Journal of Oral Biosciences (2016) 1–9

Contents lists available at ScienceDirect

Journal of Oral Biosciences

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

Editorial

# Oral biosciences: The annual review 2015

A B S T R A C T

*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: "Novel challenge for bone formation and bone resorption," "The front line of research on oral microbiota," "Clinical insight into the study of orofacial pain," "Carving a disease by omics," "The front line of bioimaging—a new light shining on oral biosciences," "Biodental engineering—integration of biology and material science," "Translational dental research over the CCN family," "Salivary glands," "Break the negative spiral consisting of periodontitis, diabetes, and Alzheimer's disease: extending healthy life expectancy through oral health," "Immunology and oncology," "Oral microbiome and biofilm research: new concepts and new approaches," "Bone remodeling mechanisms of bone resorption and bone formation," and "The front line of oral biofilm research," in addition to review articles by invited authors in the field of microbiology.
*Conclusion:* These reviews published 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.


## 1. Introduction

In addition to original articles, the *Journal of Oral Biosciences* also publishes review articles by the 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 2015, we published special issues featuring the following reviews: "Novel challenge for bone formation and bone resorption," "The front line of research on oral microbiota," "Clinical insight into the study of orofacial pain," "Carving a disease by omics," "The front line of bioimaging—new light shining on oral biosciences," "Biodental engineering—integration of biology and material science," "Translational dental research over the CCN family," "Salivary glands," "Break the negative spiral consisting of periodontitis, diabetes and Alzheimer's disease: extending healthy life expectancy through oral health," "Immunology and oncology," "Oral microbiome and biofilm research: new concepts and new approaches," "Bone remodeling mechanisms of bone resorption and bone formation," and "The front line of oral biofilm research," in addition to the review articles by the invited authors in the field of microbiology. These reviews published 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. Novel challenge for bone formation and bone resorption

It is well known that sympathetic nerve activity and hormone serum levels show circadian rhythms, and have been identified in most animals [1–3]. Although circadian rhythms are also prevalent in bone metabolism, the underlying molecular mechanisms are poorly understood. Recently, clock genes were discovered to be the modulators of circadian rhythmicity in animals. In their review article [4], Kondo and Togari focused on their recent findings regarding the circadian regulation of bone metabolism by β-adrenergic signaling, glucocorticoids, and clock genes [5–7]. They demonstrated that β-adrenergic signaling and/or glucocorticoids are mediators of circadian rhythms from the suprachiasmatic nuclei (SCN), where the main circadian rhythm is regulated by endogenous circadian clocks, to peripheral osteoblasts. In addition, glucocorticoids are one of the most important factors in the transmission of circadian timing from the SCN to peripheral osteoclasts. Finally, the osteoclast peripheral clock may regulate the circadian rhythm of bone resorption by regulating the expression of osteoclast-related genes such as cathepsin K (*mCtsk*) and nuclear factor of activated T-cells cytoplasmic 1 (*mNfatc1*) [6]. Thus, the clock gene, muscle Arnt-like protein (BMAL), contributes to osteoclast circadian rhythm.

Regarding osteoclast differentiation from hematopoietic stem cells, recent studies have found that two proteins, receptor activator of NF-κB (RANK) and its ligand (RANKL), are crucial for osteoclast development [8,9]. It has been reported that mice lacking both NF-κB1 and NF-κB2 develop typical osteopetrosis accompanied by a dramatic reduction in osteoclast number due to defective tracking of the osteoclast lineage [10,11], suggesting that osteoclast differentiation depends on RANKL-induced NF-κB activation in the osteoclast precursors. A recent study reported that in vitro inactivation of NF-κB using specific inhibitors and in vivo expression of dominant-negative IKKβ in osteoblasts enhanced osteoblastic bone formation [12], suggesting that NF-κB regulates both osteoblastic bone formation and osteoclastic bone resorption.

http://dx.doi.org/10.1016/j.job.2015.12.001
1349-0079/

In their review article [13], Jimi and colleagues focused on the recent discoveries, highlighting the roles of the "classical" and "alternative" NF-κB signaling pathways in bone morphogenetic protein (BMP) induced osteoblast differentiation and bone formation, and discussed the possibility that inhibition of NF-κB might promote BMP-induced bone regeneration for the treatment of bone diseases. Activation of the classical and alternative NF-κB pathways negatively regulates osteoblastic bone formation by modulating BMP/Smad signaling through two distinct mechanisms: inhibition of BMP-induced Smad DNA binding, and Smad1/5/8 phosphorylation [14–16]. Specific inhibitors of the NF-κB pathways seem to be efficient not only in preventing bone loss, but also in stimulating bone formation, which is referred to as "One bite provides dual tastes." Thus, NF-κB-selective inhibitors may have the potential to improve BMP-induced bone regeneration.

## 3. The front line of research on oral microbiota

Anaerobic cultural methods continue to expand our understanding of the oral microbiota of periodontitis and dental caries, although approaches for strain identification have evolved from biochemical tests to 16S rRNA sequence-based identification. Tanner, in her review article [17] based on her findings [18–22], focused on selective anaerobic culture studies that have provided the basis of our understanding of the oral microbiota. Non-cultural molecular analyses of plaque samples, mainly based on analysis of the 16S rRNA gene, have highlighted both the strengths and limitations of the culture-based methods in describing the complete oral microbiota. Nevertheless, when bacteria are detected by molecular methods, the focus then becomes to devise methods to cultivate them [23] which frequently involves the use of anaerobic methods. Anaerobic culture of bacteria associated with advanced periodontitis and dental caries, compared to healthy, non-diseased, sites has proven extremely valuable in expanding our knowledge of the bacteria associated with these major clinical conditions of the oral cavity. Anaerobic culture studies have enabled the rapid detection and identification of species using molecular methods that can be used in studies of larger populations of subjects. However, it can process only a limited number of samples. Furthermore, species in lower proportions of the overall microbiota, and species for which the nutritional requirements are as yet unknown, remain undetected by anaerobic culture [23]. A finding of clinical importance is that the pathogens in advanced periodontal and carious lesions were detected in the initial stages of the disease as well, suggesting that they can be suitable candidates for disease risk assessment. Since dental pathogens may also colonize healthy sites, assessment of periodontal and caries risk will require the addition of other risk markers—for example, host factors in periodontitis [24], and diet in dental caries [25].

Oral malodor in humans has long been a major health concern and may serve as a useful assessment tool for evaluating patients in a critical condition. Epidemiological studies have found that poor oral hygiene is associated with an increased risk of squamous cell carcinoma of the head, neck, and esophagus [26,27]; some have shown that the association might be causal [28–30]. Malodor originating in the oral cavity is an indicator of the metabolic output of the oral microbial communities as a whole. It is possible that the oral malodorous gases indicate not only halitosis, but also the pathogenicity of oral microbiota. In their review article [31], Tanda and colleagues focused on the role of microorganisms in producing malodorous gases, as well as the development of analytical techniques for the treatment of halitosis. Since most oral malodor originates from microbial activities in the mouth [30], and microbial activities cause aspiration pneumonia in hospitalized patients [32], oral malodor can serve as an indicator of the oral condition of critically ill patients. The oral cavity is easily exposed to tobacco smoke and alcohol, which are not only prominent risk factors for carcinogenesis, but also the strongest factors that increase microbial acetaldehyde production [33]. Hydrogen sulfide has been recognized as both a major cause of halitosis and as a gaseous-signaling molecule that might modulate cell physiology [34]. Continuous advances in the analytical techniques examining oral malodorous gases for the treatment of halitosis would enable better risk assessment of aspiration pneumonia and oral cancer in the future. Furthermore, metabolic approaches to oral malodor [35] may also elucidate the mechanisms underlying the production of gaseous metabolites relevant to these diseases.

## 4. Clinical insight into the study of orofacial pain

Allodynia and/or hyperalgesia frequently occur in the orofacial region following trigeminal nerve injury or orofacial inflammation [36]. Pathological pain associated with such an injury/inflammation is severe and difficult to treat, and occurs in wide areas innervated by the injured as well as uninjured nerve fibers. Similar symptoms have been observed in uninflamed as well as inflamed areas [37]. It is very important to understand the mechanisms underlying extraterritorial orofacial pain associated with trigeminal nerve injury or orofacial inflammation in order to develop appropriate measures for the treatment of patients with extraterritorial orofacial pain. Sugimoto and colleagues described recent findings in animal models, and the future directions of investigations of pathological pain mechanisms in their review article [38]. They summarized the current understanding of orofacial pain mechanisms as follows: (1) neurotransmitters are released from the somata of trigeminal ganglion (TG) neurons involved in peripheral sensitization; (2) the neurotransmitters released from the TG neurons are depressed after botulinum toxin-type A (BoNT/A) administration, suggesting that BoNT/A decreases neurotransmitter release to reduce neuropathic pain behavior; (3) glial cells are involved in the orofacial pathological pain associated with trigeminal nerve injury or orofacial inflammation along with the trigeminal spinal subnucleus caudalis and C1–C2 nociceptive neurons; (4) the trigeminal sensory nuclear complex, especially the trigeminal spinal subnucleus oralis, is structurally and functionally involved in orofacial pain sensations in normal and pathological pain conditions after peripheral nerve injuries; (5) neuroimaging analyses have suggested functional changes in the central and peripheral nervous systems in neuropathic pain conditions.

## 5. Carving a disease by omics

The CCN family is a group of matricellular proteins with six distinct members in mammals; of these, CCN2 is required for the proper development of the olfactory central nervous system [39], pancreas [40], hair follicles [41], and skeletal system [42] and is involved in multiple steps of orofacial development [43,44]. Specifically, CCN2 is important for skeletal development with the support of complex gene regulatory systems in the relevant cells, including osteoblasts, chondrocytes, and osteoclasts [42,45–47]. Kubota and colleagues focused on the biological roles of CCN2 in different microenvironments in their review article [48]. Since the proteins of the CCN family perform their functions through the manipulation of multiple molecular counterparts in the microenvironment, via molecular networks, the biological outcomes yielded by these proteins are sometimes unpredictable. Through combinatory investigation with metabolomic and transcriptomic