Journal of Oral Biosciences 61 (2019) 1–4

Contents lists available at ScienceDirect

Journal of Oral Biosciences

journal homepage: www.elsevier.com/locate/job

Editorial

Oral biosciences: The annual review 2018

A B S T R A C T

Background: The *Journal of Oral Biosciences* is devoted to the advancement and dissemination of fundamental knowledge regarding every aspect of oral biosciences.
Highlight: This editorial review features summaries of review articles in the fields of "Bone Biology," "Epigenomics," "Periodontium," and "Amelogenesis" in addition to review articles by winners of the Lion Dental Research Award ("Role of non-canonical Wnt signaling pathways in bone resorption," "Mechanisms of orofacial sensory processing in the rat insular cortex," and "Analysis of the mechanism in salivary gland development using gene database") and the Rising Members Award ("Synergistic findings from microbiological and evolutional analyses of virulence factors among pathogenic streptococcal species" and "Free fatty acids may be involved in the pathogenesis of oral-related and cardiovascular diseases"), presented by the Japanese Association for Oral Biology.
Conclusion: These reviews published in the *Journal of Oral Biosciences* have inspired the readers of the Journal to broaden their knowledge of various aspects in the oral biosciences. This editorial review summarizes these exciting articles.

1. Introduction

In addition to original articles, the *Journal of Oral Biosciences* also publishes review articles by winners of the Lion Dental Research Award ("Role of non-canonical Wnt signaling pathways in bone resorption," "Mechanisms of orofacial sensory processing in the rat insular cortex," and "Analysis of the mechanism in salivary gland development using gene database") and the Rising Members Award ("Synergistic findings from microbiological and evolutional analyses of virulence factors among pathogenic streptococcal species" and "Free fatty acids may be involved in the pathogenesis of oral-related and cardiovascular diseases"), presented by the Japanese Association for Oral Biology. The Journal also publishes review articles in the fields of "Bone Biology," "Epigenomics," "Periodontium," and "Amelogenesis." These reviews, presented in the *Journal of Oral Biosciences*, have inspired the readers to broaden their knowledge of various aspects of the oral biosciences. In this editorial review, we have summarized these exciting articles.

2. JAOB/Lion dental research award

Bone remodeling is necessary for maintaining bone mass and calcium concentrations in bodily fluids. Disruptions in the balance between bone resorption and formation lead to the development of osteopenia or osteopetrosis. Various signaling pathways, such as Wnt signaling pathways, have been implicated in the regulation of the balance between bone resorption and formation. Wnt ligands activate canonical β-catenin-dependent and non-canonical β-catenin-independent signaling pathways [1]. When the Wnt ligand binds to a receptor complex composed of Frizzled receptor and low-density lipoprotein receptor-related protein 5 (Lrp5) or Lrp6, β-catenin accumulates in the cytoplasm due to the suppressed activity of its degradation complex. The accumulated β-catenin then translocates to the nucleus and induces the expression of target genes, including T-cell factor and lymphoid enhancer factor. It has been shown that activation of the Wnt/β-catenin signaling pathways in mature osteoblasts induces the expression of osteoprotegerin (OPG), which in turn suppresses bone resorption [2]. However, the involvement of the non-canonical Wnt signaling pathways in bone resorption remains unclear. In their review article, Kobayashi and colleagues describe the mechanisms by which non-canonical Wnt5a signaling promotes osteoclast differentiation and function [3]. Wnt5a is a typical non-canonical Wnt ligand that activates β-catenin-independent signaling with co-receptors, such as receptor tyrosine kinase-like orphan receptors (Rors) 1/2 [4]. Kobayashi and colleagues demonstrated that Wnt5a secreted from osteoblasts binds to Ror2 receptors and promotes the expression of receptor activator of NF-κB (Rank) through activation of c-Jun N-terminal kinases, thereby enhancing Rank ligand (Rankl)-induced osteoclastogenesis [5]. Furthermore, they clarified that Wnt16, an inhibitory Wnt ligand of osteoclastogenesis, tightly regulates bone resorption in conjunction with Wnt5a [6]. Thus, these Wnt ligands tightly regulate osteoclast differentiation and function to maintain bone mass under physiological conditions.

Orofacial structures process multiple sensations, and dental nociception, gustation, and periodontal ligament (PDL) sensations are specific to this region. This sensory information is processed in the primary sensory cortices, including the somatosensory, visual, and auditory cortices; however, accumulating evidence suggests that, in addition to the primary (S1) and secondary somatosensory (S2) cortices, orofacial sensations also involve the insular cortex (IC). Kobayashi and colleagues quantified the spatiotemporal profiles of the electrical and mechanical stimulation-induced excitation that propagates across cortical areas, including the S1, S2, and

https://doi.org/10.1016/j.job.2019.01.003
1349-0079/

IC, with a focus on physiological functions, especially orofacial somatosensation, in the rat IC [7] based on previous findings [8–12]. Orofacial structures receive abundant and distinctive types of sensory information. By integrating all these types of information, humans can perform the fine and powerful motions involved in mastication and swallowing, and thus enjoy eating food. The IC, in cooperation with the S1 and S2, likely plays a central role in the integration of these types of sensory information. Moreover, the IC receives limbic information, which might play a role in integrating sensory information with emotions.

Salivary gland hypofunction, also known as xerostomia, which can be caused by radiation therapy for head and neck cancers and Sjögren's syndrome, leads to various oral health problems and profoundly reduces quality of life. In their review article, Sakai and colleagues investigated the mechanism of salivary gland development and described approaches for salivary gland regeneration [13]. The salivary glands are formed by branching morphogenesis, which involves cell proliferation, cleft formation, differentiation, cell migration, and apoptosis, as well as reciprocal interactions between epithelial, mesenchymal, neuronal, and endothelial cells [14]. Fibronectin is an important molecule in cleft initiation [14], and its accumulation rapidly induces the expression of BTB [POZ] domain containing 7 (Btbd7), which induces the expression of *Snail2* and suppresses E-cadherin, a cell-cell adhesion molecule [15]. T7-SAGE databases were created of both the cleft and endbud of the salivary gland epithelium. In these databases, fibronectin and Btbd7 were shown to be important inducers in branching morphogenesis. Understanding the mechanism of salivary gland development could provide a model for gland restoration, and the establishment of a database of effective inducers if salivary gland development may be useful for the restoration of damaged salivary glands.

3. JAOB/Rising members award

A variety of bacteria and other microorganisms inhabit the human body, and Streptococci are major colonizers of the skin and mucosa at various body sites, including the oral cavity. Some streptococcal species have adapted to the host environment and exist as non-pathogenic commensal bacteria, while others have acquired virulence factors and have become important pathogens, and *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus pneumoniae*, are important human pathogens that cause serious bacterial infections. [16]. In his review article, Yamaguchi discussed the recently reported virulence factors of pathogenic *S. pyogenes*, *S. agalactiae*, and *S. pneumonia* [17] based on their published data [18,19]. They reported that pathogenic bacteria are evolving to adapt to the host environments under the selective pressure exerted by the host immune system, antimicrobial drugs, and vaccines [20,21]. Generally, microbiological analyses are performed on only a few representative bacterial strains, which can reveal the relationships between genes and phenotypes, whereas genome-wide association studies (GWAS) can reveal correlations. The application of GWAS makes it possible to trace bacterial evolution in nearly real-time. Continued innovations in analysis technologies are vital to minimize pathogen outbreaks and the global spread of multidrug-resistant bacteria.

Obesity is a global health issue that is associated with an increased risk of metabolic diseases, which cause increased morbidity and mortality. Overweight and obese people have a greater than 10-fold higher risk of developing type 2 diabetes (T2D) compared to normal-weight people [22]. In obese individuals and patients with T2D, blood levels of free fatty acids (FFAs) are elevated [23], and saturated fatty acids (SFAs), such as palmitate (Pal) and stearate, can induce pro-inflammatory responses mainly via the Toll-like receptor (TLR) signaling pathway [24,25]. In his review article [26], Shikama highlighted recent findings on the potential involvement of Pal in the pathogenesis of periodontitis, primary Sjögren's syndrome (SS), and cardiovascular diseases and discussed the potential of lipid profile improvement as a new strategy for the treatment of these diseases. Although the molecular mechanisms underlying the relationship between metabolic disorders and SS are largely unknown, Shikama and colleagues demonstrated that Pal can induce IL-6 secretion and α-fodrin cleavage in salivary gland epithelial cell lines, suggesting a possible link between the pathogenesis of primary SS and Pal levels in the blood [27]. They also showed that Pal induced IL-6, IL-8, and CXCL1 secretion in human gingival fibroblasts (HGFs), and that docosahexaenoic acid (DHA) suppressed Pal-induced IL-6 and IL-8 production. Treatment of HGFs with a CD36 inhibitor also inhibited Pal-induced pro-inflammatory responses. They also demonstrated that *P. gingivalis* LPS and heat-killed *P. gingivalis* augmented Pal-induced chemokine secretion in HGFs [28]. The molecular mechanisms of vascular inflammation and atherosclerosis have been extensively studied, and the crucial role of vascular endothelial cell adhesion molecules, such as ICAM-1 and E-selectin, in the interaction between leukocytes and the vascular endothelium has been established. The Pal-induced increase in the ratio of IL-1β/IL-1Ra (β/Ra9) secretion in monocytes can upregulate endothelial adhesion molecules, which may enhance leukocyte adhesion to the endothelium [29]. These results demonstrate the importance of FFAs in the pathogenesis of oral-related and cardiovascular diseases and suggest that supplementation with polyunsaturated fatty acids or derivatives may be beneficial for the treatment of primary SS, periodontitis, and cardiovascular diseases.

4. Bone biology

Bone is one of the largest tissues in the human body; it provides structural support to the body and also functions as an endocrine organ that affects global metabolism and energy balance [30]. Synthesis of the biomechanical signals and the interactions of bone with biochemical and neural signals maintain bone mass and bone matrix quality, which allow it to tolerate large physical loads [31]. Wang and Kamioka discuss the endocrine role of bone and the interactions of bone with the nervous system, vasculature, muscle, and fat tissue as well as the functional significance of these connections in their review article [32]. Osteocytes have endocrine functions [33–35], and osteoblasts affect glucose metabolism [36]. In addition, osteocytes play an important role in mineral homeostasis, which can affect bone mass density [37]. The cellular biorhythm, which assigns a different timing to the peak energy consumption of individual cells, and cell migration appear to be effective solutions to energy support limitations, which could greatly improve the efficiency of energy support. Sclerostin is the key regulator of bone modeling and remodeling, and its expression can be influenced by mechanical stimuli and hormonal signals from other organ systems. Serum sclerostin, an inhibitor of Wnt signaling, can also influence global energy metabolism to balance energy consumption between bone and other organ systems. Studies of the connections between bones and other organ systems suggest the possible existence of a temporospatial pattern of energy metabolism that acts through cellular biorhythms and cell migration.

5. Epigenomics

Epigenetic processes regulate gene activity without altering DNA sequences through various mechanisms, such as DNA

methylation, histone modifications, and non-coding RNAs [38]. These epigenetic processes have been shown to be significantly associated with various oral health problems, including periodontitis and oral cancer. In their review article, Singh and colleagues reviewed detailed epigenetic mechanisms and their possible applications in oral health and dental medicine as biomarkers and for personalized medicine [39]. In periodontitis, in which inflammation is mainly caused by inflammatory products released by bacteria, epigenetic modifications play a vital role in regulating the host immune response, especially at the biofilm-gingival interface. Since epigenetic modifications may occur in conjunction with other epigenetic processes, various studies have focused on the changes in DNA methylation and histone modification [40,41]. A few studies have focused on the role of histone modifications and histone deacetylases (HDACs) in periodontitis, while other studies have examined the microRNA (miRNA) profiles in periodontal diseases [42–44]. Various studies have suggested both hypermethylation and hypomethylation as early events in oral cancer. There is a need to explore the effects of epigenetic changes on the pathogenesis of periodontitis and oral cancer and to understand the dysregulated signaling pathways in these diseases. By evaluating the information in these studies, including the related exposomes, genomes, epigenomes, proteomes, and metabolomes, a personalized medicine approach can be developed for the treatment of periodontal diseases using biomarkers that will allow dentists and clinicians to decide if a specific pathology in a specific individual will respond to a specific therapy.

6. Periodontium

High mobility group box 1 (HMGB1) is one of the most abundant nuclear non-histone proteins [45], and it functions as a DNA chaperone that regulates transcription [46]. HMGB1 is secreted by activated dendritic cells, macrophages, and necrotic cells. In their review article, Kanzaki and Nakamura reviewed the relationship between orthodontic tooth movement (OTM) and HMGB1 [47]. PDL cells play a pivotal role in the site-specific, mechanical force-mediated bone remodeling that occurs during OTM. HMGB1 is released from the necrosed cells and is closely related to the activation of inflammatory cells; thus, the appearance of hyalinized necrotic tissue in the PDL at the initial stage of OTM strongly indicates that HMGB1 is involved in the reaction of the cells in the PDL. HMGB1 plays some important roles in the reaction of PDL during OTM. HMGB1 modulates RANKL-mediated osteoclastogenesis [48], and several osteogenic differentiation parameters, such as alkaline phosphatase (ALP), osteopontin, osteocalcin, runt-related transcription factor 2 (RUNX2), bone morphogenetic protein 2, 4 (BMP2, 4), and cementum protein 1 (CEMP1), were significantly induced by HMGB1 [49]. In addition, heat shock protein (HSP) directly modulates osteoclastogenesis and osteoblastogenesis via the induction of cytokines and protects cells from autophagy [50–53]. In conclusion, orthodontic force induces HMGB1 transcription in PDL cells, which induces osteoclastogenic and osteoblastogenic cytokine expression. HMGB1 functions as an accessory regulator of tissue remodeling, including bone resorption and bone formation, during OTM.

7. Amelogenesis

The enamel proteins present in secretory-stage (immature) enamel, in descending order of abundance, are amelogenin, ameloblastin, and enamelin. These enamel proteins are produced and secreted by ameloblasts and are slowly processed by matrix metalloproteinase 20 (MMP20) [54,55]. These proteins are later degraded by kallikrein 4 (KLK4), which is secreted from ameloblasts during the secretory and maturation stages [56]. Transforming growth factor-β (TGF-β) isoforms secreted from ameloblasts have also been reported to be present in the enamel matrix [57]. TGF-β1 regulates the mRNA expression of both *MMP20* and *KLK4* [58,59]. Moreover, through the secretion of KLK4, TGF-β1 regulates the calcification and maturation of enamel [60]. In their review article, Yamakoshi and colleagues introduced previously obtained results regarding the regulatory mechanism of enamel formation, focusing on TGF-β1, and discussed the activation and inactivation mechanisms, protein-protein interactions, and TGF-β-induced signaling, to elucidate the dynamics at the protein and genetic levels [61]. They also reported that in enamel formation, TGF-β1 influences various enamel proteins in a complicated autocrine system. Latent TGF-β1 produced and secreted from secretory-stage ameloblasts is activated by MMP20, and TGF-β1 maintains its activity by binding to amelogenin degradation products that were also processed by MMP20. Activated TGF-β1 then travels through the aqueous phase with water-soluble, 13 kDa amelogenin, binds to its receptor on the ameloblast cell surface, and induces autocrine signaling. After the transition from the secretory stage to the maturation stage, KLK4 produced and secreted by maturation-stage ameloblasts degrades TGF-β1, which then loses its activity. Thus, this TGF-β1 autocrine system is associated with the process of enamel formation in the enamel matrix.

Ethical approval

All the animal experiments were conducted in compliance with the protocol reviewed by the Institutional Animal Care and Use Committee of referred authors' universities.

Conflicts of interest

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

References

[1] Miller JR. The Wnts. Genome Biol;3:REVIEWS3001; 2002.
[2] Glass 2nd DA, Bialek P, Ahn JD, Starbuck M, Patel MS, Clevers H, Taketo MM, Long FX, McMahon AP, Lang RA, Karsenty G. Canonical Wnt signaling in differentiated osteoblasts controls osteoclast differentiation. Dev Cell 2005;8:751–64.
[3] Kobayashi Y, Uehara S, Udagawa N. Roles of non-canonical Wnt signaling pathways in bone resorption. J Oral Biosci 2018;60:31–5.
[4] Mikels A, Minami Y, Nusse R. Ror2 receptor requires tyrosine kinase activity to mediate Wnt5A signaling. J Biol Chem 2009;284:30167–76.
[5] Maeda K, Kobayashi Y, Udagawa N, Uehara S, Ishihara A, Mizoguchi T, Kikuchi Y, Takada I, Kato S, Kani S, Nishita M, Marumo K, Martin TJ, Minami Y, Takahashi N. Wnt5a-Ror2 signaling between osteoblast-lineage cells and osteoclast precursors enhances osteoclastogenesis. Nat Med 2012;18:405–12.
[6] Kobayashi Y, Thirukonda GJ, Nakamura Y, Koide M, Yamashita T, Uehara S, Kato H, Udagawa N, Takahashi N. Wnt16 regulates osteoclast differentiation in conjunction with Wnt5a. Biochem Biophys Res Commun 2015;463:1278–83.
[7] Kobayashi M. Mechanisms of orofacial sensory processing in the rat insular cortex. J Oral Biosci 2018;60:59–64.
[8] Nakamura H, Kato R, Shirakawa T, Koshikawa N, Kobayashi M. Spatiotemporal profiles of dental pulp nociception in rat cerebral cortex: an optical imaging study. J Comp Neurol 2015;523:1162–74.
[9] Nakamura H, Shirakawa T, Koshikawa N, Kobayashi M. Distinct excitation to pulpal stimuli between somatosensory and insular cortices. J Dent Res 2016;95:180–7.
[10] Horinuki E, Shinoda M, Shimizu N, Koshikawa N, Kobayashi M. Orthodontic force facilitates cortical responses to periodontal stimulation. J Dent Res 2015;94:1158–66.
[11] Horinuki E, Yamamoto K, Shimizu N, Koshikawa N, Kobayashi M. Sequential changes in cortical excitation during orthodontic treatment. J Dent Res 2016;95:897–905.
[12] Kaneko M, Horinuki E, Shimizu N, Kobayashi M. Physiological profiles of cortical responses to mechanical stimulation of the tooth in the rat: an optical imaging study. Neuroscience. 2017;358:170–80.
[13] Sakai T, Minagi HO, Obana-Koshino A, Sakai M. Analysis of the mechanism in

salivary gland development using gene database. J Oral Biosci 2018;60:83–6.
[14] Sakai T, Larsen M, Yamada KM. Fibronectin requirement in branching morphogenesis. Nature 2003;423:876–81.
[15] Onodera T, Sakai T, Hsu JC, Matsumoto K, Chiorini JA, Yamada KM. Btbd7 regulates epithelial cell dynamics and branching morphogenesis. Science. 2010;329:562–5.
[16] Kilian M, Riley DR, Jensen A, Bruggemann H, Tettelin H. Parallel evolution of Streptococcus pneumoniae and Streptococcus mitis to pathogenic and mutualistic lifestyles. Mbio 2014;5 [e01490–14].
[17] Yamaguchi M. Synergistic findings from microbiological and evolutional analyses of virulence factors among pathogenic streptococcal species. J Oral Biosci 2018;60:36–40.
[18] Yamaguchi M, Hirose Y, Nakata M, Uchiyama S, Yamaguchi Y, Goto K, Sumitomo T, Lewis AL, Kawabata S, Nizet V. Evolutionary inactivation of a sialidase in group B Streptococcus. Sci Rep 2016;6:28852.
[19] Yamaguchi M, Kawabata S. Streptococcal enolase and immune evasion. In: Henderson B, editor. Moonlighting proteins: novel virulence factors in bacterial infections. Hoboken, NJ, USA: Wiley-Blackwell; 2017. p. 269–89.
[20] Walker CLF, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, O'Brien KL, Campbell H, Black RE. Childhood pneumonia and diarrhoea 1 global burden of childhood pneumonia and diarrhoea. Lancet 2013;381:1405–16.
[21] Weinberger DM, Malley R, Lipsitch M. Serotype replacement in disease after pneumococcal vaccination. Lancet 2011;378:1962–73.
[22] Kopelman P. Health risks associated with overweight and obesity. Obes Rev 2007;8:13–7.
[23] Boden G. Interaction between free fatty acids and glucose metabolism. Curr Opin Clin Nutr 2002;5:545–9.
[24] Maloney E, Sweet IR, Hockenbery DM, Pham M, Rizzo NO, Tateya S, Handa P, Schwartz MW, Kim F. Activation of NF-kappa B by palmitate in endothelial cells: a key role for NADPH oxidase-derived superoxide in response to TLR4 activation. Arterioscler Thromb Vasc Biol 2009;29:1370–5.
[25] Snodgrass RG, Huang S, Choi IW, Rutledge JC, Hwang DH. Inflammasome-mediated secretion of IL-1 beta in human monocytes through TLR2 activation; modulation by dietary fatty acids. J Immunol 2013;191:4337–47.
[26] Shikama Y. Free fatty acids may be involved in the pathogenesis of oral-related and cardiovascular diseases. J Oral Biosci 2018;60:65–9.
[27] Shikama Y, Ishimaru N, Kudo Y, Bando Y, Aki N, Hayashi Y, Funaki M. Effects of free fatty acids on human salivary gland epithelial cells. J Dent Res 2013;92:540–6.
[28] Shikama Y, Kudo Y, Ishimaru N, Funaki M. Possible involvement of palmitate in pathogenesis of periodontitis. J Cell Physiol 2015;230:2981–9.
[29] Shikama Y, Aki N, Hata A, Nishimura M, Oyadomari S, Funaki M. Palmitate-stimulated monocytes induce adhesion molecule expression in endothelial cells via IL-1 signaling pathway. J Cell Physiol 2015;230:732–42.
[30] Zhang Q, Riddle RC, Clemens TL. Bone and the regulation of global energy balance. J Intern Med 2015;277:681–9.
[31] Findlay DM. Biology of bone and the interaction of bone with other organ systems. In: Pivonka P, editor. Multiscale mechanobiology of bone remodeling and adaptation: Cham. Switzerland: Springer International; 2017. p. 259–87.
[32] Wang ZY, Kamioka H. The temporospatial pattern of energy metabolism coordinates the interactions between the bones and other organ systems. J Oral Biosci 2018;60:8–14.
[33] Sato M, Asada N, Kawano Y, Wakahashi K, Minagawa K, Kawano H, Sada A, Ikeda K, Matsui T, Katayama Y. Osteocytes regulate primary lymphoid organs and fat metabolism. Cell Metab 2013;18:749–58.
[34] Moverare-Skrtic S, Henning P, Liu XW, Nagano K, Saito H, Borjesson AE, Sjogren K, Windahl SH, Farman H, Kindlund B, Engdahl C, Koskela A, Zhang FP, Eriksson EE, Zaman F, Hammarstedt A, Isaksson H, Bally M, Kassem A, Lindholm C, Sandberg O, Aspenberg P, Savendahl L, Feng JQ, Tuckermann J, Tuukkanen J, Poutanen M, Baron R, Lerner UH, Gori F, Ohlsson C. Osteoblast-derived WNT16 represses osteoclastogenesis and prevents cortical bone fragility fractures. Nat Med 2014;20:1279–88.
[35] Oldknow KJ, MacRae VE, Farquharson C. Endocrine role of bone: recent and emerging perspectives beyond osteocalcin. J Endocrinol 2015;225:R1–19.
[36] Yoshikawa Y, Kode A, Xu LL, Mosialou I, Silva BC, Ferron M, Clemens TL, Economides AN, Kousteni S. Genetic evidence points to an osteocalcin-independent influence of osteoblasts on energy metabolism. J Bone Miner Res 2011;26:2012–25.
[37] Xiong JH, Piemontese M, Onal M, Campbell J, Goellner JJ, Dusevich V, Bonewald L, Manolagas SC, O'Brien CA. Osteocytes, not osteoblasts or lining cells, are the main source of the RANKL required for osteoclast formation in remodeling bone. PLoS One 2015;10:e0138189.
[38] Descalzi G, Ikegami D, Ushijima T, Nestler EJ, Zachariou V, Narita M. Epigenetic mechanisms of chronic pain. Trends Neurosci 2015;38:237–46.
[39] Singh A, Gill G, Jakhu H. Epigenetics and its implications for oral health. J Oral Biosci 2018;60:41–8.
[40] Kim Y, Kim K, Park D, Lee E, Lee H, Lee YS, Choe J, Kim YM, Jeoung D. DNA methyl transferase I acts as a negative regulator of allergic skin inflammation. Mol Immunol 2013;53:1–14.
[41] Valinluck V, Sowers LC. Endogenous cytosine damage products alter the site selectivity of human DNA maintenance methyltransferase DNMT1. Cancer Res 2007;67:946–50.
[42] Stoecklin-Wasmer C, Guarnieri P, Celenti R, Demmer RT, Kebschull M, Papapanou PN. MicroRNAs and their target genes in gingival tissues. J Dent Res 2012;91:934–40.
[43] Xie YF, Shu R, Jiang SY, Liu DL, Zhang XL. Comparison of microRNA profiles of human periodontal diseased and healthy gingival tissues. Int J Oral Sci 2011;3:125–34.
[44] Lee YH, Na HS, Jeong SY, Jeong SH, Park HR, Chung J. Comparison of inflammatory microRNA expression in healthy and periodontitis tissues. Biocell 2011;35:43–9.
[45] Bianchi ME, Beltrame M. Flexing DNA: hmg-box proteins and their partners. Am J Hum Genet 1998;63:1573–7.
[46] Bonaldi T, Langst G, Strohner R, Becker PB, Bianchi ME. The DNA chaperone HMGB1 facilitates ACF/CHRAC-dependent nucleosome sliding. EMBO J 2002;21:6865–73.
[47] Kanzaki H, Nakamura Y. Orthodontic tooth movement and HMGB1. J Oral Biosci 2018;60:49–53.
[48] Zhou Z, Han JY, Xi CX, Xie JX, Feng X, Wang CY, Mei L, Xiong WC. HMGB1 regulates RANKL-induced osteoclastogenesis in a manner dependent on RAGE. J Bone Miner Res 2008;23:1084–96.
[49] Wolf M, Lossdorfer S, Romer P, Craveiro RB, Deschner J, Jager A. Anabolic properties of high mobility group box protein-1 in human periodontal ligament cells in vitro. Mediat Inflamm 2014;2014:347585.
[50] Baba S, Kuroda N, Arai C, Nakamura Y, Sato T. Immunocompetent cells and cytokine expression in the rat periodontal ligament at the initial stage of orthodontic tooth movement. Arch Oral Biol 2011;56:466–73.
[51] Arai C, Nomura Y, Ishikawa M, Noda K, Choi JW, Yashiro Y, Hanada N, Nakamura Y. HSPA1A is upregulated in periodontal ligament at early stage of tooth movement in rats. Histochem Cell Biol 2010;134:337–43.
[52] Arai C, Nomura Y, Matsuzawa M, Hanada N, Nakamura Y. Extracellular HSP72 induces proinflammatory cytokines in human periodontal ligament fibroblast cells through the TLR4/NF-kappa B pathway in vitro. Arch Oral Biol 2017;83:181–6.
[53] Nakamura Y, Hirashita A, Kuwabara Y. The localization of acid-phosphatase activity in osteoblasts incident to experimental tooth movement. Acta Histochem Cytochem 1984;17:571–82.
[54] Hu JCC, Sun XL, Zhang CH, Liu SX, Bartlett JD, Simmer JP. Enamelysin and kallikrein-4 mRNA expression in developing mouse molars. Eur J Oral Sci 2002;110:307–15.
[55] Begue-Kirn C, Krebsbach PH, Bartlett JD, Butler WT. Dentin sialoprotein, dentin phosphoprotein, enamelysin and ameloblastin: tooth-specific molecules that are distinctively expressed during murine dental differentiation. Eur J Oral Sci 1998;106:963–70.
[56] Simmer JP, Hu YY, Richardson AS, Bartlett JD, Hu JCC. Why does enamel in Klk4-null mice break above the dentino-enamel junction? Cells Tissues Organs 2011;194:211–5.
[57] Benedete APS, Sobral APV, Lima DMC, Kamibeppu L, Soares FA, Lourenco SV. Expression of transforming growth factor-beta 1, -beta 2, and -beta 3 in human developing teeth: immunolocalization according to the odontogenesis phases. Pediatr Dev Pathol 2008;11:206–12.
[58] Gao YG, Zhang L, Xiang LL, Li BH, Liu XY, Wang YM, Sun Y. Transforming growth factor-beta 1 regulates expression of the matrix metalloproteinase 20 (Mmp20) gene through a mechanism involving the transcription factor, myocyte enhancer factor-2C, in ameloblast lineage cells. Eur J Oral Sci 2014;122:114–20.
[59] Suzuki M, Shin M, Simmer JP, Bartlett JD. Fluoride affects enamel protein content via TGF-beta 1-mediated KLK4 inhibition. J Dent Res 2014;93:1022–7.
[60] Cho A, Haruyama N, Hall B, Danton MJS, Zhang L, Arany P, Mooney DJ, Harichane Y, Goldberg M, Gibson CW, Kulkarni AB. TGF-beta regulates enamel mineralization and maturation through KLK4 expression. PLoS One 2013;8:e82267.
[61] Kobayashi S, Yamakoshi Y, Asada Y. TGF-beta autocrine signaling at secretory-stage enamel. J Oral Biosci 2018;60:70–5.

Vice Editor-in-Chief
Hayato Ohshima *
Division of Anatomy and Cell Biology of the Hard Tissue, Department of Tissue Regeneration and Reconstruction, Niigata University Graduate School of Medical and Dental Sciences,
2-5274 Gakkocho-dori, Chuo-ku, Niigata 951-8514, Japan
E-mail address: histoman@dent.niigata-u.ac.jp

Editor-in-Chief
Norio Amizuka
Department of Developmental Biology of Hard Tissue, Graduate School of Dental Medicine, Faculty of Dental Medicine, Hokkaido University, Kita 13 Nishi 7 Kita-ku, Sapporo 060-8586, Japan

Received 15 January 2019; accepted 21 January 2019

Available online 29 January 2019

* Corresponding author