3rd Symposium

九州大学大学院歯学研究院主催
日本学術振興会　頭脳循環を加速する
戦略的国際研究ネットワーク推進プログラム

口腔から健康長寿を支えるプロジェクト推進に向けた研究拠点構築プログラム

3rd Symposium

2017年 2月12日(日) 10:00～18:00

福岡リーセントホテル

○会期：平成 29 年 2 月 12 日（日）10:00～18:00

○会場：福岡リーセントホテル　舞鶴の間　：下図参照

住所：福岡市東区箱崎 2-52-1
電話：092-641-7741

○主催：九州大学大学院　歯学研究院

日本学術振興会　頭脳循環を加速する戦略的国際研究ネットワーク推進プログラム

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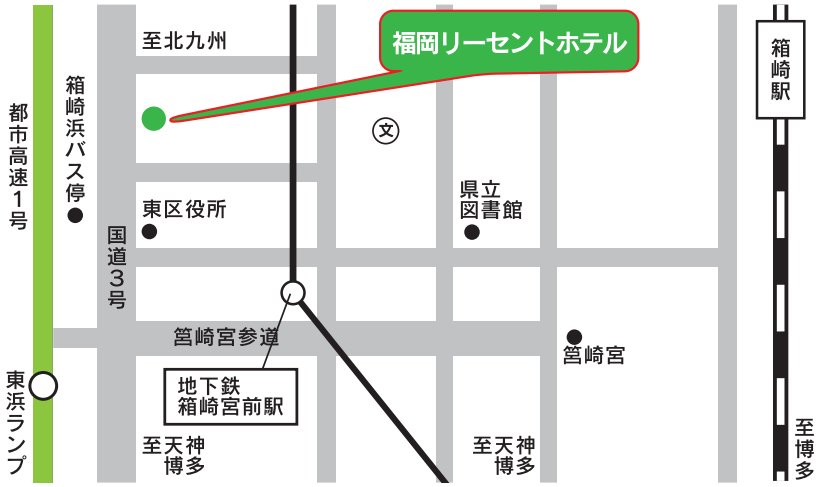
研究拠点構築プログラム



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Information for Speakers

■ *Presentation Instruments*

- Presentations are restricted to computer presentations using your own personal computer.
- Please use a computer running Windows XP,Windows Vista,Windows 7 or Machintosh OS X or later and fitted with an external monitor output terminal.
- All speakers are also requested to bring the data of your presentation on a USB or a CD-ROM.Please mark your name on the file.Please make sure that virus is executed beforehand.

■ *Making Presentations*

- For the speakers in the morning,please bring your own personal computer to the Computer Operating Desk(on the left hand side facing toward inside the presentation venue)until 9:30.
- For the speakers in the afternoon,please bring your own personal computer to the Computer Operating Desk until 12:30.
- All speakers are requested to operate the computer by themselves.
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PROGRAM

頭脳循環第三回シンポジウム

3rd Symposium:
Program for Advancing Strategic International Networks to Accelerate the Circulation of Talented Researchers

2017年2月12日

■ 10:00～　Opening remarks　Masato Hirata

■ 10:10～11:10　Session 1　Chair：Hidefumi Maeda

Dr. Yang Chai：
Molecular regulatory mechanism of mesenchymal stem cells to transit-amplifying cells transition in tissue homeostasis
George and MaryLou Boone Chair in Craniofacial Molecular Biology
Director, Center for Craniofacial Molecular Biology
Associate Dean of Research, Ostrow School of Dentistry
University of Southern California

■ 11:10～11:40

Dr. Takayoshi Yamaza：
Orofacial stem cell-based medicine
Department of Molecular Cell Biology and Oral Anatomy, Kyushu University Graduate School of Dental Science

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■ 13:00～14:00　Session 2　Chair：Fusanori Nishimura

Dr. Dana Graves：
Mechanisms of Diabetes Impaired Wound Healing
Vice Dean for Scholarship and Research & Interim Chair of Periodontics Department, University of Pennsylvania School of Dental Medicine

■ 14:00～14:30

Dr. Fusanori Nishimura：
Adipose tissue inflammation may be a key player in systemic expansion of periodontal inflammation
Section of Periodontology, Department of Oral Rehabilitation, Kyushu University Faculty of Dental Science

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■ 14:50～15:50　Session 3　Chair：Seiji Nakamura

Dr. Shiv Pillai：
Epigenetic Regulation of Lymphocytes in Health and Disease
Ragon Institute of MGH, MIT and Harvard
Harvard Medical School

■ 15:50～16:20

Dr. Masafumi Moriyama：
Possible involvement of toll-like receptors in IgG4-related dacryoadenitis and sialoadenitis
Section of Oral and Maxillofacial Oncology, Division of Maxillofacial Diagnostic and Surgical Sciences, Faculty of Dental Science, Kyushu University
OBT Research Center, Faculty of Dental Science, Kyushu University

■ 16:20～16:35

Dr. Takashi Maehara：
Human $BATF^{+}$ $IL\text{-}4^{+}$ T follicular helper cells are linked to a polarized IgG4 switching event and accumulate primarily outside germinal centers in IgG4-related disease lesions
Ragon Institute of MGH, MIT and Harvard, Massachusetts General Hospital, Harvard Medical School

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■ 16:40～17:25 Reports after circulation Chair： Noriatsu Shigemura

Dr. Urara Tanaka：Effects of Decitabine on Osteoclastogenesis and Periodontal Bone loss in Mice
Dr. Akihito Furuhashi ：Generation of Salivary Gland-like Organoids from Human Dental Follicle Epithelial Stem Cells
Dr. Shingo Takai：The function of insulin and insulinotropic peptides in taste tissue

■ 17:25 Closing remarks Kazuaki Nonaka

■ 17:30 Photo-taking

【MEMO】

Session1

Molecular regulatory mechanism of mesenchymal stem cells to transit-amplifying cells transition in tissue homeostasis

Yang Chai, DDS, PhD

Professor
George and MaryLou Boone Chair in Craniofacial Molecular Biology
Director, Center for Craniofacial Molecular Biology
Associate Dean of Research, Ostrow School of Dentistry
University of Southern California

Stem cells are remarkable. They form tissues during development, maintain tissue homeostasis and perform injury repair in adults. The mouse incisor provides an excellent model for stem cell study because it grows continuously throughout life. Stem cells residing in the proximal region of the incisor in adult mice can replenish all incisor cells within one month. We have recently shown that the mesenchymal stem cells (MSCs) in the adult mouse incisor are a Gli1+ cell population surrounding the neurovascular bundle (NVB) near the cervical loop region and that they govern tissue homeostasis and repair. The NVB secretes Shh and provides a niche for MSCs in the incisor. However, the functional significance of Shh secreted from the sensory nerve within the NVB still needs to be investigated. During normal homeostasis, MSCs exit from their niche and become transit-amplifying (TA) cells, undergoing a series of divisions before terminal differentiation. The transition process from MSC to TA cell is a common feature in diverse organs but little is known about the presumably complex signaling network that governs this transition. Our studies show that (i) secretion of Shh by the sensory nerve supports MSCs in the adult mouse incisor and that (ii) molecular signaling interactions control the MSC to TA cell transition and the fate of MSCs to maintain mesenchymal cell homeostasis in the adult mouse incisor. Our study provides important knowledge of the signaling network that regulates the transition from MSCs to TA cells in maintaining tissue homeostasis. The understanding gained from this study will serve as the foundation for future studies in MSC biology and stem cell-mediated tissue regeneration.

Supported by R37 DE012711 and R01 DE025221, NIDCR, NIH

Biography

Dr. Yang Chai is a Professor and the George and MaryLou Boone Chair in Craniofacial Biology at the University of Southern California. He serves as the Director of the Center for Craniofacial Molecular Biology (CCMB) and Associate Dean of Research at the Herman Ostrow School of Dentistry of the University of Southern California. He is most noted for his research on the molecular regulation of cranial neural crest cells during craniofacial development and malformations. Over the years, his laboratory has developed multiple genetically engineered mouse models in order to investigate how craniofacial organs such as the tooth, palate, mandible, maxilla, tongue and calvaria are formed, and how tissue-tissue interactions control patterning and morphogenesis. Dr. Chai's research work has transformed our understanding of the regulatory mechanisms of craniofacial development. He is currently also studying mesenchymal stem cells (MSCs), their niche environments, and how to use innovative 3D-printed scaffolds with MSCs to support craniofacial tissue regeneration. Most importantly, his research interest has always been focused on linking animal models with human birth defects. His research has led to the successful rescue of craniofacial malformations by manipulating signaling pathways during embryogenesis.

Dr. Chai has authored more than 140 scientific papers and numerous book chapters, and has recently edited a book on craniofacial development. His work has earned him multiple awards including the 2011 IADR (International Association of Dental Research) Distinguished Scientist Award. He is an elected member of the American Academy of Arts and Sciences (AAAS). He serves on the editorial board of *Developmental Biology*. He has also served on the Board of Scientific Counselors at the National Institute of Dental and Craniofacial Research (NIDCR), National Institute of Health (NIH) and is currently serving on the National Advisory Dental and Craniofacial Research Council for the NIDCR, NIH. He also serves on NIH study sections and reviews grant applications for the Wellcome Trust and other international research organizations. Dr. Chai earned a DMD degree from Peking University School of Stomatology as well as DDS and PhD in Craniofacial Biology from the University of Southern California.

Orofacial stem cell-based medicine

Takayoshi YAMAZA, DDS, PhD

Department of Molecular Cell Biology and Oral Anatomy, Kyushu University Graduate School of Dental Science

Over fifteen years have been passed after the first discovery of human orofacial stem cells in the world. Origin of orofacial stem cells is considered to be cranial neural crest cells (CNCCs). In embryo, neural crest cells (NCCs) separate from neural crest, which is temporally formed between ectoderm and neural plate during neural tube formation, and migrate into various places to participate in variety of organ and tissue development. During the migration, NCCs translate into mesenchymal cells (epithelial-mesenchymal transition). Particularly, CNCCs concentrate in facial and pharyngeal arches, and form not only sensory VII, IX, X cranial nerves, thymus, thyroid follicular cells, parathyroid, and cornea, but also most of orofacial mesenchymal organs including facial skeleton such as maxilla and mandible, dentin/pulp complex, cementum, periodontal ligament, and alveolar bone. Today, several types of stem cells are isolated and characterized from human orofacial tissues such as dental pulp stem cells (DPSCs), stem cells form human exfoliated deciduous teeth (SHED), stem cells from apical papilla (SCAP), periodontal ligament stem cells (PDLSCs), and gingival mesenchymal stem cells (GMSCs). Among the orofacial stem cells, SHED are considerably focused on the outstanding properties of multidifferentiation, tissue regeneration, and immunomodulation. Therefore, many basic and clinical researchers have expected the clinical success of SHED-based regenerative therapy, especially to interactive diseases. Here, among recent works on translational research, regulatory science, and reverse translational research using SHED, we will provide our current research and development for diseases of digestive system, and will discuss regarding to the future direction.

Takayoshi YAMAZA, DDS, PhD.

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Education

1994-1998	Ph.D. Kyushu University Graduate School of Dentistry, Fukuoka, Japan
1988-1994	DDS Faculty of Dentistry, Kyushu University, Fukuoka, Japan

Brief Chronology of Employment

2015-present	Associated Professor Department of Molecular Cell Biology and Oral Anatomy Kyushu University Graduate School of Dental Science
2012-2015	Lecture Department of Molecular Cell Biology and Oral Anatomy Kyushu University Graduate School of Dental Science
2006-2009	Postdoctoral Research Fellow Center for Craniofacial Molecular Biology University of Southern California School of Dentistry Los Angels, CA, USA PI: Dr. Songtao SHI, DDS, PhD
2005-2006	Postdoctoral Research Fellow National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD, USA PI: Dr. Songtao SHI, DDS, PhD
2001-2012	Assistant Professor Department of Oral Anatomy and Cell Biology Kyushu University Graduate School of Dental Science
1998-2001	Assistant Professor Department of Endodontlogy and Operative Dentistry Kyushu University Graduate School of Dental Science

【MEMO】

Session2

Mechanisms of Diabetes Impaired Wound Healing

Dana T. Graves, DDS, DMSc

Vice Dean for Scholarship and Research & Interim Chair of Periodontics Department, University of Pennsylvania School of Dental Medicine

Abstract:

Diabetes mellitus has a significant and negative impact on wound healing. It is a major contributor non-healing wounds that lead to limb amputation. Diabetic humans and animal models have impaired wound healing that is characterized by high levels of inflammation. Many of the wound healing deficits can be reversed by inhibiting inflammation. Diabetes-enhanced inflammation leads to activation of the transcription factor FOXO1 during wound healing. To investigate how FOXO1 may mediate the effect of diabetes on wound repair we examined mice with lineage specific deletion of FOXO1 in oral and dermal wounds. Deletion of Foxo1 in keratinocytes in normoglycemic wounds impaired healing but had the opposite effect in diabetic wounds. In normoglycemic conditions FOXO1 up-regulated TGF β 1 but failed to bind to the TGF β 1 promoter or stimulate TGF β 1 expression in high glucose. Instead, in high glucose FOXO1 enhanced expression of inflammatory mediators, chemokine (C-C motif) ligand 20 (CCL20) and IL-36 γ . The enhanced inflammation associated with diabetic wounds in vivo could be reversed by inhibiting FOXO1. Moreover, high levels of CCL20 and IL-36γ were detrimental to healing by interfering with cell migration in vivo and in vitro. Thus, FOXO1 can positively modulate wound healing in normal conditions by inducing TGF β 1, but in a high glucose environment fails to induce TGF β 1 and instead stimulates expression of pro-inflammatory mediators that interfere with the healing process.

Biography

Dana Graves completed his DDS training at Columbia University in 1980, and a certificate in Periodontology and DMSc in Oral Biology from Harvard University in 1984. Prior to his arrival at Penn Dental Medicine he was Assistant Professor at the University of Texas Health Science Center from 1985-87, and at Boston University Goldman School of Dental Medicine from 1987-90. He was promoted to Associate Professor from 1990-93 and then to Professor in 1993. From 2008-2010, Dr. Graves was Chair and Professor of Periodontics at University of Medicine and Dentistry of New Jersey. He arrived at Penn Dental Medicine in 2010 and is currently the Interim Chair and Professor of Periodontics and serves as Vice Dean for Scholarship and Research. He is the Associate Editor for the *Journal of Dental* Research and sees patients at the Penn Dental Faculty Practice. Dr. Graves' research focuses on inflammation and diabetes.

Adipose tissue inflammation may be a key player in systemic expansion of periodontal inflammation

Fusanori Nishimura

Section of Periodontology, Department of Oral Rehabilitation, Kyushu University Faculty of Dental Science

Periodontal treatment has been suggested to exhibit beneficial effects not only for local oral health but also for our overall general health, especially for the subjects with diabetes. In this context, we previously reported that periodontal treatment for the subjects with type 2 diabetes accompanied by severe periodontal disease who exhibited elevated level of high sensitivity c-reactive protein (hs-CRP) resulted in significant improvement in glycated hemoglobin level (Munenaga Y *et al., Diab Res Clin Pract*, 2013). On the other hand, this beneficial effect was not observed in subjects whose initial hs-CRP was not elevated even though the severity of periodontal disease was not different from high hs-CRP subjects at clinical level. Therefore, we are interested to see the differences between high and low hs-CRP groups and compared the differences of several parameters between them, and found that, although the difference itself was small, high hs-CRP group showed significantly higher body mass index than the subjects with low hs-CRP group (Nishimura F, *Current Oral Health reports*, in press, 2017). Since these subjects are all suffering from type 2 diabetes, it is very unlikely that high hs-CRP subjects are characterized by more advanced muscularity, suggesting that hs-CRP subjects had slightly matured adipose tissue. These findings also suggest that adipose tissue inflammation play crucial role in expanding periodontal inflammation to the systemic level. This would also suggest that life style intervention such as exercise and diet intervention is very important to lower the unwanted side effects of periodontal disease. It is well known that the effect of life style intervention is superior to medication in preventing type 2 diabetes for the subjects with impaired glucose tolerance, although, at the same time, complete achievement of life style intervention is quite difficult. Therefore, to overcome this problem, use of many supplemental materials are suggested. We are interested in some flavonol intake as adjunct strategy to life style intervention. Here we report recent findings indicating the beneficial effect of epicatechin, major component of cocoa flavonol, on the development of obesity and subsequent metabolic parameters (Sano T *et al., Nutr Metab Cardiovasc Dis*, in press, 2017). Based on our recent studies, we also suggest that appropriate life style intervention is an additional requirement in addition to reducing other obvious risk factors such as smoking, in the overall management of periodontal disease in subjects with diabetes.

Brief biography

Dr. Fusanori Nishimura graduated from Kyushu University Faculty of Dentistry and received DDS degree in 1985. He moved to Okayama University Dental School where he primarily studied the interaction between periodontal bacterial components and host immune responses. From 1991 to 1995, he studied at Columbia University School of Dental and Oral Surgery as post-doctoral research fellow from 1991 to 1993, and as associate research scientist from 1994 to 1995. In the United States, he studied biology and regeneration of periodontal ligament and discovered cell type specific chemoattractant against periodontal ligament cells.

Upon completion of his research in US, he moved again to Okayama University where he started the study associated with periodontal medicine. During this period, from 2002 to 2004, he served as an Editorial Board Member of the Journal of Dental research. He received Young Investigator Award from the Japan Society for Conservative Dentistry in 1999, and also received Lion Award from the Japanese Society of Periodontology in 2005. His research was further expanded in Hiroshima University where he served as Professor of the Department of Dental Science for Health Promotion at Institute of Biomedical and Health Sciences from 2006 to 2012.

In 2013, he had back to his home University, Kyushu University as Professor of Department of Periodontology, and currently still continues his research on periodontal medicine especially from the standpoint of understanding the cellular and molecular basis of periodontal micro-inflammation. Currently, he is a vice dean for international affairs and acting as a group leader of the JSPS program called “Program for advancing strategic international networks to accelerate the circulation of talented researchers”.

【MEMO】

Session3

Epigenetic Regulation of Lymphocytes in Health and Disease

Shiv Pillai

Ragon Institute of MGH, MIT and Harvard

Harvard Medical School

In this talk I will discuss the potential role of the epigenetic regulation of lymphoid cells in the generation of specific lymphocyte populations and in the pathogenesis of chronic inflammation and specific human malignancies. In particular the role of DNA methylation in B cell self-renewal and transformation will be discussed in the context of B-1 B cell self renewal and the pathogenesis of chronic lymphocytic leukemia. The use of chromatin accessibility assays on a genome wide basis to assess the "regulome" in conjunction with the transcriptome, to identify drivers of specific lymphocyte populations that can contribute to disease will be described and discussed.

Biography

Shiv Pillai MD, PhD is a Professor of Medicine and Health Sciences and Technology at Harvard Medical School. He is the Program Director of an NIH Funded Autoimmune Center of Excellence at Massachusetts General Hospital, Director of the Harvard Immunology PhD program, Director of the Masters in Medical Sciences in Immunology Program at Harvard Medical School, and Director of MD Student Research at Harvard Medical School for the Harvard-MIT Division of Health Sciences and Technology. He is a Member of the Ragon Institute of MGH, MIT and Harvard and a Member of the MGH Cancer Center.

Dr. Pillai coined the term "surrogate light chains" for proteins that he identified (with David Baltimore) as part of a novel receptor, now known as the pre-B receptor, which drives early B cell development. His laboratory provided evidence for the first ligand-independent signaling model during lymphocyte development, now a widely accepted mechanism for both pre-B receptor and pre-T receptor signaling. His laboratory also showed that Btk, the product of the gene mutated in X-linked agammaglobulinemia, is functionally linked to the pre-B receptor and the B cell receptor. This work contributed to the eventual development of Btk inhibitors now used widely in patients with chronic lymphocytic leukemia and autoimmunity. His group developed the concept of a follicular versus marginal zone B lymphoid cell-fate decision and has made many contributions to the study of B cell biology. More recently his laboratory has established that IgG4 related disease is causally linked to the clonal expansion and tissue infiltration of CD4+cytotoxic T lymphocytes.

The laboratory currently pursues three main directions:

The immunological, genetic and epigenetic mechanisms underlying chronic inflammatory diseases in humans
The group examines pathogenic mechanisms that are of importance in lupus, rheumatoid arthritis, scleroderma, sarcoidosis, and IgG4-related disease. This work has led to the detailed study of the development of human CD4+ cytotoxic T lymphocytes and their function in the context of chronic inflammation and the containment of viral infections. The role of 9-O-acetylation of sialic acid on B cells and the relevance of this modification to autoimmune susceptibility is also being investigated.

The role of DNA methylation in the B lineage
An important current direction is the role of DNA methylation in the self-renewal of B-1 B cells, and the relevance of DNA methylation to immunological memory, autoimmunity and chronic lymphocytic leukemia.

The biology of B cell memory and T follicular helper cells and its relevance to future vaccination approaches
B cell memory, T follicular helper cells and the germinal center response are being examined using large scale CRISPR screens and on the basis of whole genome chromatin accessibility screens. Applying this basic knowledge to vaccination is one of the goals of the laboratory.

Dr. Pillai received his medical degree from Christian Medical College in Vellore and trained with Dr. Bimal Bachhawat for his PhD. He performed postdoctoral research with Dr. David Baltimore at the Whitehead Institute at MIT. He is the co-author of two widely used textbooks of immunology, and is the course director of immunology courses at Harvard Medical School, Harvard College and for the Federation of Clinical Immunology Societies.

Possible involvement of toll-like receptors in IgG4-related dacryoadenitis and sialoadenitis

Masafumi Moriyama[1,2], Noriko Ishiguro[1], Akihiko Tanaka[1], Takashi Maehara[1,3], Sachiko Furukawa[1], Miho Ohta[1], Masaki Yamauchi[1], Mizuki Sakamoto[1], Jun-Nosuke Hayashida[1], and Seiji Nakamura[1].

[1] Section of Oral and Maxillofacial Oncology, Division of Maxillofacial Diagnostic and Surgical Sciences, Faculty of Dental Science, Kyushu University, Fukuoka, Japan

[2] OBT Research Center, Faculty of Dental Science, Kyushu University, Fukuoka, Japan

[3] Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

ABSTRACT

Objectives: IgG4-related dacryoadenitis and sialoadenitis (IgG4-DS) is a unique inflammatory disorder characterized by the elevation of serum IgG4 and infiltration of IgG4-positive plasma cells in lacrimal and salivary glands (SGs). Since it is well known that IgG4 is induced by T helper type 2 (Th2) cytokines such as IL-4 and IL-13, IgG4-DS is speculated to be a Th2-dominant disease. In addition, recent studies suggested that the activation of innate immunity also plays a key role in the IgG4 production upon stimulation with toll-like receptor (TLR) ligands. In this study, we thus examined the expression of TLRs in SGs from patients with IgG4-DS.

Methods: Gene expression was analyzed by DNA microarray in submandibular glands (SMGs) from patients with IgG4-DS (n=6), chronic sialoadenitis (CS) (n=3), and controls (n=3). TLR family (TLR1-10) was validated by real-time PCR and immunohistochemical staining in SGs from patient with IgG4-DS (n=15), Sjögren's syndrome (SS) (n=15), CS (n=9), and controls (n=9). Finally, we assessed the phenotype (lymphocytic infiltration, fibrosis, and weight of the affected organs) of human TLR7 (huTLR7)-transgenic C57BL/6 mice, compared with that of wild-type mice.

Results: In IgG4-DS, 5 genes of TLR family (TLR4, TLR7-10) were overexpressed by DNA microarray analysis. PCR validated significantly higher expression of TLR7 in IgG4-DS compared with that in the other groups. Immunohistochemical analysis confirmed that the expression pattern of TLR7 was similar to that of the M2 macrophage marker CD163. Recent studies demonstrated that TLR7 agonist stimulates macropages to produce IL-33, which is identified as a cytokine that activates Th2 immune responses. Therefore, we focused on the relationship between TLR7 an IL-33 in IgG4-DS. The results showed that the mRNA expression of TLR7 was positively correlated with that of IL-33 in only IgG4-DS. In huTLR7-transgenic mice, the number of infiltrating lymphocytes and fibrosis score in the SMGs and pancreas were significantly higher than those in wild-type mice.

Conclusions: Our current data suggest that TLR7-expressing M2 macrophages might promote the local inflammation in IgG4-DS.

Masafumi Moriyama, D.D.S. Ph.D.

Section of Oral and Maxillofacial Oncology
Division of Maxillofacial Diagnostic and Surgical Sciences
Faculty of Dental Science, Kyushu University

EDUCATION

1996-2003	D.D.S.	Faculty of Dentistry, Kyushu University, Fukuoka, Japan
2003-2007	Ph.D.	Section of Oral and Maxillofacial Oncology, Division of Maxillofacial Diagnostic and Surgical Sciences, Faculty of Dental Science, Kyushu University

PROFESSIONAL APPOINTMENTS

2007-2011	Clinical Fellow	Oral and Maxillofacial Surgery, Kyushu University Hospital
2012-2013	Assistant Professor	Oral and Maxillofacial Surgery, Kyushu University Hospital
2013-present	Assistant Professor	Section of Oral and Maxillofacial Oncology, Division of Maxillofacial Diagnostic and Surgical Sciences, Faculty of Dental Science, Kyushu University

2015-present Principal Investigator OBT Research Center, Faculty of Dental Science, Kyushu University

AWARDS

MEDARTIS® Award in Japan Society of Oral and Maxillofacial Surgeons	2006
2nd prize (Oral presentation category) in European Association of Oral Medicine	2006
Academic Research Award in Kyushu University Student Support Association	2008
Young Researcher's Award in Japan Society of Oral and Maxillofacial Surgeons	2013
Young Researcher's Award in Japan Society for Sjögren's syndrome	2013
Encouraging Prize in Fukuoka foundation for Sound Health	2013

Human BATF$^+$ IL-4$^+$ T follicular helper cells are linked to a polarized IgG4 switching event and accumulate primarily outside germinal centers in IgG4-related disease lesions

Takashi Maehara and Shiv Pillai

Ragon Institute of MGH, MIT and Harvard, Massachusetts General Hospital, Harvard Medical School

Background/Statement of Purpose

Although the germinal center is considered to be a major site of isotype switching, it is unclear whether class switching occurs primarily at the T-B interface outside germinal centers or within the light zone of the germinal center. We show here that IL-4 expressing T follicular helper (T_{FH}) cells are sparse in human secondary lymphoid organs and are primarily located outside germinal centers. In IgG4-related disease (IgG4-RD), a disorder characterized by polarized Ig class switching and prominent tertiary lymphoid organs, most T_{FH} cells in disease lesions make IL-4.

Methods & materials

We used quantitative multicolor immuno-fluorescence to identify IL-4 secreting T_{FH} cells in secondary lymphoid organs from healthy individuals and affected tissues from IgG4-RD and Sjögren's syndrome (SS) with active disease.

Results

The relative proportion of IL-4 expressing T_{FH} cells is 10-20 fold higher in disease lesions compared to control secondary lymphoid organs. These IL-4 expressing T_{FH} cells are found in tertiary lymphoid organs but are primarily located outside germinal centers and large numbers of IgG4 expressing B cells are also seen in their vicinity. Human IL-4$^+$ T_{FH} cells do not express GATA-3 but express BATF. In contrast to the situation in IgG4-RD, IL-4$^+$ T_{FH} cells are rarely found in or around germinal centers in SS, a disorder in which IgG4 is not elevated. The proportion of CD4$^+$IL-4$^+$BATF$^+$ T cells as well as of CD4$^+$IL-4$^+$CXCR5$^+$ T cells in IgG4-RD tissues correlates tightly with tissue IgG4 plasma cell numbers and plasma IgG4 levels in patients but not with the total plasma levels of other isotypes.

Conclusions

These data describe a T_{FH} sub-population in human tertiary lymphoid organs with IgG4-RD that is linked to a very specific Ig isotype switching event in vivo and support the view that isotype switching occurs primarily outside germinal centers.

Biography

Dr. Maehara is an oral surgeon and researchers primarily focusing on understanding the pathophysiology of oral immune disorder-related diseases and development of new therapeutic strategy against IgG4-related diseases. Currently, he is continuing his research as postdoctoral fellow for research abroad at Ragon Institute of MGH, MIT, and Harvard sponsored by JSPS, after his successful achievement at the same institute as a delegate sponsored by the "Program for advancing strategic international networks to accelerate the circulation of talented researchers" for one year also sponsored by JSPS.

【MEMO】

Reports after circulation

Effects of Decitabine on Osteoclastogenesis and Periodontal Bone loss in Mice

Urara Tanaka[1], Manju Benakanakere[2], Denis Kinane[2] and Fusanori Nishimura[1]

[1]Department of Periodontics, Kyushu University Hospital, Japan
[2]Department of Periodontics and Pathology, School of Dental Medicine, University of Pennsylvania, Philadelphia PA 19004

Objectives: Periodontitis is a common chronic inflammatory disease which is initiated by a complex microbial biofilm. We have previously shown that DNA methylation is involved in periodontal inflammation that may contribute to periodontal disease susceptibility. We sought to determine whether DNA methyl transferase inhibitor namely, Decitabine (5-aza-2'-deoxycytidine) can protect experimentally induced bone loss in mice.

Methods: We used a ligature induced periodontitis mouse model to determine the effects of Decitabine in C57BL/6J mice. Decitabine (1 mg/kg) or vehicle was applied for 5 days. Mice were sacrificed and the gingiva was excised for real-time PCR. Bone loss measurement was done by defleshing, bleaching the maxilla and subjecting it to manual measurement as well as microtomography. Images were captured and the distance between the cementoenamel junction (CEJ) - alveolar bone crest (ABC) was measured using a Nikon Digital Sight DS-U3 system. Paraffin sections of maxilla were used for TRAP staining and immunofluorescence. CD14+ monocytes were used to examine the effects of Decitabine for osteoclastogenesis in vitro. Luciferase reporter assays were performed to unravel transcriptional activation.

Results: We observed severe bone loss in the ligature induced periodontitis model and Decitabine significantly inhibited the bone loss. We found that the treatment with Decitabine significantly reduced osteoclasts both in vivo and in vitro and up-regulated the anti-inflammatory cytokines (IL-10 and TGF- β) in vitro. Furthermore Single-cell analysis of CD14+ monocytes showed that there is a possibility that Decitabine regulates some genes involved in inflammation. Bioinformatic analysis revealed that Krüppel-like Factor 2 (KLF2) is highly guanine-cytocine rich, and possess a long CpG island spanning the entire gene. As expected, Decitabine increased KLF2 mRNA expression. Luciferase reporter assay showed KLF2 up-regulated the transcriptional activity of CCAAT/enhancer binding protein beta (CEBPB) and the anti-inflammatory cytokines IL-10 and TBF- β .

Conclusions: Decitabine inhibits alveolar bone loss by limiting osteoclastogenesis in mice and shows KLF2 can regulate that. Taken together, Decitabine may have utility in treating chronic inflammatory periodontal disease in humans.

Generation of Salivary Gland-like Organoids from Human Dental Follicle Epithelial Stem Cells

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The dental follicle (DF) is a dental tissue composed of a condensation of ectomesenchymal cells that surrounds the tooth germ in early stages of tooth formation. In the present study, we aim to isolate epithelial stem cells from human DF tissues and explore their potential application in stem cell-based therapy for hyposalivation syndrome (xerostomia). We demonstrated the expression of stem cell-related proteins in the epithelial components of human DF tissues and epithelial cells can be steadily isolated and *ex vivo* expanded from human DF tissues. These DF-derived epithelial cells possess clonogenic and sphere-forming capabilities and express epithelial stem cell-related markers, thus conferring stem cell properties (hDF-EpiSCs). When culturing under special 3D induction conditions, these hDF-EpiSCs can differentiate into salivary gland (SG) acinar and duct cells and generate SG-like 3D organoids. Transplantation of hDF-EpiSCs-loaded native decellularized rat parotid gland scaffolds into renal capsule of nude mice led to the creation of SG-like tissues *in vivo*. These findings suggest that hDF-EpiSCs might be a potential source of epithelial stem cells for the development of stem cell-based therapy or bioengineering SG tissues to repair/regenerate SG dysfunction.

The function of insulin and insulinotropic peptides in taste tissue

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Recent studies revealed that the hormones and their receptors originally identified in the gut are shown to be expressed in peripheral taste tissue, but their functions are still largely unclear. Our previous study reported that an inslinotropic hormone called glucagon like peptide-1 (GLP-1) may function as a sweet-specific taste transmitter in mouse peripheral taste system. We next looked at other insulinotropic peptide called glucose-dependent insulinotropic polypeptide (GIP) and its receptor (GIPR), insulin and insulin receptor (IR) in mouse taste tissue and newly developed 3-dimentional cell culture 'taste organoid'. In immunohistochemical experiments, GIPR was mainly coexpressed with T1R3 (a component of sweet taste receptor), not with GAD67 (a sour taste cell marker), in both anterior and posterior part of tongue and the taste organoids. IR was also expressed in a subset of taste cells. Furthermore, when insulin was added to the culture medium, the taste organoids grew faster and larger, and they contained more taste cells compared to them in the medium without insulin. These results suggest that these two hormones may be involved in taste sensation and/or taste cell proliferation.

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