Tokyo Dental College

Research Project

Asian Rising Stars Symposium 2025

July 19, 2025

Well-being Society Achieved by Maintaining and Improving

Oral-Maxillofacial Function at Every Stage of Life

(***Well-being Project***)

Program and Abstracts

Saturday, July 19
Tokyo Dental College Research Project
Asian Rising Stars Symposium 2025

Program

13：00–13：05：Opening Remarks
Akira Katakura（Dean, Tokyo Dental College）

Session Ⅰ Moderator： Norio Kasahara（Department of Histology and Developmental Biology, Tokyo Dental College）
Yuichiro Kikuchi（Department of Microbiology, Tokyo Dental College）

13：05–13：35：Lecture Ⅰ
Influence of the MCT1 inhibitor AZD3965 on the radio-sensitivity of HPV-negative and HPV-positive HNSCC cell lines exposed to carbon-ion irradiation

Akihiro Nishiyama（Department of Oral Pathobiological Science and Surgery, Tokyo Dental College）

13：35–14：05：Lecture Ⅱ
Oral Genomics on the Cloud: An Interdisciplinary Perspective

Yu-Cheng Lin（Department of Dentistry, National Yang Ming Chiao Tung University）

Session Ⅱ Moderator： Tatsukuni Ohno（Department of Biochemistry, Tokyo Dental College）
Kei Kitamura（Department of Histology and Developmental Biology, Tokyo Dental College）

14：05–14：35：Lecture Ⅲ
Bridging Oral Microbiota and Orofacial Pain Disorders：The Case of Burning mouth syndrome and Temporomandibular disorders

Byeong-min Lee（Department of oral medicine, Seoul National University Dental Hospital）

14：35–15：05：Lecture Ⅳ
Functional crosstalks between Piezo1-TRPV1/TRPA1 channels via intracellular arachidonic acid cascade in odontoblasts

Ryuya Kurashima（Department of Physiology, Tokyo Dental College）

15：05–15：20：Coffee Break（15 min）

Session Ⅲ Moderator： Toshihide Mizoguchi（Oral Health Science Center, Tokyo Dental College）

15：20-16：00：Keynote Lecture

Promoting Odontoblast Differentiation and Dentin Regeneration through Wnt Signaling Activation via Sugar Chain Modification of Cell Surface Heparan Sulfate Proteoglycans

Takashi Yamashiro（The Osaka University Dental Hospital, Department of Orthodontics, Graduate School of Dentistry, The University of Osaka）

Session Ⅳ Moderator： Ryouichi Satou（Department of Epidemiology and Public Health, Tokyo Dental College）
Takenobu Ishii（Department of Orthodontics, Tokyo Dental College）

16：00-16：30：Lecture Ⅴ

Fundamental Strategies Toward Bioengineered Tooth Development

Eun-Jung Kim（Division in Anatomy and Developmental Biology, Department of Oral Biology, Taste Research Center, Oral Science Research Center, BK21 FOUR Project, Yonsei University College of Dentistry）

16：30-17：00：Lecture Ⅵ

Mesenchymal stem cell sensory nerve niche regulates tooth homeostasis, development and repair

Fei Pei（Department of Cariology and endodontics
School & Hospital of Stomatology, Wuhan University）

17：00-17：05：Closing Remarks

Akira Yamaguchi（Well-being Project advisor, Tokyo Dental College）

[Lecture Ⅰ]

Influence of the MCT1 inhibitor AZD3965 on the radio-sensitivity of HPV-negative and HPV-positive HNSCC cell lines exposed to carbon-ion irradiation

Akihiro Nishiyama, DDS, PhD

Senior Assistant Professor
Department of Oral Pathobiological Science and Surgery, Tokyo Dental College

Abstract：
Besides surgery, radiotherapy, in combination with chemotherapy, is the major treatment option for head and neck squamous cell carcinomas(HNSCC). Next to classical photon-based irradiation, particle therapy is gaining increasing interest. Previous reports implicated AZD3965, an inhibitor of the monocarboxylate(lactate)transporter 1(MCT1), as a promising radio-sensitizing drug for HNSCC. Here, the effects of carbon irradiation with and without AZD3965 on HPV-positive and HPV-negative HNSCC cell lines are investigated. Three HPV-negative and three HPV-positive HNSCC cell lines were grown under standard conditions until they reached 80% confluence. Seven hundred thousand cells were added to each well of a six-well plate the day before irradiation. 8 h after cell seeding, AZD3965(1 μmol/L)or the same volume of DMSO(control)was added to the cell medium, and incubation was continued for 24 more hours. Irradiation of cells was performed at the Marburg Ion-Beam Therapy Center with 4 Gy of carbon ions (C12). Non-irradiated control cells were carried along. Subsequently, cells were incubated for 24 h and prepared for cell cycle analysis. All cell lines responded to particle irradiation with a cell cycle block. The most pronounced effect was observed in HPV-positive HNSCC cell lines. Deploying AZD3965, HPV-neg HNSCC cells exhibited a significantly increased cell cycle block, whereas only a minor effect was seen in HPV-postive HNSCC cells. Inhibiting MCT1 using AZD3965 could radiosensitize, in particular, HPV-negative HNSCC cell lines, which can be explained by previous observations demonstrating a higher preference for ATP production via glycolysis in HPV-negative HNSCC cells compared to HPV-positive HNSCC cells.

Curriculum Vitae

2002-2008 DDS, Kanagawa Dental College
2012-2016 PhD, Tokyo Dental College Graduate School Ph.D., Course
2016 Resident, Department of Oral Pathobiological Science and Surgery, Tokyo Dental College
2017 Assistant Professor, Department of Oral Pathobiological Science and Surgery, Tokyo Dental College
2022 Senior Assistant Professor, Department of Oral Pathobiological Science and Surgery, Tokyo Dental College
2024-2025 Visiting researcher, Philipps-Universität Marburg und Universitätsklinik Gießen und Marburg Klinik und Poliklinik für Mund-,KieferundGesichtschirurgie, Klinik für Hals-, Nasen- und Ohrenheilkunde, Kopf- und Hals-Chirurgie

Research Fields of Interest

1. Regeneration of peripheral nerve
2. Head and Neck Cancer（metabolism of squamous cell carcinoma）

Selected Publications

1. **A. Nishiyama**, K. Odaka, M. Koyachi, K. Sugahara, A. Katakura
   Alternative technique to repair damaged inferior alveolar nerve using data fusion from computed tomographic and magnetic resonance imaging, **British Journal of Oral and Maxillofacial Surgery,** 2022；60(2)207-208
2. Keisuke Sugahara, Hiroki Bessho, **Akihiro Nishiyama**, Yu Koyama, Masahide Koyachi, Tomoaki Toyoda, Kiyohiro Kasahara, Akira Watanabe, Masayuki Takano, Akira Katakura
   The utility of custom-developed tooth extraction simulator - A comparative analysis from beginner to trainer. **Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology,** 2021；33(1)43-47
3. **A Nishiyama,** M Sato, M Kimura, A Katakura, M Tazaki, Y Shibukawa
   Intercellular signal communication among odontoblasts and trigeminal ganglion neurons via glutamate. **Cell calcium**, 2016；60(5)341-355
4. Yoshiyuki Shibukawa, Masaki Sato, Maki Kimura, Ubaidus Sobhan, Miyuki Shimada, **Akihiro Nishiyama**, Aya Kawaguchi, Manabu Soya, Hidetaka Kuroda, Akira Katakura, Tatsuya Ichinohe, Masakazu Tazaki
   Odontoblasts as sensory receptors：transient receptor potential channels, pannexin-1, and ionotropic ATP receptors mediate intercellular odontoblast- neuron signal transduction. Pflugers Arch. 2015；467(4)

［Lecture Ⅱ］

Oral Genomics on the Cloud: An Interdisciplinary Perspective

Yu-Cheng Lin, DDS, MS, PhD

Assistant Professor
Department of Dentistry, National Yang Ming Chiao Tung University

Abstract：
The study of oral genomics—including both host and microbial components—is critical for advancing precision oral health. However, the complexity of high-throughput sequencing data remains a major barrier for clinicians and researchers without computational expertise. To bridge this gap, we have developed fully automated, user-friendly bioinformatics pipelines tailored for oral microbiome and cancer genomics research. These systems integrate established tools—for sequence processing, microbial taxonomy profiling, and somatic variant calling—to deliver results in clean, structured, and accessible formats. To ensure reproducibility and minimize errors, we adopt a test-driven development approach and continuously refine our workflows for improved accuracy. Furthermore, the computational demands of large-scale sequencing data posed a critical challenge. To address this, we have collaborated with industry partners to implement scalable, cloud-based infrastructures capable of handling the sheer volume of data. In this talk, I will demonstrate the practical usability of our systems through two case studies, including analyses of the oral cancer–associated microbiome, and a customized cBioPortal platform for oral cancer research. By lowering technical barriers, our pipeline enables more effective interdisciplinary collaboration among clinicians, biologists, and data scientists.

Curriculum Vitae

2008	DDS	School of Dentistry, National Taiwan University, Taipei, Taiwan
2010	MS	Institute of Microbiology and Biochemistry, National Taiwan University, Taipei, Taiwan
2018	PhD	Department of Biological Sciences, Columbia University, New York, USA
2018-2019		Postdoctoral Fellow New England Biolabs, Boston, USA
2019-2021		Scientist, Computational Biology LifeMine Therapeutics, New York, USA
2021-Present		Assistant Professor Department of Dentistry National Yang Ming Chiao Tung University, Taipei, Taiwan

Research Fields of Interest

Bioinformatics, Next-Generation Sequencing, Oral Microbiome, Cancer Genomics

Selected Publications

1. Yang C-C, Washio J, Lin Y-C, Hsu M-L, Wang D-H, Tsai F-T, Lin Y-M, Tu H-F, Chang H-C & Takahashi N(2025)Microbiome Signatures and Dysbiotic Patterns in Oral Cancer and Precancerous Lesions. Oral Diseases, https://doi.org/10.1111/odi.15317.
2. Chang H-C, Yang C-C, Loi L-K, Hung C-H, Wu C-H & Lin Y-C(2024)Interplay of p62-mTORC1 and EGFR Signaling Promotes Cisplatin Resistance in Oral Cancer. Heliyon, https://doi.org/10.1016/j.heliyon.2024.e28406.
3. Tsai F-T, Yang C-C, Lin Y-C, Hsu M-L, Hong G, Yang M-C, Wang D-H, Huang L-J, Lin C-T, Hsu W-E & Tu H-F(2024)Temporal stability of tongue microbiota in older patients – A pilot study. Journal of Dental Sciences, https://doi.org/10.1016/j.jds.2024.01.012.
4. Wang D-H, Tsai F-T, Tu H-F, Yang C-C, Hsu M-L, Huang L-J, Lin C-T, Hsu W-E & Lin Y-C(2023)Profiles of oral microbiome associated with nasogastric tube feeding. Journal of Oral Microbiology, doi.org/10.1080/20002297.2023.2200898.
5. Tsai F-T, Wang D-H, Yang C-C, Lin Y-C, Huang L-J, Tsai W-Y, Li C-W, Hsu W-E, Tu H-F & Hsu M-L(2022)Locational effects on oral microbiota among long-term care patients. Journal of Oral Microbiology, 14(1):2033003.
6. Yang W*, Lin Y-C*, Johnson W, Dai N, Vaisvila R, Weigele P, Lee Y-J, Corrêa IR Jr, Schildkraut I & Ettwiller L(2021/11). A Genome-Phenome Association study in native microbiomes identifies a mechanism for cytosine modification in DNA and RNA. eLife, 10:e70021. *These authors contributed equally.

［Lecture Ⅲ］

Bridging Oral Microbiota and Orofacial Pain Disorders：The Case of Burning mouth syndrome and Temporomandibular disorders

Byeong-min Lee, D.D.S., Ph.D.

Researcher
Department of oral medicine
Seoul National University Dental Hospital

Abstract：
Building on our recent finding that primary burning-mouth syndrome(BMS)is marked by a Streptococcus-rich, diversity-poor salivary microbiota with predicted up-regulation of neuro-immune metabolic pathways, this presentation extends that dysbiosis-pain paradigm to temporomandibular disorders(TMD). Using the same 16S rRNA sequencing workflow, we analysed saliva from well-phenotyped TMD patients spanning muscular and arthrogenous subtypes and stratified by pain intensity. Microbiome profiles segregated along pain gradients and converged with the BMS signature, showing consistent enrichment of acidogenic Streptococcus and Veillonella species, loss of butyrate-producing taxa, and up-regulation of pathways for tryptophan-derived neuromodulators and Toll-like-receptor signalling. These shared microbial patterns mirrored overlapping clinical features—burning sensations, mechanical allodynia, and psychosocial distress—implying a common dysbiosis-driven neuro-immune mechanism across mucosal and musculoskeletal orofacial pain. Through case-control studies in both disorders, I aim to elucidate the relationships between patients' clinical and psychological characteristics and their salivary microbiota profiles, and to discuss the potential of these findings for biomarker discovery and the development of related therapeutic strategies. By juxtaposing two seemingly disparate conditions, this work positions the oral microbiome as a tractable interface between local ecology and trigeminal pain processing, laying a foundation for longitudinal and interventional studies aimed at progressing from association to causation. While based on cross-sectional data, this work juxtaposes two seemingly disparate conditions to suggest that the oral microbiome may serve as a modifiable interface between local ecology and trigeminal pain processing, thereby informing hypotheses for future longitudinal and interventional research.

Curriculum Vitae

Education

2006.03. ~ 2011.2. B.S., School of Chemical and biological engineering, Seoul national university

2011.03. ~ 2021.2. D.D.S. -Ph.D. program, School of Dentistry, Seoul national university

Thesis : 'Application of novel drug delivery system for pain control', Supervisor : Professor Gehoon Chung, DDS., Ph.D., Seoul National University

Other research experience

2008.01. ~ 2008.03. Undergraduate R.A. in Molecular Medicine and Biopharmaceutical Science Lab, Dept. of Nuclear medicine, Seoul national university

2015.06. ~ 2015.07. Visiting research in Dr. Junhyong Kim's Lab. in University of Pennsylvania

Research Fields of Interest

Orofacial pain, Temporomandibular disorder, Dental sensory system, Trigeminal nervous system, Pain diagnosis and management

Publications (Only first-author papers are listed)

1. Lee, B. M., Moon, W., Baek, K., Park, K. H., Chung, S. H., & Chung, G.(2023). Ultraviolet irradiation confers titanium oxide oleophilicity. Journal of Materials Science, 58(12), 5258-5268.
2. Lee, B. M., Park, J. W., Jo, J. H., Oh, B., & Chung, G.(2022). Comparative analysis of the oral microbiome of burning mouth syndrome patients. Journal of Oral Microbiology, 14(1), 2052632.
3. Byeong-Min Lee*, Chisong Lee*, Shayan Fakhraei Lahiji, Ui-Won Jung , Gehoon Chung#, HyungilJung#, Dissolving Microneedles for Rapid and Painless Local Anesthesia. Pharmaceutics (2020)12(4) : 366.
4. Byeong-min Lee, Yoonsun Jang, Giyeon Park, Sang Ho Oh , Teo Jeon Shin#, Gehoon Chung#, Dexmedetomidine Modulates Transient Receptor Potential Vanilloid Subtype 1. Biochemical and Biophysical Research Communications(2020)522(4) : 832-837. Kihwan Lee*, Byeong-Min
5. Lee*, Chul-Kyu Park , Yong Ho Kim#, Gehoon Chung#, Ion Channels Involved in Tooth Pain. International Journal of Molecular Sciences(2019)20(9), 2266.

[Lecture Ⅳ]

Functional crosstalks between Piezo1-TRPV1/TRPA1 channels via intracellular arachidonic acid cascade in odontoblasts

Ryuya Kurashima, DDS., PhD

PhD student
Department of Physiology, Tokyo Dental College

Abstract：
Various stimuli to the exposed surface of dentin induce deformation of odontoblast cell membrane by dentinal fluid movement inside the dentinal tubules, which activates mechanosensitive ion channels, such as transient receptor potential channel subfamilies(TRPV1, TRPV2, TRPV4 and TRPA1), and Piezo1 channels(Piezo1), leading to an intracellular free Ca^{2+} concentration ($[Ca^{2+}]_i$)increase in odontoblasts. Interestingly, inhibition of Piezo1 exhibited an obviously higher suppressive effect on the $[Ca^{2+}]_i$ increase by mechanical stimulation to odontoblasts, compared to the inhibition of the other TRP channels. Although Piezo1 activation mediated mechanosensitive Ca^{2+} influx, it reduced dentin mineralization levels. We, thus, aimed to clarify how Piezo1 provides most upstream signal for mechanosensitive processes, as well as modulatory processes in dentinogenesis, by regulating other plasma membrane proteins and/or intracellular molecules as downstream signals in odontoblasts. Direct mechanical stimulation to acutely isolated odontoblasts induced biphasic $[Ca^{2+}]_i$ increases consist of an initial-transient component mediated by Piezo1, TRPV1 and TRPA1, along with TRPV4, as well as a steady-state component by TRPV1 activations. A pharmacological Piezo1 activator, Yoda1, elicited triphasic $[Ca^{2+}]_i$ increases composed of an initial-peak component via Piezo1, a second-peak component by TRPV1 and TRPA1, and a steady-state component mediated by TRPV1 activations. Direct mechanical stimulation-induced $[Ca^{2+}]_i$ increases were inhibited by cytosolic phospholipase A2(PLA2)and cyclooxygenase(COX)inhibitors. COX activator elicited $[Ca^{2+}]_i$ increase, which was sensitive to each TRPV1 and TRPA1 antagonist. Yoda1-induced Piezo1 activation reduced dentin mineralization levels, while inhibitors for cPLA2 and COX did not affect the reduction. Our results demonstrated that Piezo1 orchestrates mechanotransduction processes in odontoblasts. Activation of intracellular cPLA2-indued COX1 activity following Piezo1 activation produces arachidonic acid metabolites, which are capable to activate TRPV1 persistently and TRPA1 transiently. Thus, functional Piezo1-TRP coupling in association with cPLA2-COX signaling mediates mechanosensory process for occurrence of dentinal sensitivity.

Curriculum Vitae

2015-2021　Tokyo Dental College（DDS）
2021-2022　Tokyo Dental College Suidobashi Hospital（intern）
2022-present　Tokyo Dental College Graduate School of Dental Science（PhD）

Research Fields of Interest

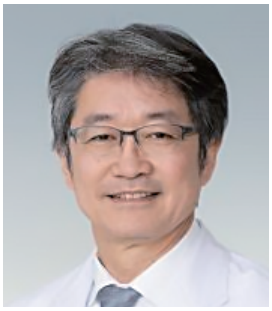
Odontoblast physiology, Mechanosensitive ion channels, Intracellular signaling, Ca2+ imaging, ATP dynamics

Selected Publications

1. Ohyama S., Ouchi T., Kimura M., Kurashima R., Yasumatsu K., Nishida D., Hitomi S., Ubaidus S., Kuroda H., Ito S., Takano M., Ono K., Mizoguchi T., Katakura A. and Shibukawa Y. Piezo1-pannexin-1-P2X3 axis in odontoblasts and neurons mediates sensory transduction in dentinal sensitivity. Frontiers in Physiology, 13：891759, 2022
2. Ouchi T., Kono K., Satou R., Kurashima R., Yamaguchi K., Kimura M. and Shibukawa Y. Upregulation of Amy1 in the salivary glands of mice exposed to a lunar gravity environment using the multiple artificial gravity research system. Frontiers in Physiology, 15：1417719, 2024
3. Kimura M., Nomura S., Ouchi T., Kurashima R., Nakano R., Sekiya H., Kuroda H., Kono K. and Shibukawa Y. Intracellular cAMP signaling-induced Ca influx mediated by calcium homeostasis modulator 1(CALHM1)in human odontoblasts. Pflügers Archiv - European Journal of Physiology, 477(2)：273-290, 2025
4. Ouchi T., Ando M., Kurashima R., Kimura M., Saito N., Iwasaki A., Sekiya H., Nakajima K., Hasegawa T., Mizoguchi T. and Shibukawa Y. Pericytes are odontoblast progenitor cells depending on ER-stress. Journal of Dental Research, 104(6)：656-667, 2025

[Keynote Lecture]

Promoting Odontoblast Differentiation and Dentin Regeneration through Wnt Signaling Activation via Sugar Chain Modification of Cell Surface Heparan Sulfate Proteoglycans



Takashi Yamashiro, DDS, PhD

Director
The Osaka University Dental Hospital
Chair and Professor
Department of Orthodontics,
Graduate School of Dentistry,
The University of Osaka

Abstract：
Dental pulp is a valuable source of stem cells capable of differentiating into various cell types, making it highly promising for regenerative medicine. In clinical dentistry, procedures such as direct pulp capping are employed to preserve pulp vitality and stimulate reparative dentin formation, thereby extending tooth longevity. However, efficient differentiation of dental pulp cells into odontoblasts—the cells responsible for dentin production—remains a significant challenge. A key objective in reparative dentin formation is to induce dentin-specific matrix proteins like Dspp and Dmp1, rather than generating bone-like tissue. To achieve this, our research has focused on activating canonical Wnt signaling, which promotes odontoblast differentiation. However, unregulated Wnt activation poses a potential tumorigenic risk, requiring safer strategies for clinical application. We investigated the role of heparan sulfate proteoglycans(HSPGs)on the surfaces of dental pulp cells and odontoblasts. HSPGs regulate growth factor signaling by modulating ligand-receptor interactions. We discovered that Wnt10a binds strongly to HSPGs, and that selective desulfation at the 6-O position—catalyzed by Sulf1/2 enzymes—enhances Wnt signaling by increasing ligand accessibility to receptors. Based on this, we proposed a novel method to promote odontoblast differentiation through glycan modification. Initial experiments using perchloric acid, a potent oxidizer, confirmed that Wnt signaling and odontoblast markers are upregulated. However, its uncontrolled radical activity raised safety concerns. We subsequently evaluated MA-T, an alternative reagent that generates radicals under controlled conditions. MA-T successfully promoted odontoblast differentiation at much lower concentrations and without cytotoxicity. This presentation will outline recent findings in odontoblast differentiation and reparative dentin formation, highlighting novel experimental strategies—particularly glycan-based modulation of Wnt signaling—as a safe

Curriculum Vitae

Takashi Yamashiro is a Professor and Chairman of the Department of Orthodontics at Osaka University and a director of Osaka University Dental Hospital. He received his DDS degree and completed his postgraduate orthodontic training at Osaka University. He also obtained his Ph.D. from Osaka University, and his post-doctoral studies in developmental biology were conducted at the Institute of Biotechnology at the University of Helsinki. Dr Yamashiro is certified by the Japanese Board of Orthodontics and is a member of the Angle Society of Orthodontics. He has also been awarded the Fellowship of Dental Surgery from the Royal College of Surgeons of Edinburgh. His scientific interests include the biological and molecular mechanisms of palatogenesis, tooth development, and craniofacial development.

Selected Publications

1. Tsujimoto T, Ou Y, Suzuki M, Murata Y, Inubushi T, Nagata M, Ishihara Y, Yonei A, Miyashita Y, Asano Y, Sakai N, Sakata Y, Ogino H, Yamashiro T, Kurosaka H. Compromised actin dynamics underlie the orofacial cleft in Baraitser-Winter Cerebrofrontofacial syndrome with a variant in ACTB. Hum Mol Genet. 2024 Nov 8；33(22)：1975-1985. doi：10.1093/hmg/ddae133.
2. Yoshida N, Inubushi T, Hirose T, Aoyama G, Kurosaka H, Yamashiro T. The roles of JAK2/STAT3 signaling in fusion of the secondary palate. Dis Model Mech. 2023 Oct 1；16(10). doi：10.1242/dmm.050085.
3. Kurosaka H, Mushiake J, Saha M, Wu Y, Wang Q, Kikuchi M, Nakaya A, Yamamoto S, Inubushi T, Koga S, Sandell LL, Trainor PA, Yamashiro T. Synergistic role of retinoic acid signaling and Gata3 during primitive choanae formation. Hum Mol Genet. 2021 Nov 30；30(24)：2383-2392. doi：10.1093/hmg/ddab205.
4. Inubushi T, Nag P, Sasaki JI, Shiraishi Y, Yamashiro T. The significant role of glycosaminoglycans in tooth development. Glycobiology. 2024 Apr 19；34(5). doi：10.1093/glycob/cwae024.
5. Hayano S, Kurosaka H, Yanagita T, Kalus I, Milz F, Ishihara Y, Islam MN, Kawanabe N, Saito M, Kamioka H, Adachi T, Dierks T, Yamashiro T. Roles of heparan sulfate sulfation in dentinogenesis. J Biol Chem. 2012 Apr 6；287(15)：12217-29.

［Lecture Ⅴ］

Fundamental Strategies Toward Bioengineered Tooth Development

Eun-Jung Kim, phD.（research associate professor）

Division in Anatomy and Developmental Biology, Department of Oral Biology, Taste Research Center, Oral Science Research Center, BK21 FOUR Project, Yonsei University College of Dentistry,

Abstract：

Tooth loss remains a major clinical challenge, and stem cell-based approaches offer promising solutions for dental tissue regeneration. In this study, we established a xeno-free, feeder-free protocol to differentiate human induced pluripotent stem cells（hiPSCs）into both dental epithelial cells（DECs）and dental mesenchymal cells（DMCs）. These hiPSC-derived cells were recombined and encapsulated in various biomaterials—GelMA, collagen, and agar matrices—to evaluate their mineralization potency. Functional assays confirmed that these differentiated cells contribute to mineralized tissue formation both in vitro and in vivo.

To further enhance the regenerative application of dental mesenchyme, we investigated the role of positional information in tooth development. Using mouse tooth germs at the cap stage, we dissected lingual and buccal mesenchymal regions and performed bulk RNA sequencing. Gene ontology analysis revealed that the lingual mesenchyme is enriched in odontogenesis and patterning genes, while the buccal mesenchyme shows higher expression of stem cell maintenance and regeneration-related genes. Functional reaggregation and transplantation analyses confirmed that only the lingual mesenchyme retains strong odontogenic potential.

Together, these findings highlight the critical role of positional identity in dental mesenchyme and the importance of precise cell characterization for tooth bioengineering. Our hiPSC-derived dental cells, combined with insights into regional mesenchymal specification, provide a robust platform for developing functional bioengineered teeth and advancing regenerative dental medicine.

Curriculum Vitae

2016-present	Research Associate professor	College of Dentistry, Yonsei University,
2012-2016	Postdoctral Researcher	College of Dentistry, Yonsei University,
2008-2012	PhD	College of Dentistry, Yonsei University,
2001-2003	Master	Department of Medical Science, Yonsei University,
1996-2000	Bachelor	Department of Biology, Hanyang University,

- Kim EJ, Kim HY, Lee S, Kim J, Li S, Adpaikar AA, Baskaran KS, Jung HS(2025)Prespecified dental mesenchymal cells for the making a tooth. International Journal of Oral Science, In Press.
- Kim EJ, Kim KH, Kim HY, Lee, DJ, Li S, Han Ngoc Mai, Jung HS(2024). Harnessing the dental cells derived from human induced pluripotent stem cells for hard tissue engineering. Journal of Advanced Research, 61：119-131.
- Kim EJ, Kim KH, Kim HY, Li S, Jung HS(2023) Fabrication of functional ameloblasts from hiPSCs for dental application. Frontiers in Cell and Developmental Biology. 11：1164811
- Kim EJ, Kim KH, Li L, Tang Q, Kim KH, Ohshima H, Jung HS(2023)Cuspal Shape Alterations by Bmp4 Directing Cell Proliferation and Apoptosis. Journal of Dental Research. 29；220345231167769
- Kim EJ, Kaushal K, Tyagi A, Karapurkar JK, Haq S, Jung HS, Kim KS, Ramakrishna S.(2022) Genome-wide screening for deubiquitinase subfamily identifies ubiquitin-specific protease 49 as a novel regulator of odontogenesis. Cell Death and Differentiation. 29(9)：1689-1704.

[Lecture Ⅵ]

Mesenchymal stem cell sensory nerve niche regulates tooth homeostasis, development and repair

Fei Pei, DDS, PhD

Lecturer/ Associate Chief Physician
Department of Cariology and endodontics
School & Hospital of Stomatology, Wuhan University

Abstract：
Mesenchymal stem cells(MSCs)reside in microenvironments(niches), where sensory nerves are emerging as critical components. However, their role in regulating the behavior of MSCs remains largely unknown. Using the continuously growing mouse incisor as a model, we found that sensory nerve depletion(via Advillin-CreER；DTA mice)reduced MSCs and impaired incisor growth. We performed scRNAseq of trigeminal ganglion at adult stage and postnatal day 3 (PN3, initial stage of tooth root development), integrated with tooth datasets, and identified FGF signaling as a key mediator of neuron-tooth cell crosstalk. Mechanistically, sensory neuron-derived FGF1 sustain MSCs through FGFR1 in Gli1+MSCs(via Gli1CreER；Fgfr1fl/fl mice)and activated mTOR/autophagy axis. Disrupting this axis recapitulated sensory nerve ablation phenotypes, including abnormal dentin formation, decreased MSCs, and impaired odontoblast differentiation. During tooth root development, sensory nerve regulated progenitor cells by binding to FGFR2. Deletion of FGFR2 in Gli1+cells by generating Gli1CreER；Fgfr2fl/fl mice led to shortened roots with impaired proliferation and differentiation of progenitor cells. Beyond homeostasis and development, sensory nerve also orchestrated tooth repair by modulating immune and endothelial cell. Together, our work unveils sensory nerve niche that governs tooth homeostasis, development and repair.

Curriculum Vitae

2012	DDS, School & Hospital of Stomatology, Wuhan University
2017	PhD, School & Hospital of Stomatology, Wuhan University
2017-Prsent	Lecturer
2019-2023	Postdoctoral Fellow, University of Southern California
2023-Present	Associate Chief Physician, Wuhan University

Research Field of Interest

1. Mesenchymal stem cell niche
2. Tooth development
3. Craniofacial sensory nerve

Selected Honors

1. Outstanding Young Researcher Award, The 13th National Annual Conference of Oral Biomedicine of Chinese Stomatological Association, 2023
2. Innovative Scientific Achievement Award, Herman Ostrow School of Dentistry of USC, 2023
3. IADR Chinese Divisional Travel Award, 2017

Selected Publications

1. Pei, F., Guo, T., Zhang, M., Ma, L., Jing, J., Feng, J., Ho, T.V., Wen, Q., and Chai, Y.(2024). FGF signaling modulates mechanotransduction/WNT signaling in progenitors during tooth root development. Bone Res 12, 37. 10.1038/s41413-024-00345-5.
2. Pei, F., Ma, L., Guo, T., Zhang, M., Jing, J., Wen, Q., Feng, J., Lei, J., He, J., Janeckova, E., et al.(2024). Sensory nerve regulates progenitor cells via FGF-SHH axis in tooth root morphogenesis. Development 151. 10.1242/dev.202043.
3. Pei, F., Ma, L., Jing, J., Feng, J., Yuan, Y., Guo, T., Han, X., Ho, T.-V., Lei, J., He, J., et al.(2023). Sensory nerve niche regulates mesenchymal stem cell homeostasis via FGF/mTOR/autophagy axis. Nat Commun 14, 344. 10.1038/s41467-023-35977-4.
4. Guo, T., Pei, F., Zhang, M., Yamada, T., Feng, J., Jing, J., Ho, T.V., and Chai, Y.(2024). Vascular architecture regulates mesenchymal stromal cell heterogeneity via P53-PDGF signaling in the mouse incisor. Cell Stem Cell 31, 904-920 e906. 10.1016/j.stem.2024.04.011.
5. Zhan Y；Wang H；Zhang L；Pei F*；Chen Z*；HDAC6 Regulates the Fusion of Autophagosome and Lysosome to Involve in Odontoblast Differentiation, Frontiers in cell and developmental biology, 2020, 8(605609)(*：co-responding)