Kick Off 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

Kick Off Symposium

2015年 2月27日(金) 10:00～18:00

福岡リーセントホテル

○会期：平成 27 年 2 月 27 日 （金）10:00～18:00

○会場：福岡リーセントホテル　舞鶴の間 A：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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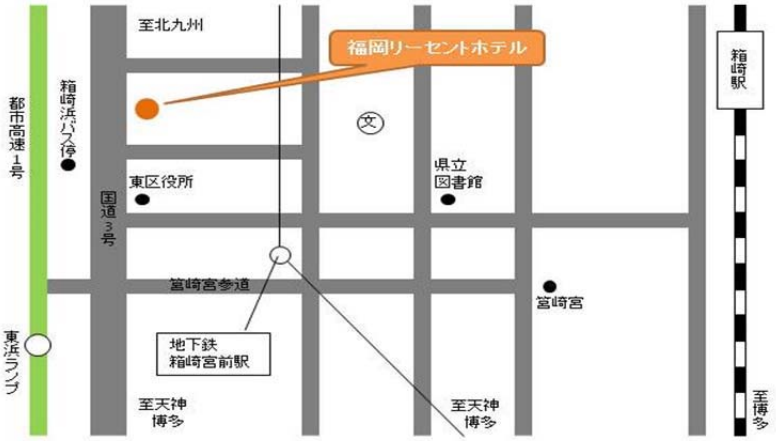

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Information for Speakers

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PROGRAM

頭脳循環キックオフシンポジウム

Kick Off Symposium:
Program for Advancing Strategic International Networks to Accelerate the Circulation of Talented Researchers

2015 年 2 月 27 日

■ 10:00～10: 30　Opening remarks　Fusanori Nishimura

Program for Advancing Strategic International Networks to Accelerate the Circulation of Talented Researchers

■ 10:30～11:50　Plenary Lecture 1　　Chair:　Fusanori Nishimura

Denis F. Kinane :
Innate and Inflammatory host defenses against the oral biofilm
Morton Amsterdam Dean of the University of Pennsylvania School of Dental Medicine.Professor of Pathology and of Periodontics

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■ 13:00～14:00　Plenary Lecture 2　　Chair:　Hiroshi　Nakanishi

Sim K. Singhrao　: Periodontitis and Alzheimer's disease
University of Central Lancashire, School of Medicine and Dentistry

■ 14:00～14:10　Coffee Break

■ 14:10～15:00　Special Lecture 1　　Chair:　Kazuaki Nonaka

Han-Sung Jung :
Teeth of the development, by the morphogenesis, for the future
Yonsei University College of Dentistry,

■ 15:00～15:50　Special Lecture 2　　Chair:　Zhou Wu

Jianchun Yu　: Nutrition, inflammation and Mental Health
Peking Union Medical College and Postgraduate School

■ 15:50～16:00　Coffee Break

■ 16:00～17:20　Session by talented researchers for next circulation

Chair:　Takayoshi Yamaza

16:00～16:20　**Akihiro Furuhashi**
16:20～16:40　**Hiroki Kato**
16:40～17:00　**Shingo Takai**
17:00～17:20　**Urara Tanaka**
17:20～17:40　**Haruyoshi Yamaza**

■ 17:40～17:50　Closing remarks

ABSTRACTS

Opening remarks

Establishment of research base for the projects promoting healthy longevity from oral health

Fusanori Nishimura

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

Oral health greatly contributes not only to the maintenance of quality of life in the elderly by recovering mastication function, but also to the maintenance of cognitive function, prevention of life-style related diseases such as obesity and diabetes, and maintenance of immune homeostasis, all of which contributes to the establishment of societies full of health longevity. Additionally, in the oral tissue or organs, stem cells are relatively abundant, and thus, are easy to extract.
Therefore, much attention has been being paid to the utilization of these cells for therapeutic purpose against life-threatening diseases such as some autoimmune diseases and fatal liver disease.

We, Kyushu University Faculty of Dental Science, consider “oral health sciences” which promotes general health from oral health and “research on tissue regeneration and reconstruction” as two major subjects and aim to build the world-wide research base with full of originality in these fields. For that purpose, we re-confirm our mission as research-oriented university and are trying to make any efforts to educate undergraduate and graduate students full of research-minds, and to grow the next leaders in these fields. To achieve our important mission, we create IN-CROSS-OUT network with top-ranking laboratories in the world and aims to be the international research hub in a next decade.

This year, we were able to get support from JSPS to promote our mission named “program for advancing strategic international networks to accelerate the circulation of talented researchers”. Our great partners are University of Pennsylvania, Harvard University, Monell Chemical Senses center, University of Michigan, and University of Southern California. Here I will introduce the summary of our project named “Establishment of research base for the projects promoting healthy longevity from oral health” as an introduction of this three- year program. I hope the program would produce great outcomes.

In 2017, we, Kyushu University Faculty of Dental Science, will celebrate 50th years of anniversary. We all wish our dreams to build top-ranking research base come true when we celebrate 50th years anniversary.

Plenary lecture 1

Innate and Inflammatory host defenses against the oral biofilm

Denis F. Kinane

Morton Amsterdam Dean of the University of Pennsylvania
School of Dental Medicine.
Professor of Pathology and of Periodontics

This talk will address the innate and inflammatory host responses to the microbial biofilm that constitutes the subgingival dental plaque. The host response to infection draws upon the innate, inflammatory and adaptive immune systems, whose role is to provide the appropriate response to the offending microorganisms. In some cases, this will be little or no response when encountering 'commensals', and in other cases a gradated response depending very much on the host's own determination of the pathogenic nature of the microbial insult: and herein lies the root of variation in host responses that govern individual susceptibility. In some individuals and with some bacteria this will be an innate- only response, others will need to invoke the inflammatory response, and yet others will require the adaptive immune response – be it cellular, humoral or both – to reduce or remove the challenge from the microbes. Of course these responses would be somewhat easier to predict with a single pathogen challenge, and become infinitely more complex as the biofilm

increases in complexity. In addition the host aspect of this interaction is immensely complex due to environmental exposures which overlay on marked genetic variation in the host response found in individual subjects. A further complexity that of epigenetic variation will also be addressed in this presentation. An understanding of the interaction of structural and defensive host cells with the biofilm is pivotal to understanding periodontal disease etiology and to developing tailored therapeutics. Thus, this talk addresses predominantly the innate responses of epithelial cells, exposed to the biofilm

CURRICULUM VITAE

Denis F. Kinane, BDS, PhD, is the Morton Amsterdam Dean of the University of Pennsylvania School of Dental Medicine. He also holds appointments as Professor of Pathology and of Periodontics. Prior to joining Penn Dental Medicine in July 2009, Dr. Kinane served, as the Associate Dean for Research and Enterprise, Director of the Oral Health and Systemic Disease Research Group, and Delta Dental Endowed Professor in the Department of Periodontics and Endodontics at the University of Louisville School of Dentistry. He was also Professor of Microbiology and Immunology there.

A native of Scotland, Dr. Kinane spent much of his distinguished career there, earning his bachelor of dental surgery and his PhD in microbiology and immunology from the University of Edinburgh in 1980 and 1983 respectively, and serving on the University of Glasgow Dental School faculty for 14 years, where he held the posts of Professor and Chair of Periodontology and Oral Immunology and Associate Dean for Research and Enterprise. Dr. Kinane is a member of the Faculties of Dental Surgery of the Royal College of Surgeons of Edinburgh in restorative dentistry and the Royal College of Physicians and Surgeons of Glasgow in periodontics and oral medicine.

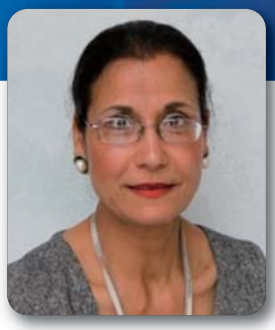
An active clinician and researcher, his research interests focus on periodontal immune and inflammatory processes, mainly addressing the causes, development, and susceptibility markers of periodontal disease. His work also examines the relationships between periodontal disease and systemic health and diseases such as diabetes and heart disease, involving research into inflammation, immunity, microbial pathogenesis, genetics, and systemic disease markers. Among his recent studies, has been an NIH-funded investigation into what genes make people more susceptible to inflammation, gingivitis, and periodontitis (Epigenetics and cell receptors in Disease Susceptibility).

An internationally respected lecturer, Dr. Kinane is widely published in U.S. and international peer-reviewed journals and serves of the editorial boards of the Journal of Clinical Periodontology, Clinical Oral Implants Research, Oral Diseases, British Dental Journal, Journal of Periodontal Research, Genes and Immunity, and Journal of Dental Research. He was a member of the Executive Committee of the European Academy of Periodontology and served as Chair of the Gordon Conference on Periodontal Research, 2006-2009. Dr. Kinane is a highly sought-after international speaker, frequently presents at symposia, conferences nationally and internationally. He regularly organizes international clinical and research symposia, including the 2013 and 2015 Penn Perio Conference and the 2009 Gordon Conference. In Periodontology

【MEMO】

Plenary lecture 2

Periodontal pathogens and Alzheimer's disease: Is there an association?



Sim K. Singhrao*, Lakshmyya Kesavalu1, StJohn Crean

*The presenting authorOral & Dental Sciences Research Group,
University of Central Lancashire,
Preston, U.K. and 1Department of Periodontology and Oral Biology,
College of Dentistry, University of Florida, Gainesville, Florida, USA

The concept of chronic periodontal disease (PD) playing a role in Alzheimer's disease (AD) comes from the seminal studies conducted by Kondo et al.,(1994) and Stein et al., (2007) who have suggested a strong association between tooth loss due to PD and the development of AD. Chronic, inflammatory, periodontal disease has a complex subgingival polymicrobial aetiology involving key pathogens (Porphyromonas gingivalis Treponema denticola and Tannerella forsythia). These pathogens are also linked with the development of other remote body organ inflammatory pathologies including AD. AD is associated with memory loss and a number of aggregated hallmark proteins such as Aß4 deposits, hyperphosphorylated neurofibrillary tangles, neuronal loss and loss of synapses. Riviere et al., (2002) initiated experimental investigations and reported the detection of seven oral species of the genus Treponema in brains of AD patients. Miklossy previously reported that various types of spirochetes, belonging to the order Spirochaetales play a direct role in AD development (Miklossy 2011). Our investigation examined brain samples obtained from the "Brains for Dementia Research" tissue bank, UK donated by ten patients with confirmed AD which were age-matched with individuals without dementia. This study exclusively demonstrated the presence of lipopolysaccharide from P. gingivalis in brains from subjects having suffered from AD. A subsequent collaborative study was performed for proof of concept using ApoE^{null} mice animal models of experimental periodontitis whereby mice were orally infected (N=12) with 10^9 P. gingivalis, T. denticola, T. forsythia and Fusobacterium nucleatum as mono- and polymicrobial infections. Following chronic oral infection, mice were sacrificed after 12 and 24 weeks. Genomic DNA was isolated from brain tissue of mice infected with P. gingivalis, T. denticola, T. forsythia and to assess if these three infecting pathogens accessed the brain. Their molecular identity was determined using universal 16s rDNA gene primers and specific primer sets for each organism. Nucleotide sequencing demonstrated 6 out of 12 ApoE^{null} mice brains contained the P. gingivalis genomic DNA at 12 weeks (P = 0.006), and increased to 9 out of 12 at 24 weeks (P = 0.0001). Furthermore in-situ hybridisation has recently demonstrated the presence of clusters of P. gingivalis in these mice brains supporting our published data. Next, the innate immune responses were detected by using antibodies against complement activation products of C3 convertase stage and the membrane attack complex. Microglia in both infected and control groups demonstrated strong intracellular labelling with C3 and C9, presumed on-going biosynthesis, but the pyramidal neurons of the hippocampus in 4 out of 12 infected mice brains were clearly labelled with C3 activation fragments (P = 0.032). Statistically significant complement activation with bystander injury of CA pyramidal neurons in the hippocampus up to 24 weeks of infection was only observed in the P. gingivalis infected group. The data from the human brains and that from the animal model suggests an emerging indirect link between PD and AD. Further research is needed to assess the direct role of several oral infections in AD mouse models over longer infection episodes.

CURRICULUM VITAE

Sim's interest in research in neurodegenerative diseases was nurtured by the influence of her mentor Dr Gillian Cole (Consultant Neuropathologist) and later by Dr James W. Neal (Consultant Neuropathologist). Sim obtained her M. Phil. degree at Cardiff University. Sim moved from the pathology Department to pursue her PhD in the Complement Biology Group at Cardiff University headed by Professor B. Paul Morgan (Biochemistry and Immunology). This was a very interesting time for establishing the inflammatory hypothesis of Alzheimer's disease. Following three postdoctoral research posts on aspects of non-CNS inflammatory diseases at Cardiff, Sim took up her current Senior Research fellow position in the School of Medicine and Dentistry at the University of Central Lancashire, where she is pursuing research in periodontal disease and its association with Alzheimer's disease in support of the aetiological hypothesis.

Publications

1. Singhrao SK, Nicholson K, Crean S (2012) Informed choices for challenging specimens when choosing methacrylate resin systems for histology. Microsc Res Tech. 75(5):576-85.
2. Singhrao SK (2013) C1q, the classical complement pathway protein binds Hirano bodies in Pick's disease. Microsc Res Tech 76(6):606-11.
3. Poole S, Singhrao SK, Kesavalu L, Curtis MA, Crean S (2013) Determining the presence of periodontopathic virulence factors in short-term post-mortem Alzheimer's disease braintissue. J Alzheimers Dis 36(4):665-77.
4. Dillon A, Achilles-Day U, Singhrao SK, Pearce M, Morton LHG, Crean S (2014) Biocide sensitivity of Vermamoeba vermiformis isolated from dental-unit-waterline systems.
5. International Biodeterioration & Biodegradation 88:97-105.
6. Dillon A, Singhrao SK, Achilles-Day U, Pearce M, Morton LHG, Crean S (2014) Vermamoeba vermiformis does not propagate Legionella pneumophila subsp. Pascullei in a simulated laboratory dental-unit-waterline system. International Biodeterioration & Biodegradation 90:1-7.
7. Lal S, Singhrao SK, Bricknell M, Pearce M, Morton LHG, Ahmed W, Crean S (2014) Monitoring dental unit water line output water by current in-office test kits. Curr Microbiol 69(2):135-142.
8. Singhrao SK, Harding A, Simmons T, Robinson S, Kesavalu L, Crean StJ (2014) Oral inflammation, tooth loss, risk factors and association with progression of Alzheimer's disease. J Alzheimers Dis. 1;42(3):723-37.
9. Poole S, Singhrao SK, Chukkapalli S, Rivera M, Velsko I, Kesavalu L, Crean StJ Active invasion of an oral bacterium and infection-induced complement activation in $ApoE^{null}$ mice brains. Accepted 2014 JAD

【MEMO】

Special lecture 1

Teeth of the development, by the morphogenesis, for the future

Han-Sung Jung

Yonsei University College of Dentistry, Seoul, Korea

Tooth development is regulated by progressive and mutual interactions between epithelium and mesenchyme. The molecular mechanisms underlying this instruction are well-preserved and most of the contributing molecules belong to several signalling families. Research focusing on mouse teeth has uncovered many aspects of tooth development, including molecular and evolutionary detailed and in addition offered a valuable system to analyse the regulation of epithelial stem cells. In mice, the spatial and temporal regulation of cell differentiation and the mechanisms of patterning during development can be analysed both in vivo and in vitro.

The mouse teeth that modulating the balance between inductive and inhibitory signals constitutes a key mechanism regulating the epithelial stem cells and cellular differentiation. I would share current ideas with additional maintenance for the location of the putative dental stem cells and for the stemness. Fine-tuning of the signalling in the regulation of the tooth morphogenesis, and that altering the levels of an inhibitor can cause variation in the tooth patterning. Furthermore, clinical implications including in the diagnosis, prevention and treatment of congenital defects as well as in the design of regenerative therapies would be of fundamental importance in Oral Biosciences.

CURRICULUM VITAE

Education:

1997 PhD, Dept. of Anatomy & Developmental Biology, University College London, UK.

1993 BSc, Dept. of Anatomy & Developmental Biology, University College London, UK.

Position:

2000 ~ present	Assistant, Associate and Professor, Yonsei University, Korea.
2013 ~ present	Adjunct Professor, Guangzhou Medical University, China
2012 ~ present	Adjunct Professor, The University of Hong kong
2010 ~ present	Adjunct Professor, Kanagawa Dental College, Japan
2003 ~ present	Adjunct Professor, Tokyo Dental College, Japan
1999 ― 2000	Instructor, Harvard Medical School, USA.
1997 ― 1999	Post-doctoral fellow, University of Helsinki, Finland.

Publications:

Lai WF, Lee JM, Jung HS. (2014) Molecular and engineering approaches to regenerate and repair teeth in mammals. *Cell Mol Life Sci*.71(9):1691-701

Kim EJ, Cho SW, Shin JO, Lee MJ, Kim KS, Jung HS (2013). Ihh and Runx2/Runx3 signaling interact to coordinate early chondrogenesis: a mouse model. PLoS One 8:e55296 Nakagawa E, Zhang L, Shin JO, Kim EJ, Cho SW, Ohshima H, Chen Z, Jung HS (2012) The novel expression of Oct3/4 and Bmi1 in the root development of mouse molars. Cell Tissue Res.
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【MEMO】

Special lecture 2

Nutrition, inflammation and Mental Health

Yu Jianchun

Professor in Dept. of General Surgery,
Peking Union Medical College Hospital, Peking Union Medical College

Chronic low-grade inflammation has been known to associate with many systemic diseases, including obesity, inflammatory bowel diseases. The low-grade chronic inflammation results in oxidative stress and DNA damage in several of cells, including adipocytes, macrophages, and the damaged cells produce cytokines to secondarily amplify inflammation. It is well accepted that chronic systemic inflammation for continuous cytokine production involves in the pathogenesis of neurodegenerative diseases, including Alzheimer's diseases.

On the other hand, stress may induces oxidative stress refers to the effect of greater than normal production of free radical molecules in the mitochondria during energy metabolism and the potential damage to lipid to cell membranes are particularly vulnerable to damage by free radicals. In clinically, acute stress may be related to gut problems such as acid stomach, diarrhea, constipation, and irritable bowel syndrome, and chronic stress may result in mental health problems, including depression.

The concept of "Surgeon General's report on mental health" is first given by the U.S Surgeon General David Satcher in the early of 1999, because the nutrients necessary for keeping a healthy heart as well as a healthy brain. The mental health problems is rising in the West countries during the 21th century in place of the explosion of heart disease during the 20th century. Depression is now the second-leading cause of global disability and mental health problems make high cost each year in the developing countries.

Nutrition is known as one of the major factors influencing the translation of genotype to the phenotype. This reflects the principles and application of systems biology, which sees health as the reflection of the genetic molecular, and biochemical interactions between bodily systems, a network of relationships that has the capacity for self-regulation. In this talk, I will introduce the concept about "Mental health is influenced by nutrition" and discuss how nutrition, including functional medicine for reduction of inflammation as well as oxidation stress. We need more basic and clinical evidence to expand the concept in near future.

CURRICULUM VITAE

Education:

1980-1985 Bethune Medical College, JiLin University, China.（Bechler Degree in Medicine）

1985-1988 Peking Union Medical College Hospital Chinese Academy of Medical Sciences, Beijing, China. (MD Degree in General Surgery)

1995-1998 Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China.（PhD Degree in General Surgery）

Position:

1985-1989 Resident in Dept. of surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China.

1990-1994 Attending Surgeon in Dept. of surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China.

1995-1996 Visiting scholar for Department of Surgery, Okayama University, Japan.

1997 Visiting scholar for Nutrition Science Institute of Stuttgart University, Germany.

1998 MDS Harris training in global Standard Operating Procedures for the position of Study Coordinator, USA.

2002 Laparoscopic surgery training, training center in Union Christian Hospital，Hong Kong，China

2011 Bariatric (Laparoscopic) surgery training, in training center in YiDa University Hospital，Taiwan.

1995-1999 Associate professor: Dept. of general surgery, Peking Union Medical College Hospital. Chinese Academy of Medical Sciences, Beijing, China.

2000- Professor: Dept. of surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China.

Award:

Ministry of Health for medical and health technology second prize, 1996.

United Nations Information System Technology Prize for Invention and Innovation in China: parenteral and enteral nutrition improvement, 1996.

Medical and health science and technology, Beijing, second prize, 2000.

The National Science and Technology Progress Award, 2002.

Beijing Medical Society best work and Contribution Award, 2010.

Chinese Medical Society of Parenteral and Enteral Nutrition Committee: Excellence Award Perioperative enteral nutrition and parenteral nutrition controlled prospective multicenter clinical study, 2010.

Peking Union Medical College Outstanding Teacher Award, 2002, 2005, 2005, 2009, 2009, 2010, 2011, 2012

Beijing Parenteral Enteral Nutrition Board of Medicine Award, 2010.

Chinese Nutrition Society Award for Outstanding Paper, 2010.

Beijing science and technology award, 2012.

Chinese science and technology award (second prize), 2013.

Publications:

(Some papers within 5 years)

Jianchun Yu. Bariatric Surgery in Adolescents: a multidisciplinary Approach. Essentials and Controversies in Bariatric Surgery Edited by Chih-Kun Huang (Copyright C©2014 INTECH (First published October, 2014)

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Wu Q, Yu JC, Kang WM, Ma ZQ. Short-term effects of supplementary feeding with enteral nutrition via jejunostomy catheter on post-gastrectomy gastric cancer patients. Chin Med J (Engl)., 124(20): 3297-301., 2011.

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Wang J, Yu JC, Kang WM, Ma ZQ. Superiority of a fish oil-enriched emulsion to medium-chain triacylglycerols/long-chain triacylglycerols in gastrointestinal surgery patients: A randomized clinical trial. Nutrition., Nov 22, 2011.

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【MEMO】

Presentation by talented researchers for next circulation

Soft Tissue Response to Dental Implant Materials

Akihiro Furuhashi, Yasunori Ayukawa, Ikiru Atsuta, Yunia Dwi Rakhmatia, Noriyuki Yasunami, Kiyoshi Koyano

Section of Implant and Rehabilitative Dentistry, Division of Oral Rehabilitation,
Faculty of Dental Science, Kyushu University

Objectives:
As implants are inserted into jaw bone and penetrating oral mucosa into the oral environment, a number of stimuli attack the gingival margin. Around dental implant, weak epithelial attachment has been reported. For the long time stability of dental implants, understanding of the relationship between soft tissue and dental implant materials are important. Thus, the purpose of our research is to evaluate the soft tissue reaction to dental implant materials.
Materials and Methods:
In the first research, the difference of soft tissue reaction to the various titanium surface topographies such as rough surface, machined surface, micro-grooved surface was evaluated in vitro and in vivo. In the second research, the difference of soft tissue reaction to various kinds of materials such as titanium, zirconia, platinum-gold alloy was evaluated in vitro and in vivo. In the third research, the effect of titanium surface modification with hydrothermal treatment with CaCl2 solution on soft tissue was evaluated in vitro and in vivo.
Results:
From the first and the second researches, it is revealed that titanium surface topography and the dental implant materials have some influences on the soft tissue response.
From the third research, it is revealed that calcium-modified titanium surface has some positive effect on soft tissue attachment to dental implant.
Discussion and Conclusion:
For the long time stability of dental implant, consideration for the selection of implant surface topography, materials in the trans-mucosal part might be important. In the present study, novel surface treatment with calcium hydrothermal procedure showed the potential for the enhancement of soft tissue attachment.

Tom70 is essential for PINK1 import into mitochondria

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PTEN induced kinase 1 (PINK1) is a serine/threonine kinase in the outer membrane of mitochondria (OMM), and known as a responsible gene of Parkinson's disease (PD). The precursor of PINK1 is synthesized in the cytosol and then imported into the mitochondria via the translocase of the OMM (TOM) complex. However, a large part of PINK1 import mechanism remains unclear. In this study, we examined using cell-free system the mechanism by which PINK1 is targeted to and assembled into mitochondria. Surprisingly, the main component of the import channel, Tom40 was not necessary for PINK1 import. Furthermore, we revealed that the import receptor Tom70 is essential for PINK1 import. In addition, we observed that although PINK1 has predicted mitochondrial targeting signal, it was not processed by the mitochondrial processing peptidase. Thus, our results suggest that PINK1 is imported into mitochondria by a unique pathway that is independent of the TOM core complex but crucially depends on the import receptor Tom70.

Glucagon like peptide-1 (GLP-1) underlies sweet taste transmission

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Recent studies demonstrated that taste bud cells express several gut peptides, such as GLP-1 (glucagon like peptide-1), NPY (neuropeptide Y), and glucagon, and secrete these peptides in response to various taste stimuli. Interestingly, the secretion patterns of peptides are correlated with taste qualities, suggesting the possibility that these gut peptides would contribute to taste quality coding. In this study, we report that around a half of GLP-1 expressing taste cells possess sweet taste receptor subunit T1R3, and GLP-1 receptor is expressed in gustatory nerve neurons in wild type mice. Mice genetically lacking of GLP-1 receptor showed decreased behavioral responses to sweet compounds in short-time lick test and reduced sweet taste responses in chorda tympani (CT) nerve recordings. Additionally, we measured GLP-1 concentrations released from single taste buds, and cells in response to various kinds of taste stimuli by using ELISA method. As a result, we found that GLP-1 is secreted from a subset of sweet responsive cells by sweet taste stimulation in a concentration dependent manner. Furthermore, i.v. injection of GLP-1 produced transient increase of neural activities in a subset of sweet specific single nerve fibers without affecting those of other taste fibers. All these findings suggest that GLP-1 may be involved in normal sweet taste signal transmission in mice.

Suppression of Sprouty2 enhances cell proliferation and migration in periodontal ligament cells

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Objectives: The periodontal ligament (PDL) plays an important role as a reservoir of mesenchymal stem cell. The cells in PDL tissue are critical participants during periodontal tissue regeneration. Sprouty (Spry) is an intracellular protein includes four mammalian homologs, which are expressed in most tissues. Mammalian Spry proteins were originally identified as an inhibitor of fibroblast growth factor (FGF) receptor, and it functions as a negative regulator of receptor tyrosine kinases (RTKs) signaling. However, Spry2 does not affect epidermal growth factor (EGF)-induced ERK activation. Since both FGF and EGF have been suggested as possible growth factor for periodontal cytokine therapy, we aimed to investigate whether Spry2 could be new therapeutic targets for enhancing periodontal tissue regeneration.

Methods: We used multipotent clonal human PDL cell line 1-17. The cells were transfected with small interfering RNA (siRNA) specific for Spry2. Using WST-8 assay and Ki-67 staining, growth factor-induced cell proliferation was investigated. In order to evaluate osteoblastic differentiation, ALP staining and Real-time PCR detecting genes associated with calcification were performed. Cell migration was assessed by a scratch wound healing assay and boyden chamber assay, and lamellipodia formation was confirmed by fluorescence microscope.

Results: Transfection of Spry2 siRNA enhanced bFGF+EGF-induced ERK activation in 1-17 cells. Spry2 siRNA 1-17 cells stimulated by bFGF+EGF proliferated faster than control cells.

Migration activity and lamellipodia formation of bFGF+EGF-stimulated Spry2 siRNA 1-17 cells were promoted compared with control cells accompanied by increase in PI3K, Akt and Rac1 activity. On the other hand, osteoblastic differentiation of Spry2 siRNA 1-17 cells was inhibited.

Conclusions: bFGF+EGF induced proliferation and migration was up-regulated in Spry2 siRNA 1-17 cells, whereas osteogenic differentiation was inhibited. Since selective proliferation and migration of PDL cells are important for periodontal tissue regeneration, Spry2 could be new therapeutic targets for periodontal regeneration.

Dihydroorotate dehydrogenase depletion hampersmitochondrial function and osteogenic differentiation in osteoblasts

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Mutation of the dihydroorotate dehydrogenase (DHODH) gene is responsible for Miller syndrome which is characterized by craniofacial malformations in association with limb abnormalities. We previously demonstrated that the DHODH enzyme is involved in forming a mitochondrial supercomplex in HeLa cells. Moreover, mutated DHODH led to protein instability, loss of enzyme activity, and increased reactive oxygen species. In order to explore the etiology of Miller syndrome in more detail, we here investigated the effects of DHODH inhibition in cells involved in skeletal structure. MC3T3-E1 cells are derived from mouse calvaria osteoblast precursor cells. DHODH in MC3T3-E1 cells was knocked down by specific siRNAs after which cell proliferation, ATP production and expression of bone-related genes were investigated. After depletion of DHODH using specific siRNAs, inhibition of cell proliferation and cell cycle arrest occurred in MC3T3-E1 cells. In addition, ATP production was reduced in whole cells, especially in mitochondria.
Furthermore, mRNA levels of the osteogenic genes Runt-related transcription factor 2 (Runx2) and Osteocalcin (Ocn) decreased in DHODH siRNA-treated cells compared to controls. These data suggest that depletion of DHODH affects the differentiation and maturation of osteoblasts.