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Editorial

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ABSTRACT

Background: The *Journal of Oral Biosciences* is devoted to the advancement and dissemination of fundamental knowledge concerning every aspect of oral biosciences.
Highlight: This review article features the following topics that were presented in symposia held during the annual meeting of the Japanese Association for Oral Biology: “Multidimensional Bioimaging on Biofunction,” “The Front Line of Research on Saliva and Salivary Gland,” “Research on the Front Line in Recovery of Oral Sensory Function under Neuropathic Condition,” “Mechanism for Generation and Transport of Intracellular Organelles,” “Forefront of Research to Understand the Oral Micro-ecosystems,” and “A New Horizon of Imaging for Bone Cells: How Far Can We Observe the Mechanisms Underlying Bone Biology?,” in addition to review articles in the field of “Head and Neck Cancer,” “Amelogenesis,” “Biofilm,” and “Dentin Sensitivity.”
Conclusion: These reviews in the *Journal of Oral Biosciences* have inspired its readers to broaden their knowledge regarding the various aspects of oral biosciences. The current editorial review introduces these exciting review articles.

1. Introduction

In addition to original articles, the *Journal of Oral Biosciences* also publishes review articles by prizewinners of the “Lion Dental Research Award” and “Rising Members Award,” presented by the Japanese Association for Oral Biology. The Journal also publishes review articles featuring recent information presented in symposia held during the annual meeting of the Association. In 2017, we published special issues featuring the following reviews: “Multidimensional Bioimaging on Biofunction,” “The Front Line of Research on Saliva and Salivary Gland,” “Research on the Front Line in Recovery of Oral Sensory Function under Neuropathic Condition,” “Mechanism for Generation and Transport of Intracellular Organelles,” “Forefront of Research to Understand the Oral Micro-ecosystems,” and “A New Horizon of Imaging for Bone Cells: How Far Can We Observe the Mechanisms Underlying Bone Biology?,” in addition to review articles in the field of “Head and Neck Cancer,” “Amelogenesis,” “Biofilm,” and “Dentin Sensitivity.” These reviews in the *Journal of Oral Biosciences* have inspired the readers of the Journal to broaden their knowledge regarding various aspects of oral biosciences. The current editorial review introduces these exciting review articles.

2. Multidimensional bioimaging on biofunction

Embryonic tissue development is a highly organized process with biological robustness for reproducibility in the formation of morphologically and functionally proper tissues. Cyclic or periodic waves, such as a molecular clock, have been proposed to contribute to such robustness. Iimura and colleagues successfully identified a possible rhythmic action in developing zebrafish embryos using a combined approach of live imaging and mathematical modeling [1]. Iimura and Lee introduced these experimental and theoretical approaches that are used to understand asynchronous cell cycle progression, the rhythmic growth mode of tissue development, and the potential of the live imaging-based mathematical approach for biomedical research in their review article [2]. Quantitative imaging and mathematical modeling can be compatible with molecular ohmics such as genomics and proteomics. Additional integrative approaches would widen and deepen our understanding of biomedical mechanisms to undoubtedly lead to advances in biodentistry and biomedicine.

3. The front line of research on saliva and salivary gland

Rab proteins play important roles in eukaryotic intracellular membrane trafficking and constitute the largest subfamily among the Ras superfamily of small GTPases [3–5]. Parotid acinar cells are amylase-secreting exocrine cells that have many secretory granules and vesicles containing amylase [6]. Amylase release via granule exocytosis by isoproterenol (IPR), a β-agonist, occurs through multiple membrane trafficking steps. Rab proteins and their effectors are heavily involved in the membrane trafficking pathways. Imai and colleagues reported on the function of Rab proteins in parotid acinar cells and demonstrated that Rab27 and its effectors and regulators are involved in the control of

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IPR-induced amylase release [7–11]. Imai and Tsujimura summarized the roles of Rab27 and its effectors and regulators in IPR-stimulated amylase release from parotid acinar cells in their review article [12]. IPR stimulation induces amylase release via granule exocytosis, while secretory granules containing GTP-Rab27 are concomitantly inactivated by EBP50-PDZ interactor of 64 kDa (EPI64), to enhance the GTPase activity of Rab27 at the luminal membrane. The resulting GDP-Rab27 is translocated by a GDP dissociation inhibitor (GDI) to the cytosol from the luminal site. Finally, GDP bound to Rab27 is exchanged for GTP by the guanine nucleotide exchange factor (GEF) activity of MAP-kinase activating death domain protein (MADD) in the cytosol to restart the GDP/GTP cycle of Rab27.

Most of the established biological functions of saliva such as wound repair, pain control, buffering, dilution and cleaning, digestion, lubrication, and protection of tooth enamel as well as its antimicrobial properties are conferred by parent proteins and, occasionally, their processed forms [13]. These biological functions are associated with systemic health as well as oral health. The environment of the oral cavity, the "port of entry" of the gastrointestinal tract, is likened to a high-performance and elaborate incubator because the pH and temperature in the cavity and gastrointestinal tract are precisely controlled. The oral cavity contains culture media rich in nutrients supplied by dietary foods, in which notable proteolytic events take place on salivary and dietary proteins. The peptide fragments created by proteases from oral epithelial cells, bacteria, and a serum-like gingival crevicular transudate play important roles in both the oral cavity and further downstream in the alimentary canal. Despite the identification of more than 4000 different salivary peptides and protein species [14], the physiological functions of salivary peptides remain to be understood. Saito and colleagues summarized the identified bioactive peptides that are hidden in human salivary parent proteins such as statherin, histatin 3, histatin 1, three proline-rich proteins (PRPs) [P-B1 (alias SMR3A), P-B (SMR3B), and BPLP (basic proline-rich lacrimal protein)], and mucin 7 (MG2) in their review article [15]. It must be taken into consideration that bioactive peptides can be generated by proteolytic cleavage of known salivary proteins.

Hemodynamics in the salivary gland are largely regulated by both the sympathetic and parasympathetic nervous systems [16]. The parasympathetic vasodilator response is due to both cholinergic and non-cholinergic neurotransmitters, such as vasoactive intestinal peptide (VIP) [17–19], whereas the sympathetic vasoconstrictor response is mainly due to α-adrenoceptor activation and neuropeptide Y, and only a small portion of the vasodilator response is attributable to β-adrenoceptor activation [20]. Thus, the autonomic nervous system is involved in regulating the secretion and hemodynamics of the salivary gland. In addition to salivary secretion, trigeminal sensory input induces cholinergic as well as non-cholinergic parasympathetic reflex vasodilation in the salivary glands [17–19]. However, the sympathetic vasoconstrictive nerve fibers to the salivary glands remain in a state of tonic control. Therefore, parasympathetic vasoactive nerve fibers predominantly contribute to vasodilation under reflex conditions such as during feeding [16]. This glandular vasodilation is thought to be important in the regulation of glandular hemodynamics due to the rapidly increased blood flow. Parasympathetic reflex vasodilation in the salivary glands, especially in the submandibular gland, has been previously examined [17–19]. Sato and Ishii focused on the differences in parasympathetic vasodilation among the major salivary glands, the interaction between cholinergic and non-cholinergic vasodilator mechanisms, and the physiological role of parasympathetic vasodilation in the salivary glands in their review article [21]. Trigeminal sensory input elicits parasympathetic vasodilation in the salivary glands, which is mainly evoked by cholinergic fibers in the submandibular and parotid glands, and by cholinergic and VIP-ergic fibers in the sublingual gland. The differences in the mechanisms underlying parasympathetic vasodilation may be functionally related to differences in secretory types among the major salivary glands.

In several rodent species, there is an additional duct segment interposed between the intercalated and typical striated ducts. This portion of the duct system is characterized by the presence of numerous secretory granules (SG), which are localized to the apical cytoplasm, and referred to as a granular duct [22]. The oral antibacterial activity of endogenous salivary peroxidase (PO) is widely accepted in the field of dentistry, and PO is known to be a clinically important salivary enzyme [23] that is found in a variety of glands [24–27]. The 3,3'-diaminobenzidine tetrazolium (DAB)-based staining methods have been developed to detect the localization of PO activity. PO activity is present in the secretory material of the acinar cells of the rat submandibular gland, suggesting that this enzyme could be used as a convenient marker of differentiated acinar cells during rat salivary gland development [28]. Moriguchi and colleagues summarized the localization differences of endogenous PO activity among human, rodent (rat and hamster), and insectivora (*Suncus murinus*) salivary glands using the DAB staining method in their review article [29] based on their previous studies [30–33]. Moreover, reflectance-mode confocal laser scanning microscopy was employed to visualize sites of PO activity in the ectopic sublingual gland-like tissue of the hamster submandibular gland, revealing an important addition to the utility of this cytochemical technique.

4. Research on the front line in recovery of oral sensory function under neuropathic condition

Neuroglial cells (astroglia and microglia) are involved in orofacial neuropathic pain [34–38]. In the central nervous system (CNS), astroglia modulate synaptic transmission by regulating the external chemical environment [39–42], and microglial activation precedes the astroglial activation under neuropathic pain conditions [35,37,38]. Astroglia are involved in the uptake of extra-synaptic glutamate by neurons and in the synthesis of glutamine from glutamate in a reaction catalyzed by glutamine synthetase. Neurons use the glutamine to produce glutamate and replenish the glutamate supply [36,43–46], a process that is referred to as the glutamate–glutamine shuttle. This process plays an important role in mediating central sensitization and neuronal excitability during neuropathic pain [43–46] and is involved in mediating central sensitization in the trigeminal spinal subnucleus caudalis (Sp5C) during neuropathic pain conditions [34–36,40,43–46]. Recently, Kitagawa and colleagues demonstrated that microglia and astroglia are also activated in the trigeminal motor nucleus during the modulation of orofacial motor behavior under neuropathic conditions [46,47]. Kitagawa and colleagues highlighted the involvement of neuroglia in modulating orofacial motor behavior in neuropathic pain in their review article [48]. The findings that microglia are activated earlier than astroglia during neuropathic pain suggest the involvement of microglia in pain initiation and astroglia in the maintenance of the chronic neuropathic pain condition.

5. Mechanism for generation and transport of intracellular organelles

After synthesis at the endoplasmic reticulum (ER), proteins are delivered to specific destinations where they perform their given functions. Sorting signals have been reported to be present in the