity of the mutants was almost the same as that of FUT8 wild type. However, the immunoprecipitation and native-PAGE analysis showed that FUT8ΔStem mutants impaired multimer formation in cells, whereas FUT8 WT forms a multimer. Furthermore, FUT8ΔStem mutants showed the lower expression levels, the more ER localization and the shorter protein half-lives than FUT8 WT, suggesting that the loss of the stem region causes the destabilization of FUT8 protein. Our findings strongly suggest that FUT8 stem region is critical for the multimer formation.

Session B Room 2-4

Acquisition of Anti-SARS-CoV-2 Spike Human Monoclonal Antibody from Single B Cells of COVID-19 Infected Patients Using Cell-free Protein Synthesis System

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Our group has developed a rapid monoclonal antibody acquisition method (named Ecobody technology), in which antibody genes from isolated single B cells from peripheral blood or tissues of animals are amplified by single-cell reverse transcription and several rounds of PCR, followed by cell- free protein synthesis, resulting in a generation of Fab fragment in a very high-throughput manner. In this study, antibodies were conducted against spike proteins, which are membrane proteins of novel coronaviruses and are attracting attention as targets for antibodies to be used in diagnosis and vaccines. B cells were collected from patients infected with human novel coronaviruses, and B cells presenting antigen-specific antibodies were selected using antigen-binding beads. After isolation of each cell, the antibody gene was obtained by reverse transcription PCR and two-step PCR. In addition, using a cell-free protein synthesis system, the binding ability to Spike protein was clarified by ELSA. We are going to evaluate the activity in detail by ELISA and to analyze the sequence in detail.

Session B　Room 2-5

Analysis of bst1+ that regulates lifespan in fission yeast

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Fission yeast, Schizosaccharomyces pombe is a powerful tool for studying lifespan at the cellular level, because it is easy to analyze genetically. In a previous study, screening was conducted to obtain long-lived mutant strains of fission yeast and to identify the mutation sites. Among these strains, a number of particularly long-lived strains were found to contain independent mutations in bst1 + gene. We found that the longevity of fission yeast is controlled by mutation or deletion of bst1 +. We also found that deletion of the bst1+ caused abnormal cell morphology and worsened growth in a medium with glycerol as the main carbon source. These findings will contribute to further understanding of cell life span.

Session B　Room 2-6

Role of NPY-CRH neural axis in the PVH in carbohydrate selection in mice

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Our lab revealed a subpopulation of corticotropin releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus (PVH), is necessary for a high carbohydrate diet (HCD) selection over a high fat diet (HFD). Neuropeptide Y (NPY) injection into the intracerebroventricular (ICV) also increases an HCD intake. However, the relationship between PVH CRH neurons and NPY is poorly understood. Here, I investigated their functional connection in mice. Injection of NPY into ICV or intra-PVH increased HCD selection over HFD. In contrast, chemogenetic inhibition of CRH neurons in the PVH by introduction of AAV encoding Cre-dependent hM4Di-mcherry into the PVH of CRH-ires-Cre mice, significantly suppressed the NPY-induced increase in HCD intake without a change in HFD intake. To study the physiological relevance of the NPY-CRH axis for HCD selection, I examined HCD and HFD selection after systemic injection of 2-deoxy-D-glucose (2DG) that induces a whole-body glucopenia. 2DG injection largely increased HCD selection, and this increase was significantly suppressed by inhibition of PVH CRH neurons. Furthermore, injection of NPY receptor antagonists (Y1R and Y5R) in the PVH suppressed the 2DG-induced HCD selection. These results suggest that NPY-CRH axis in the PVH plays an important role in the glucoprivation-induced carbohydrate selection.

Session B　Room 2-7

FIB/SEM analyses for mitochondrial in the axon initial segments (AIS) and microglial activation around AIS after nerve injury

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Tamada H et al. In response to axon injury, the appropriate disassembly of the axon initial segment (AIS) occurs; however, the details of environmental changes of AIS after axon injury have not well known. In this study, the mitochondrial localization in AIS and the activation of microglia around AIS was analyzed with a Focused Ion Beam/Scanning Electron Microscopy (FIB/SEM). Very few mitochondria were observed in the normal AIS, although abundant mitochondria were surprisingly located in the AIS after injury. The finding suggests that drastically alternations of mitochondrial sorting system in AIS allow the mitochondria influx to axons after injury. FIB/SEM also showed that microglia adhered directly to AIS membrane along the whole length without insertion of any other elements. Some microglia whose processes were attached to AIS were also adhering to other distinct nerve-injured motor neuronal cell body. The unique membrane-associated proteins of the AIS would be lost after injury because the microglia could not distinguish between somatic and AIS membrane under the condition. In conclusion, the precise three-dimensional ultrastructural analysis revealed the drastic changes of AIS in both the extracellular and intracellular milieu after injury, which would be crucial responses for injured neuron to survive and regenerate.

Session B　Room 3-1

Exercise-induced changes in the hypothalamic neural circuits controlling energy metabolism

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【Favorite Technique】 Injection to soleus or brown adipose tissue, stereotaxic injection of the mouse brain, etc.
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Regular exercise affects energy metabolism at multiple levels. The hypothalamus in the brain detects the energy status in the body and controls the energy metabolism of peripheral tissues through the autonomic nervous system. This neural circuit connecting the hypothalamus and peripheral tissues could play an important role in the changes in energy metabolism caused by exercise, but its actual involvement remains less clear. In this study, we investigated whether regular voluntary exercise affects neurons in the hypothalamus that control peripheral tissues, thereby altering energy metabolism. We used a retrograde viral tracer, pseudorabies virus (PRV) to identify hypothalamic neurons projecting to skeletal muscle and brown adipose tissue (BAT). We inoculated PRVs into the skeletal muscles and BAT of exercised or non-exercised mice and analyzed the number of virus-infected cells in the hypothalamus. We found that the number of virus-infected cells in several hypothalamic regions increased with exercise. These regions included the lateral hypothalamic area and dorsomedial hypothalamic nucleus. In contrast, no such difference was observed in the primary motor cortex. These results suggest the possibility that exercise may increase the number of hypothalamic neurons that control skeletal muscle and BAT and induce changes in energy metabolism.

Session B　Room 3-2

Comprehensive Analysis of Pathways Involved in Liposomal Gene Transfer

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Liposome is a non-viral carrier composed of a bilayer of lipid amphipathic molecules, and usually used to encapsulate the active substance such as drug, DNA, mRNA within the lipid bilayer or inside the liposome. The great success in COVID-19 vaccine proved the possibility of the liposome technology. The susceptibility of cells to liposomal gene transduction is various depending on cell types. Although most cell lines are easily transduced, floating primary cells such as T cells are very difficult to transduce with liposome. If the lipofection of T cells becomes feasible, repeated treatment with gene-modified T cells will be promising option devoid of viral vectors. To enhance the lipofection efficacy, we sought to look for molecules involved in pinocytosis or phagocytosis and other critical intracellular molecules during lipofection process. We hypothesized that could determine candidate genes critical for liposomal-based gene transfection by screening deletion mutants that have become resistant to lipofection. After concentrating cells with specific gene mutation, we can identify the mutated genes by next generation sequencing. Once we identified the critical molecules, now we may search for methods such as small molecule treatment or modification of culture conditions to improve lipofection efficiency.

Session B　Room 3-3

Asteltoxin suppresses extaracellular vesicle secretion though AMPK/mTOR-mediated activation of lysosome function

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Exosome is a type of Extracellular vesicle (EV) originating from intraluminal vesicles (ILVs) within multivesicular bodies (MVBs). When MVBs fuse with the plasma membrane, ILVs are secreted into the extracellular space as an EV. Conversely, fusion of MVB with lysosome leads to ILV degradation. EVs were demonstrated to play a crucial role in cancer progression. Therefore, cancer-derived EVs are attractive therapeutic targets. To date, several EV inhibitors have been are reported, however, the efficacy and selectivity of these inhibitors are limited. We screened the fungal natural product library and identified asteltoxin, which inhibits a mitochondrial ATP synthase, as a novel EV inhibitor. We found that asteltoxin inhibits EV secretion without causing mitochondrial damage at low concentrations. We also found that asteltoxin decreased cellular ATP levels and downregulated the AMPK/mTOR pathway signaling, which is a major regulator of lysosome function, resulting in promotion of lysosome activity. Furthermore, electron microscopy analysis revealed that asteltoxin increased the lysosomes number, whereas decreased MVBs number. These findings suggest that asteltoxin is a unique EV inhibitor that controls MVB fate through AMPK/mTOR-mediated activation of lysosome function.

Session B　Room 3-4

Graphical Extraction of Intra-acinar Airways from Micro-CT Volumes of Resected Human Lungs

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We propose a graphical extraction method of ductal microstructures from lung micro-focus X-ray CT (μCT) volumes. High-resolution CT systems called μCT enable us to capture the microstructures of the human lung. However, observation of the intra-acinar airways (i.e., the respiratory bronchioles and the alveolar ducts) from lung μCT volumes is challenging due to the complex distribution and other confusing microstructures. Visualization of the intra-acinar airways is desirable to facilitate observation for physicians. We combine a tubular structural filter and a graph construction method to visualize the complex tree-like structure of these ducts. Our method consists of two stages. In stage 1, we obtain the intra-acinar airway skeletons from a down-sampled lung μCT volume by applying Sato's vesselness filter on the distance map of the lumen regions. In stage 2, we convert an intra-acinar airway skeleton into the tree-like structure of the intra-acinar airways. We applied our method to two specimens of the human lungs. The respiratory bronchioles and the alveolar ducts were graphically extracted. We ensured that the number of extracted segments corresponded to the anatomical findings. The result suggested that our method is promising toward accurate segmentation of the intra-acinar airways.

Session B　Room 3-5

Secondhand aerosol exposure from heated tobacco products and its socioeconomic inequalities in Japan: The JASTIS study 2017-2020

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【Introduction】 The growing use of heated tobacco products (HTPs) has raised concerns about secondhand aerosol (SHA) from HTPs, but few studies have been reported on it. This study aimed to investigate the trends in SHA exposure and their socioeconomic inequalities in Japan. 【Methods】 The prevalence of SHA exposure from 2017 to 2020 was estimated using longitudinal internet survey data of 5,221 participants, aged 20-69 years in 2017 (baseline). Multivariable modified Poisson regression models were applied to examine the association between socioeconomic status (i.e., educational attainment and equivalent income) at baseline and SHA exposure in 2020 with adjustments for sex and age. 【Results】 The estimated prevalence of SHA exposure has consistently increased from 4.5% in 2017 to 10.8% in 2020. Lower educational attainment was associated with a higher risk of SHA exposure (p for trend = 0.010). The covariate-adjusted risks of SHA exposure in participants with a low-education and middle-education level were 1.57 and 1.34 times higher, respectively, than in those with a high-education level. However, such inequalities in risks of SHA exposure across equivalent income categories were not observed. 【Conclusions】 Our study revealed a rapid increase in SHA exposure and the existence of educational inequalities in SHA exposure.

Session B Room 3-6

A hydrophobic residue is critical for species-specific aggregation of canine SOD1 with E40K mutation in canine degenerative myelopathy

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Canine degenerative myelopathy (DM), an inherited fatal neurodegenerative disease characterized by progressive motor neuron loss of the spinal cord, is caused by homozygous mutations in Cu/Zn-superoxide dismutase (SOD1) in similar to amyotrophic lateral sclerosis (ALS). Canine SOD1 with E40K mutation (cSOD1E40K), the most common mutation in DM, aggregates in the canine spinal cords and cultured cells. On the other hand, human SOD1 with E40K (hSOD1E40K) does not form aggregates. To elucidate responsible residues for the species-specific aggregation of cSOD1E40K, we replaced residues in exon 4 of cSOD1E40K with the corresponding residues of hSOD1. We found that M117L mutation inhibited the aggregation by increasing the stability of cSOD1E40K and also improved the cell viability. Our data suggest that the Leu117 in hSOD1 plays a key role in stabilization of the hydrophobic region, and thus Met117 in cSOD1 can contribute to the vulnerability for E40K mutation due to the less stable hydrophobic interactions. Enhancing the stability of hydrophobic region in canine SOD1 provides a clue for developing novel therapeutic strategies for DM.

Session B Room 3-7

A Novel Antibody Drug Conjugate Targeting CCR8+ Tumor-infiltrating Regulatory T Cells Induces a Strong Antitumor Immunity

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【Favorite Technique】 establish experimental tumor metastasis model by intravenous injection, prepare antibody by hybridoma cell
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Regulatory T (Treg) cells, an immunosuppressive subset of CD4+ T cells are known to play a key role in the maintenance of self-tolerance. In tumor immunity, Treg cells suppress antitumor immune responses, thereby promoting the tumor development and progression. It has been shown that CCR8 discriminate Treg cells within tumor from those in PBMCs at individual RNA level. Moreover, anti-CCR8 monoclonal antibody (mAb) treatment significantly reduced tumor growth and prolonged survival in mouse models. Thus, CCR8 could be an attractive target to deplete tumor-infiltrating Treg cells without affecting immune homeostasis. In this study, CCR8 expression by lymphocytes in the tumor microenvironment and peripheral blood of cancer patients were analyzed with flow cytometry. It showed that high CCR8 expression was a distinguished feature of tumor-infiltrating eTreg cells compared to tumor-infiltrating other T cell types and peripheral eTreg cells. In addition, I examined cytotoxic efficacy of a novel CCR8-targeted reagent (anti-CCR8 antibody drug conjugate: CCR8-300460) as a Treg cell-target therapy. CCR8-300460 specifically killed a CCR8-expressing T cell leukemia line, implying the potential as a cytotoxic agent to kill CCR8-expressing cells. However, it showed a low efficiency of depleting eTreg cells in tumor-infiltrating lymphocytes isolated from patients with cancer.

【References】

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2. George et al, Immunity, 45, 1122-1134 (2016).

Session C Room 1-1

Genome-wide CRISPR screen in human CAR-T cells identifies CUL5 as negative regulator of CAR-T cells effector function

【Presenter】 Yoshitaka Adachi
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In vivo expansion and long-term maintenance are the hallmark of treatment success after CD19 CAR-T therapy. To identify specific candidate genes which can regulate CAR-T cell function, we utilized genome-wide CRISPR-Cas9 knockout screening in human CAR-T cells. We transduced human CD8 positive T cells with genome-wide sgRNA lentiviral library and CD19 CAR retrovirus sequentially, and also electroporated Cas9 protein into them for gene knockout. Genome-wide screening identified that CUL5 gene knockout enhanced expansion potential in vitro. We found that CUL5 knockout promoted cell division of CAR-T cells. CUL5 knockout also increased the frequency of the effector memory subset and produced high IFN-γ post Ag stimulation. RNA-seq analysis showed that CUL5 knockout enhanced the activity of JAK-STAT pathway. Consistent with the result of RNA-seq, flow cytometric analysis of intracellular phosphoproteins revealed that CUL5 knockout enhanced phospho-STAT5 and phospho-STAT3 signals compared with control CD19 CAR-T cells. Introduction of CUL5 knockout CD19CAR-T cells significantly resulted in prolonged survival of NOG mice with Raji tumors compared with results from controls. In conclusion, these results suggested that genome-wide CRISPR-Cas9 knockout screening is the promising method to identify genes regulating human CAR-T cells function and develop clinically relevant gene-edited CAR-T cells.

Session C Room 1-2

Biochemical analysis of molecular mechanisms dealing with AP site-HMCES cross-link

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An apurinic/apyrimidinic (AP) site is one of lesions in DNA which constantly arises. The deoxyribose moiety at an AP site exists as an equilibrium mixture between the ring furanose form and the open-chain aldehyde form, and the latter is unstable. As a consequence of this instability, DNA containing AP sites is prone to strand scission. HMCES (embryonic stem cell-specific 5-hydroxymethylcytosine-binding protein) covalently binds to an aldehyde form of AP site in single-stranded DNA, and forms a stable HMCES cross-link via a stable thiazolidine ring (thia-HMCES) to shield AP sites from the strand scission. Subsequently, the thia-HMCES can be dissolved proteolytically, passively leaving peptide chain with thiazolidine ring (thia-pep). Although the mechanism of the thia-HMCES formation has been well analyzed, it remains unknown how cellular function deals with the thia-HMCES and thia-pep. This study focused on exploration of molecular mechanisms dealing with the thia-HMCES and thia-pep using model substrates of thia-HMCES and thia-pep. In this presentation, I discuss the replication mechanisms of thia-HMCES and thia-pep, and the repair mechanisms of thia-pep.

Session C　Room 1-3

Elucidation of the pathogenesis of Alzheimer's disease focusing on the white matter function

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【Favorite Technique】 two-photon microscopy, open skull
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Alzheimer's disease (AD) is a neurodegenerative disorder characterized by short-term memory impairment. The pathological feature of AD is the accumulation of amyloid-β protein that cause neuronal death and chronic inflammation. In addition, recent studies showed that pathological changes in white matter (WM) detected by MRI correlate with cognitive decline. However, the mechanism of WM pathology in AD remains unclear. Here, we focused on the myelin, the component of WM, to understand the pathological mechanism of WM in APP knock-in mice (AD mice). To evaluate the myelin structure and proteins expression, we used brain sections from WT and AD mice at 2, 4, and 6 months of age. Significant impairment of myelin microstructure was detected by electron microscopy at 4 and 6 months of age in AD mice. The expression levels of myelin-related proteins did not change at 4 months, but increased in 6 months AD mice, suggesting their remodeling caused by myelin damage. Furthermore, spatial learning was impaired in 6 months AD mice, correlating with the time dependent myelin damages. We now visualize the Ca^{2+} responses of oligodendrocytes and axons using two-photon microscopy, and evaluate axonal conduction velocity to verify the regulatory mechanisms of WM functions that contribute to learning.

Session C　Room 1-4

Structure of glycyrrhizin binding to the scaffolding protein ZO1-PDZ1 domain of tight junctions and its function

【Presenter】 Emi Hibino
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【Affiliation】 Nagoya University Graduate School of Pharmaceutical Sciences
【Favorite Technique】 Detection and analysis of protein-protein interactions and ligand-protein interactions by multidimensional NMR measurement of proteins, large-scale synthesis of recombinant proteins using an E. coli expression system, and large-scale synthesis of 15N- and 13C-labeled proteins for multidimensional NMR measurements.
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Glycyrrhizin (GA) is the principal active ingredient of a medicinal herb licorice, and has been reported to have various pharmacological activities including anti-inflammation. GA may act as in an enhancer of epithelial tight junctions (TJs), that are intercellular adhesion complexes, by blocking the inflammatory protein HMGB1. However, other molecular targets of the various activities of GA are still unclear. Recently, we found that GA directly binds to the first PDZ domain of ZO-1 (ZO1-PDZ1), one of the component molecules of TJs. We also calculated the complex structure using trNOE and CSP data. We confirmed the validity of the structure by NMR measurements using structural analogues of GA as well as ZO1-PDZ1 mutants. To evaluate the physiological effect of GA on TJs against the epithelial cell monolayer, trans-epithelial electrical resistance (TEER) of the cultured Caco-2 cells exposed to GA was assessed. We succeeded in reproduce the results reported previously(1), in which high-dose GA could prolong the TJ-opening activity of deoxycholate. Our results suggest that GA blocks the interaction of TJs through ZO-1, and that the function of GA depends on the condition since GA should open the TJs without inflammatory proteins.

【Reference】

1. Sakai M et al. J Pharm Pharmacol, 51(1), 27-33 (1999).

Session C　Room 1-5

Characterization of compound heterozygous mutation derived from DOK7-related-CMS patient

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Congenital myasthenic syndromes (CMS) are a group of heterogeneous diseases characterized by fatigue and weakness. These inherited diseases are responsible for a specialized structure neuromuscular junction (NMJ) dysfunction that affects the signaling transmission between motoneuron and skeleton muscle. Up to date, overpass 30 kinds of protein have been identified related to CMS. Within these molecules, the downstream of tyrosine kinase 7 (DOK7) contribute to the most prevalent form of limb-girdle myasthenia. Dozens of mutations on DOK7 have been identified since it was first reported in 2007. However, just part of mutations are characterized. The role of DOK7 in the assembly of NMJ and the exactly pathogenic mechanism are still unknown. In our lab, we identified compound heterozygous mutations (c.653-1G>C; c.190G>A) in a DOK7-CMS patient, and these two mutations were first reported in Japan. Our aim is to characterize these two mutations.

Session C　Room 1-6

AI-based live-cell-image analysis for spinal and bulbar muscular atrophy pathology

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【Objective】Spinal and bulbar muscular atrophy (SBMA) is a neuromuscular disease caused by CAG repeat expansions in the androgen receptor gene. We demonstrate an AI-based cell-morphologic analysis to determine pathological processes and to find novel therapeutics for SBMA.【Methods】We used a muscular C2C12 cell model of SBMA (97Q cells) and control (24Q cells). We administered 5 alpha-dihydrotestosterone (DHT) which is known to aggravate the pathogenesis of SBMA, and pioglitazone (PG) which is reported to increase the viability of 97Q cells, and evaluated whether the image analysis could reproduce the effect of the drugs. We performed gene expression analysis to identify genes that were dysregulated in 97Q cells. Based on the results, we selected drugs that target the signaling pathway associated with the identified genes. We applied these and performed the image analysis.【Results】The clustering of DHT-treated 97Q cells moved away from that of 24Q cells. In contrast, the clustering of PG-treated 97Q cells shifted toward that of 24Q cells. From gene expression analysis, we selected naratriptan (NRT), p38 inhibitor, NFkB inhibitor, N-acetylcystein and nifedipine. NRT and p38 inhibitor-treated 97Q cells shifted toward 24Q cells. All others make no change.【Conclusions】We develop an AI platform for evaluating living cells to determine the efficacy of drugs.

Session C　Room 1-7

Prediction of the Splicing Effects of Single-Nucleotide Variants (SNVs) at 1st nucleotide of an exon

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【Objective】Various tools have been developed in recent years to predict the effect of SNVs on splicing. However, no tools have been reported to predict the splicing effects of SNVs at the first nucleotide G of an exon. Various factors significantly contribute to the splicing pattern of SNVs at the first nucleotide G of an exon, including the AG-dependence of the 3' splice site (ss) and interaction with U2AF35. Also, there is not enough information about the functional study of splicing in the recent databases.【Methods】Around 380 Papers reporting a total of 130 SNVs were individually scrutinized.We employed 124 features and considered both linear and non-linear models, including Gradient Boosting , Random Forest, and Support Vector Classifier (SVC). The models were generated by 65 splicing-affecting SNVs in the Human Gene Mutation Database (HGMD) and 94 neutral SNVs with a minor allele frequency of $0.1 \leq MAF < 0.5$ in the dbSNP database. GridsSearch optimizes hyperparameters. Cross-validation was performed rigorously to avoid overfitting.【Results】Gradient Boosting had the best model evaluation, the area under the receiver operating characteristic curve (AUROC) and the area under the precision-recall curve (AUPR) were on average 0.88 and 0.86, respectively.【Conclusions】The performance of our model is higher than other available tools. We will generate a web service that accepts a genomic coordinate according to either GRCh37/hg19 or GRCh38/hg38. The program automatically will generate three possible SNVs at the coordinate and predicts a probability of aberrant splicing.

Session C　Room 2-1

Neuroinflammation in Toll-like receptor 7 agonist-induced mouse model for systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease affecting multiple organs as well as peripheral and central nervous system (CNS) involvement. Previous studies have reported a higher risk of developing dementia in the patients with SLE. However, the mechanisms of systemic and central immune system crosstalk in SLE are not fully elucidated. In this study, we examined the neuroinflammation in the brains of Toll-like receptor 7 (TLR7) agonist-induced SLE model mice, which are established by the chronic skin administration of imiquimod (IMQ) on the ear of wild-type C57BL/6 mice at 6 weeks of age. We confirmed a significant increase in splenic weight and an elevated level of anti-nuclear antibody in serum of IMQ-treated mice as a hallmark of SLE. IMQ-induced SLE mice also showed increases in Cxcl10 mRNA in isolated-microglia and astrocytes. In addition, activated (A1) astrocyte markers such as H-2d and Fkbp5 were upregulated in the isolated astrocytes from IMQ-induced SLE mice. These results suggest that SLE model may upregulate the expression levels of chemokines in CNS through peripheral TLR7-induced systemic inflammation and activated glial cells. We plan to investigate neuroinflammation and cognitive function in a TLR7 agonist-induced model and the genetic SLE model, B6lpr/lpr mice.

Session C　Room 2-2

Epstein-Barr Virus BBLF1 is Involved in Efficient Virus Egress

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【Favorite Technique】 Fluorescence microscopy, gene knockout in BAC system.
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Viral particles of all herpesviruses contain a proteinaceous tegument between the nucleocapsid and envelope of the virus particle. Tegument proteins play multiple roles in virus lifecycle, including modulation of cell environment in primary infection, virion morphogenesis, and immune evasion, but their functions are not fully understood. Epstein-Barr Virus (EBV), a herpesvirus family member, causes several cancers, including lymphoma and gastric carcinoma. The EBV BBLF1 is one of the tegument proteins conserved across all herpesvirus subfamilies. To analyze the biological function of BBLF1, we generated a BBLF1 knockout virus using a bacterial artificial chromosome encoding the entire EBV genome and established stably infected cell lines. BBLF1 knockout did not affect viral gene expression and DNA replication under the productive cycle but caused a significant reduction of extracellular virion production. On the other hand, its knockout increased intracellular virion production and then accumulated virion was observed by transmission electron microscopy. These data demonstrate the role of BBLF1 to achieve the optimal release of virus particles.

Session C　Room 2-3

Analysis of Dynamic Postural Control Related to Trunk-Lower Extremity Coordination on Gait Initiation

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【Favorite Technique】 Gait analysis using a wearable device (accelerometer)
Visualization of time series data, waveform analysis, multiple (MATLAB)
Stability research related to dynamic postural control
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A walking process from gait initiation (GI) to steady-state gait was repeated in daily living. COP-COM separation index (CI) can evaluate the stability of voluntary movement in stair climbing and standing position, however, it's unknown to be applied for GI. The aim of this study is to clarify whether CI can evaluate stability on GI. 11 young people and 23 elderly people aged 65 years or older walked 5 times on a 10m walking path at comfortable speed. A foot pressure distribution sensor and motion capture were used to obtain COP and COM trajectory respectively. Main outcome were CI in ML and AP direction (CI_ML, CI_AP), other outcomes were gait parameters, movement performance, questionnaire about daily living. Analysis was executed from starting movement to 3rd heel contact. Elderly people were divided into two groups (elder (H), elder (L)) based on balance ability. Significant differences between elder (L) and other two groups were found in CI_AP. A correlation between Both of CI and velocity was significant. Both of CI influenced gait velocity. CI_ML direction affected 3rd step length. CI_AP affected 1st and 2nd step length. The overall results indicate that CI can evaluate gait stability on GI related to coordination of the trunk and lower limbs.

Session C Room 2-4

Synaptic inputs from motor cortex do not have a role in motor-related membrane potential dynamics in mouse somatosensory cortex

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Body movements influence signal processing in sensory cortex. However, the underlying cellular and circuit mechanisms remain unclear. In primary somatosensory cortex (S1), membrane potential (Vm) dynamics of neurons is heavily affected by spontaneous whisker movements (WMs). Whisker motor cortex (wM1), which is important for triggering WMs, has abundant axonal projections to S1. Here, using in vivo whole-cell patch-clamp or nanoelectrode intracellular recordings in awake behaving mice, we investigated the contribution of wM1→S1 inputs to WM-induced Vm changes in S1 neurons. A brief (1-2 ms) optogenetic stimulation of wM1 typically induced tri-phasic responses in S1 neurons: early excitation, late inhibition, and rebound excitation. We analyzed the correlation among the amplitudes of these responses and WM-induced Vm changes in S1 neurons. However, we did not find any strong correlations among these parameters, and some of positive correlation found in intracellular recordings were not reproduced in patch-clamp recordings. Thus, even with the rich innervation from wM1 that is activated at the onset of WMs, wM1 activity may not be a major cause of WM-induced Vm dynamics in S1 neurons. We are currently testing this hypothesis by directly inhibiting wM1→S1 synaptic inputs by optogenetics.

Session C Room 2-5

Matrix remodeling-associated protein 8 is a marker of a subset of cancer-associated fibroblasts in pancreatic cancer

【Presenter】 Ryosuke Ichihara
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【Favorite Technique】 RNA in situ hybridization, immunohistochemistry staining and transplantation of mouse PDAC cells into mice, etc.
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Cancer-associated fibroblasts (CAFs), a compartment of the tumor microenvironment, were previously thought to be a uniform cell population that promotes cancer progression. However, recent studies have shown that CAFs are heterogeneous and that there are at least two types of CAFs, i.e., cancer-promoting and -restraining CAFs. We previously identified Meflin as a candidate marker of cancer-restraining CAFs (rCAFs) in pancreatic ductal adenocarcinoma (PDAC). The precise nature of rCAFs, however, has remained elusive owing to a lack of understanding of their comprehensive gene signatures. Here, we screened genes whose expression correlated with Meflin in single-cell transcriptomic analyses of human cancers. Among the identified genes, we identified matrix remodeling-associated protein 8 (MXRA8), which encodes a type I transmembrane protein with unknown molecular function. Analysis of MXRA8 expression in human PDAC samples showed that MXRA8 was differentially co-expressed with other CAF markers. Moreover, in patients with PDAC or syngeneic tumors developed in MXRA8-knockout mice, MXRA8 expression did not affect the roles of CAFs in cancer progression, and the biological importance of MXRA8+ CAFs is still unclear. Overall, we identified MXRA8 as a new CAF marker; further studies are needed to determine the relevance of this marker.

Session C Room 2-6

The downregulation of PTBP1 promotes alternative splicing of AGRN mRNA essential for AChR clustering

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Agrin is a ubiquitously expressed proteoglycan with tissue-specific isoforms that are involved in a variety of biological processes. However, only the neuron-specific isoforms (neural agrin) induce clustering of acetylcholine receptors, which is required to form neuromuscular junctions (NMJ). The presence of three alternative exons designated “exon Y,” “exon Z8,” and “exon Z11” induces neural agrin, but the underlying mechanism is unknown. The search for cis-elements in the human AGRN gene revealed that binding sites for polypyrimidine tract binding protein 1, a splicing repressor, are enriched near the Y and Z exons. Silencing PTBP1 with siRNA promotes the inclusion of both Y and Z exons in the neuronal cell line. Mutagenesis of PTBP1 binding sites with minigenes identified an intronic silencer element recognized by PTBP1 in the polypyrimidine (PY) tract upstream of the Y exon, which was confirmed by artificial tethering analyses. Additionally, the in vitro binding assay demonstrated that PTBP1 competes with U2AF65 for binding to the Y exon’s PY tract, thereby inhibiting its splicing. Besides that, differentiation of neuronal cells decreases PTBP1 expression, whereas the inclusions of both the Y and Z exons increase. We propose that downregulation of PTBP1 in mature neurons is required for NMJ formation by promoting neuron-specific AGRN mRNA splicing.

Session C Room 2-7

A central oxytocin neural pathway that regulates metabolism

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【Favorite Technique】 Brain slice patch-clamp recording, In vivo physiological experiments, Nanoinjection into the brain.
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Oxytocin (OXT), a neuropeptide produced in the paraventricular hypothalamic nucleus (PVH), contributes to a variety of behaviors, such as maternal, sexual and social behaviors. OXT neurons, which are activated by various emotional cues, send their axons throughout the central nervous system, and dysfunction of the OXT neural network has been linked to Prader-Willi syndrome, a condition in which severe obesity develops. However, it is unknown how the OXT neural network contributes to the regulation of energy homeostasis. We developed a new adeno-associated virus (AAV) that enables amplified expression of exogenous genes in OXT neurons, and found that OXTergic neurons in the PVH project to the rostral medullary raphe region (rMR), which harbors sympathetic premotor neurons that control metabolic heat production in brown adipose tissue (BAT). In vivo optogenetic stimulation of the PVH→rMR OXTergic neural pathway not only elicits BAT thermogenic and cardiac responses, but also potentiates sympathetic responses evoked by glutamatergic transmission in the rMR. These findings provide a novel OXT neural pathway from the hypothalamus to the medulla oblongata, through which emotionally driven OXT signaling enhances metabolic functions and thereby impacts whole-body energy balance.

Session C　Room 2-8

Exercise-induced Ampk activation ameliorates polyglutamine-mediated neuromuscular degeneration in SBMA mice

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【Objective】Spinal and bulbar muscular atrophy (SBMA) is a hereditary neuromuscular disease caused by expanded CAG repeats in the androgen receptor (AR) gene. The aim of this study is to investigate the effect of wheel-running exercise on clinical phenotypes and neuromuscular degeneration in a mouse model of SBMA.【Methods】We assigned SBMA model mice (AR-97Q mice) to three groups: 1) the presymptomatic exercise group (Ex-Pre): 2) the postsymptomatic exercise group (Ex-Post): 3) the sedentary control group (SED). Ex-Pre and Ex-Post mice received 1-hour forced wheel-running 5 days a week for 4 weeks.【Results】Ex-Pre mice, but not Ex-Post mice, showed improvement in motor function and survival with amelioration of neuronal and muscular histopathology. Especially, nuclear accumulation of polyglutamine (polyQ)-expanded AR in skeletal muscles and motor neurons was suppressed in Ex-Pre mice compared to that in SED mice. We found that the presymptomatic exercise activated Ampk signaling and inhibited mTOR pathway that regulates protein synthesis in the skeletal muscle. Correspondingly, pharmacological activation of Ampk inhibited protein synthesis and downregulated polyQ-expanded AR protein in C2C12 skeletal muscle cells.【Conclusions】Early physical exercise and Ampk activation may be effective for SBMA and other neuromuscular disorders caused by abnormal protein accumulation.

Session C　Room 3-1

Analysis of mechanism to control the expression of NOTCH receptors by detecting abnormal O-glycosylation

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NOTCH signaling is important for the cell fate decision. NOTCH receptors are heavily glycosylated with three kinds of O-glycans in their extracellular domain. NOTCH receptors contain about fifty O-glycosylation sites in each molecule. Some sites for O-glycosylation are essential for the expression and the function of NOTCH receptors. It is very important to maintain an adequate level of O-glycosylation enough for the cell surface expression, however, the regulation mechanism is not known. Our purpose is to reveal how to distinguish unmatured NOTCH receptors or abnormally O-glycosylated NOTCH receptors and how to lead abnormal NOTCH receptors into the degradation pathway. First, we made a NOTCH1 mutant with several mutations of O-glycosylation sites near the transmembrane region and analyzed it. Flow cytometric analysis showed that the NOTCH1 mutant did not express on the cell surface. The NOTCH1 mutant was observed in the ER resulted in accumulation. We investigated whether a specific combination of O-glycosylation sites was important for the NOTCH1 receptor to express on the cell surface, but we could not find the unique combination. Next, we performed proximity labeling to identify proteins nearby the NOTCH1 mutant. We'll discuss candidate proteins interacting with the NOTCH1 mutant.

Session C　Room 3-2

Visualizing neuronal circuit activity underling sensory abnormalities of ASD

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Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder which express sensory abnormalities. Although increased functional connectivity of thalamus-sensory cortex reported, the pathological basis of neuronal circuitry that causes sensory abnormalities remains unknown. Furthermore, the pathological reciprocal interaction between sensory abnormalities and impaired social behavior has not been demonstrated. In this study, we used previously known maternal immune activation (MIA) with Poly(I:C) mouse as ASD model. To study the functional sensory evoked response of neuronal population and their contribution on functional local circuit connectivity in ASD model mice, we visualized neuronal activities with whisker stimulation or with holographic single cell stimulation in the primary somatosensory cortex barrel field (S1BF) using in vivo two-photon holographic microscopy combined with virus targeted fluorescent expression. We defined neuronal population that showed a high cross-correlation with whisker stimuli as whisker-response cells. Whisker-response cell population in S1BF of MIA mice showed lower synchrony, and high failure response rate for 10 serial stimuli, compared to WT mice. The results suggest the variance of neuronal responses to whisker stimuli, which may lead to increased variability in the expression of higher brain functions in ASD. This study provides the pathological perspective of sensory abnormalities and their abnormal circuitry-basis of ASD.

Session C　Room 3-3

Exploring RhoGEFs involved in Cdc42 activation in excitatory synapses

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Plastic changes in the structure and function of spines in excitatory neurons, known as structural long-term potentiation (sLTP), are believed to be the basis of learning and memory. Previous studies found that Cdc42, a member of the Rho family small GTPase, is activated during sLTP triggered by single-spine glutamate stimulation, and it plays an essential role in sLTP. However, the molecules that activate Cdc42 in spines of excitatory neurons have remained elusive. Here, we focus on several Cdc42 activators called Rho guanine nucleotide exchange factor (RhoGEF) and monitor their recruitment into stimulated spines. RhoGEFs fused to BrUSLEE (a mutant of EGFP with a short fluorescent lifetime) were coexpressed with EGFP in the neurons of hippocampal slices by gene gun. The recruitment of BrUSLEE-GEF was monitored by 2-photon fluorescence lifetime imaging microscope. Among RhoGEFs, FGD1 and ARHGEF15 were recruited into the stimulated spines, implying that they activate Cdc42 in spines. We also investigated their functions by loss-of-function assay using shRNA and found that FGD1 is partially required for transient and sustained spine enlargement, and ARHGEF15 is required for the suppression of spine enlargement. These results suggest that FGD1/ARHGEF15 are Cdc42 activators involved in sLTP.

Session C　Room 3-4

Effects of sialic acid synthesis and degradation deficiency on medaka development

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Sialic acid (Sia) is a group of acidic sugars with a nine-carbon backbone. Sias are present at non-reducing termini of glycan, and their metabolic pathway has been clarified in vertebrates. It is known that mutations of Sia synthetic and degradative enzyme genes cause various symptoms such as intellectual development disorders, skeletal dysplasia, and myopathy. However, how significant these enzymes in embryogenesis and development is still unknown. Thus, in this study, we focused on the biological significance of a synthetic enzyme, SPS, and a degradative enzyme, SPL in medaka model. First, we analyzed expression profiles of SPS and SPL genes. As a result, they were expressed in all developmental stages. Next, we established SPS- or SPL-knockout (KO) medaka by CRISPR/Cas9 system, and found that the SPS-KO medaka was lethal in young fry, while the SPL-KO medaka could survive although some of them showed cardiac abnormality. Finally, we measured Sia amount of the SPS- and SPL-KO medaka, and found that Sia amount was decreased in the SPS-KO medaka, although it was unchanged in the SPL-KO medaka. These results suggest that SPS and SPL may play different roles during embryogenesis and development.

Session C　Room 3-5

CD83 marks progenitor exhausted T cell population

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T cell exhaustion is defined as a dysfunctional T cell state accompanied by chronic antigen exposure. Exhausted T cells are observed in the tumor microenvironment where antitumor T cells are continuously exposed to the tumor antigen. Recent studies have shown exhausted T cell has differentiation hierarchy which comprises progenitor and terminally exhausted T cells, and only progenitor exhausted T cells can regain effector functions upon immune checkpoint blockade. However, molecular profiles to specifically define progenitor exhausted human T cells have not been elucidated enough. Here we extensively investigated surface marker profiles that mark the progenitor exhausted T cells using the solid tumor xenograft models treated by chimeric antigen receptor (CAR)-engineered human T cells. Among the candidate genes upregulated in progenitor exhausted T cells in the publicly available RNA-seq data, we found that CD83 was specifically expressed in the CCR7+ PD1+ tumor-infiltrating CAR-T cell population compared with the CCR7- and PD1- T cells. While CD83 was robustly induced in T cells with an early memory phenotype, its upregulation was blunted along with T cell differentiation. Our data identify CD83 as a novel marker to discriminate progenitor exhausted T cells from terminally differentiated T cells among the heterogeneous intratumoral T cell population.

Session C　Room 3-6

Calcium transients control a morphogenetic cycle underlying neuronal migratory movement

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In spite of the critical importance of neuronal migration in the construction of brain architecture and neuronal circuits, morphogenetic rules operating neuronal migration during cortical layer formation have remained elusive. In particular, how numerous neurons can sequentially migrate in succession in a time-orchestrated manner within a limited space remains unsolved. We previously showed that migrating neurons responded to multiple extracellular factors that triggered Ca^{2+} influx via voltage gated Ca^{2+} channels (VGCCs), and further discovered a potential role for VGCC-driven spontaneous regenerative Ca^{2+} transients in neuronal migration. In keeping with this, we here found that radially migrating neurons in the cerebral cortex exhibited repeated spontaneous Ca^{2+} transients, while they underwent a characteristic, transient nuclear deformation or 'rounding'. Furthermore, an evoked sustained Ca^{2+} elevation was able to trigger such nucleus deformation and maintained it throughout the duration of its transients. Intriguingly, the Ca^{2+} elevation was accompanied with multiple specific nucleus/cell morphology changes during a migratory movement: an initial acceleration followed by a halt in nucleus movement, a retraction in the trailing process, as well as a block in leading process extension. Thus Ca^{2+} elevation regulated three key morphogenetic components of neuronal migration. Mechanistically, Ca^{2+} influx via L-type VGCC was essential for nucleus rounding and nucleus movement. Consistently, expression of a dominant L-type VGCC gain-of-function mutation, associated with a syndromic autism spectrum disorder, induced an excessive nuclear rounding and perturbed cell migration. Together, our results shed light on the fundamental role of Ca^{2+} transients in orchestrating multistep morphogenetic cycles underlying neuronal radial migration.

Session C　Room 3-7

Elucidation of the mechanism of reduced ICB treatment efficacy in advanced-stage cancer

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Recently, it has been shown that anti-tumor immune responses can be rescued by removing immunosuppressive factors, such as PD-1, and such immune checkpoint blockade (ICB) is becoming established as an effective therapy for intractable cancer patients. However, ICB has a limited therapeutic effect on patients of advanced-stage cancer with response rates of only 15-30%. Therefore, elucidation of the mechanism of resistance to ICB in patients with advanced-stage cancer is an urgent issue.
In this study, using a MC38-bearing mouse model, we investigated the impact of the timing of ICB administration on anti-tumor immune responses. We found that the group early administration of ICB resulted in complete, tumors regressed completely, whereas the group later administration failed to contain tumor growth. Immunological analysis showed that the advanced-stage tumor was enriched with more regulatory T cells and terminally exhausted T cells compared to the early-stage tumor. We also analyzed the function of dendritic cells (DCs) and found that the expression of molecules related to DCs activation was lower in advanced-stage cancer compared to early-stage cancer.
Taken together, our results indicate that the function of T cells and DCs is reduced, making it difficult to eliminate tumors in advanced-stage cancer.

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