Review Article

Open Access Journal of
Biomedical Science
ISSN: 2690-487X

Sclerostin in Oral Tissues: Distribution, Biological Functions and Potential Therapeutic Role

Fangyuan Shuai[1], Aileen To[2], Yan Jing[3] and Xianglong Han[1]*

[1]*State Key Laboratory of Oral Diseases, West China Hospital of Stomatology, Sichuan University, China*

[2]*Texas A&M College of Dentistry, D3 dental student, USA*

[3]*Texas A&M College of Dentistry, Department of Orthodontics, USA*

ABSTRACT

Sclerostin is a well-known osteogenic negative regulator whose biological functions have been widely studied in bone homeostasis. Targeting sclerostin via monoclonal antibodies was shown to be a powerful strategy for bone-related diseases. Traditionally, sclerostin was known as an osteocyte-specific glycoprotein. However, in recent studies, it has been shown that in addition to osteocytes, there are other cell types in oral tissues that can produce sclerostin. Sclerostin regulates the formation of dental and periodontal structures and is also involved in various physiological and pathological events in oral tissues. Thus, sclerostin modulation has been determined as a possible treatment strategy for periodontium-related diseases. To develop the therapeutic potential of sclerostin and its antibodies in the field of dentistry, researchers must clearly understand the functions of sclerostin in oral tissues. In this review, we highlight the existing awareness of sclerostin's functions in oral tissues; the roles it plays in dental and periodontal diseases and treatments; and the therapeutic potential of sclerostin and its antibodies for oral applications.

KEYWORDS: Sclerostin; Periodontium; Dentin

ABBREVIATIONS: AGEs: Advanced Glycation End-products; ALP: Alkaline Phosphatase; BSP: Bone Sialoprotein; CAP: Cementum Attachment Protein; CEMP1: Cementum Protein 1; Dkk1: Dickkopf-1; FDA: Food and Drug Administration; hDPCs: Human Dental Pulp Cells; hPDLCs: Human Periodontal Ligament Cells; IL-1: Interleukin-1; IL-6: Interleukin-6; IL-17: Interleukin-17; LRP 5/6: Low-Density Lipoprotein Receptor-related Protein 5/6; MLO-Y4: Murine Long Bone Osteocyte Y4; OCN: osteocalcin; OPN: Osteopontin; OPG: Osteoprotegerin; PDL: Periodontal Ligament; PKO: Periostin-knockout; PHDs: Proline Hydroxylase-domain Proteins; RANKL: Receptor Activator Nuclear Factor-κB Ligand; Runx2: Runt-related Transcription Factor 2; TNF-α: Tumor Necrosis Factor-α; VHL: Von Hippel-Lindau

INTRODUCTION

Sclerostin is a 190 amino acid secreted glycoprotein with a molecular mass of 24kDa and is transcribed from the Sost gene located on chromosome 17q12-21 [1-3]. As a critical regulatory factor in bone homeostasis, sclerostin has a loop structure that competitively binds to the extracellular domain of low-density lipoprotein receptor-related protein 5/6 (LRP 5/6), co-receptors of Wnt/β-catenin signaling pathway, thus directly restrains osteoblastic differentiation of mesenchymal stem cells while causing a reduction in osteoblast proliferation, differentiation and survival [4-7]. Also, inactivation of Wnt/β-catenin decreases the expression of osteoprotegerin (OPG) and increases the expression of receptor activator nuclear factor-κB ligand (RANKL), promoting osteoclast differentiation through RANKL/OPG signaling [8,9]. Additionally, in the presence of LRP5/6, sclerostin upregulated the expression of carbonic anhydrase 2, cathepsin K, and tartrate-resistant acid phosphatase form 5b in osteocyte-like cells. These mediators are associated with bone resorption, causing collagen breakdown and an increased lacunar size in bovine trabecular bone [10,11]. These findings indicate that sclerostin may contribute to osteocytic osteolysis by controlling perilacunar minerals. By

Quick Response Code:

Address for correspondence: Xianglong Han, State Key Laboratory of Oral Diseases, West China Hospital of Stomatology, Sichuan University, China

Received: October 10, 2020 **Published:** October 20, 2020

How to cite this article: Fangyuan S, Aileen T, Yan J, Xianglong H. Sclerostin in Oral Tissues: Distribution, Biological Functions and Potential Therapeutic Role. 2020 - 2(5) OAJBS.ID.000228.
DOI: 10.38125/OAJBS.000228

suppressing bone formation, promoting bone resorption, and contributing to osteocytic osteolysis through inhibition Wnt/β-catenin signaling pathway, sclerostin exerts its inhibitory effect on bone mass accrual in both trabecular and cortical bone. In contrast, deficiency or impaired function of sclerostin increases bone mass and leads to sclerosing bone dysplasias like sclerosteosis (OMIM: 269500) and van Buchem disease (OMIM: 239100) [12]. Both conditions are distinguished by sclerosing and thickening of bone in patients. In addition to bone thickening, a series of oral manifestations including partial anodontia, delayed tooth eruption, and irregular tooth shape are reported in patients with bone disorders related to sclerostin deficiency [13,14], indicating that sclerostin also affects tooth and periodontium formation. Recent studies have confirmed that in addition to osteocytes, other cells including cementocytes, periodontal ligament (PDL) cells, odontoblasts and dental pulp cells also secrete sclerostin. The sclerostin produced by these cells are expressed in the pulp and periodontium (Figure 1); (Table 1) and participates in multiple physiological and pathological events in the tooth and periodontal environment [15-20].

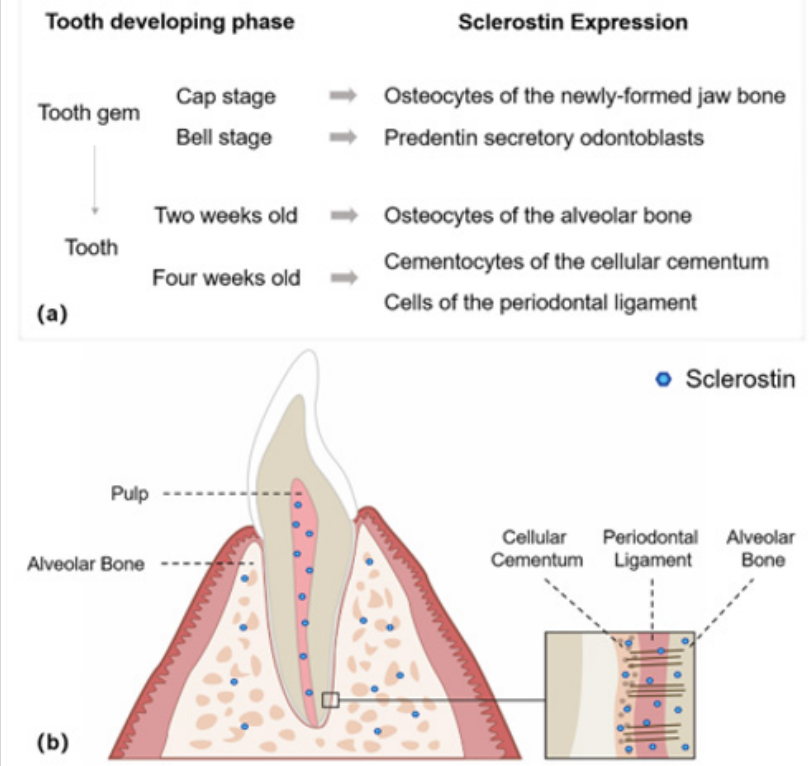

Figure 1: The expressions of sclerostin in dental tissues. (a) The earliest expression of sclerostin in dental tissues of mouse. (b) The localization of sclerostin in dental tissues.

Table 1: Sclerostin expression in oral tissues.

Cells	Sample Source	References
Osteocytes	Human and mouse alveolar bone	[15,16,34]
Cementocytes	Human and mouse cellular cementum	[14-16]
	IDG-CM6 immortalized murine cementocyte cell line	[40]
Odontoblasts	Mouse tooth germ	[20,103]
	Injured human teeth	[17]
	Human odontoblast-like cells	[77]
Pulp cells	Human dental pulp cells	[78]
Periodontal ligament cells	Mouse periodontal ligament	[15]
	Human periodontal ligament under mechanical force	[82]
	Human periodontal ligament cells	[15,31,33,82]

To date, sclerostin has been considered a potential therapeutic target for osteoporosis and other diseases related to bone metabolism. Since sclerostin is also expressed in oral tissues and implicated in dental and periodontal tissue formation, sclerostin modulation could be a potential strategy for dental and periodontal treatments. To determine the therapeutic potential of sclerostin modulation for oral applications, it is imperative to fully elucidate the expression and functions of sclerostin in oral tissues. The aim of this review is to present and discuss literature data on the expression and functions of sclerostin in dental and periodontal structures, its roles in oral diseases and treatments, and the possible treatment applications of sclerostin and its antibody in dentistry.

DISTRIBUTION AND BIOLOGICAL FUNCTIONS OF SCLEROSTIN IN ORAL TISSUES

Sclerostin and Alveolar Bone

Alveolar bone is a critical periodontal tissue which is essential for the development and eruption of the tooth [21]. Together with the attached PDL fibers, the alveolar bone maintains normal masticatory functions [21]. Similar to long bone, the alveolar bone is highly dynamic and continuously remodeled in response to mechanical loading, inflammation, and other kinds of stimulation [22]. This provides the foundation of orthodontic tooth movement, osseointegration, and oral diseases related to periodontium destruction. During development and remodeling of alveolar bone, the expression and functional involvement of sclerostin in alveolar bone and PDL has been verified [16,20,23-25]. In mice, sclerostin has been detected in osteocytes of alveolar bone and PDL cells [16,26]. Also, the deletion of Sost resulted in a significant increase in both volume and thickness of the alveolar bone in mice, indicating sclerostin plays a role in the regulation of alveolar bone homeostasis [26].

Mechanical force is essential for bone remodeling, during which osteocytes and PDL cells are the key cells in mechanotransduction and regulation of osteoblasts and osteoclasts [22,27,28]. Mechanical loading generates tension and other mechanically relevant stimuli on osteocytes and PDL cells in the periodontium which triggers bone formation leading to increased bone mass. Reduced mechanical loading due to disuse and other causes results in activation of bone resorption mediated by osteoclasts that adapts to the changed levels and distribution of strain [27-29].

As a regulator of bone homeostasis, the expression of sclerostin in osteocytes of alveolar bone and PDL cells is reported to be closely related to mechanical force. In a rat model with unilateral extraction, it was found that sclerostin expression was increased with a dramatic bone loss in the extracted side of the alveolar bone due to a lack of mechanical stimuli [30]. Additionally, *in vivo* studies have shown that compressive force biphasically regulate the expression of sclerostin in a force-dependent manner in PDL cells [31-33]. Regulated by mechanical force, sclerostin is a potential key biochemical signal in alveolar bone remodeling. *In vitro*, exogenous sclerostin abrogated the increase in trabecular bone stiffness caused by mechanical loading [10]. The deletion of Sost in mice eliminates the responses of PDL stem cells to unloading, leading to less alveolar bone loss [34]. Also, the inhibition of sclerostin restored alveolar bone loss in rats with tooth extraction [35]. These studies further support the critical roles of sclerostin in bone remodeling, in which osteocytes and PDL cells may regulate osteoblasts and osteoclasts by controlling the expression of sclerostin under mechanical stimulation.

Sclerostin and Cementum

Cementum is a thin layer of calcified tissue formed by cementoblasts that lines the anatomical root of a tooth [36]. Depending on the inclusion or non-inclusion of cementocytes, cementum is classified into cellular cementum and acellular cementum, respectively [37,38]. Cellular cementum, which is usually deposited at the apical root and covers acellular cementum, has an adaptive role during tooth movement and attrition [38]. It has been found that cementocytes and osteocytes share similar features in morphology and biology [39]. Immunohistochemical evidence has revealed that sclerostin can be secreted by cementocytes in addition to osteocytes, which is consistent with the results of *in vitro* experiments [15,16,40]. However, in contrast to bone tissues where sclerostin is expressed in all developmental stages, sclerostin expression cannot be observed at the initial stage of cementum development [16], indicating that sclerostin is not involved in cementogenesis during the initial stage.

Hypercementosis occurs in individuals with the diseases associated with the absence of sclerostin expression. It was found that sclerostin deficiency led to a thickened cementum in mice [14,26]. An explanation for this phenomenon is that apoptosis of cementoblasts increases in the presence of sclerostin which is dose dependent [41]. Furthermore, sclerostin downregulates mineralization-related genes including the genes encoding runt-related transcription factor 2 (Runx2), bone sialoprotein (BSP), osteocalcin (OCN), and osteopontin (OPN), thus inhibiting cementoblast differentiation. Additionally, sclerostin promotes the resorption of cementum by reducing OPG expression and elevating RANKL expression [41].

Similar to bone formation, Wnt/β-catenin signaling pathway is critical for cementum formation. Ablation of β-catenin leads to the absence of BSP, a marker for cementoblasts during tooth development, and severely disrupted the morphogenesis of roots. In contrast, activation of β-catenin leads to excessive cementum formation [42,43]. *In vitro*, Wnt3a, a major ligand of Wnt/β-catenin signaling pathway, promotes the differentiation of human bone marrow-derived mesenchymal stem cells as well as dental follicle cells into cementoblast-like cells [44,45]. Additionally, in human periodontal ligament cells (hPDLCs), both overexpression of β-catenin or Wnt3a, and LiCl (an addition of exogenous Wnt/β-catenin signal promotor) have been proven to increase the expression of cementogenic differentiation markers cementum attachment protein (CAP) and cementum protein 1 (CEMP1) [46]. These studies indicate that selective upregulation of Wnt/β-catenin signaling may stimulate cementum formation through activation of cementoblastic differentiation. As an inhibitor of Wnt/β-catenin signaling in osteocytes and osteoblasts, sclerostin may also control cementogenesis through Wnt/β-catenin signaling during cementum formation. To confirm this hypothesis, Han et al. [46] injected sclerostin antibody into cementum defects in rats and found upregulated Wnt/β-catenin signals and newly formed cementum incorporated with well-organized PDL collagen fibers. This study provides evidence for the implication of Wnt/β-catenin signaling pathway in the regulation of cementogenesis by sclerostin. In cementoblasts, exposure to Wnt3a or LiCl suppresses the expression of cementogenesis-related genes such as Runx2, alkaline phosphatase (ALP), BSP, and OCN [47], leading to the inhibition of cementoblast differentiation. Meanwhile, dickkopf-1 (Dkk1), a known Wnt antagonist, showed opposite effects on gene expression and cell differentiation in cementoblasts [44,47]. These results are inconsistent with sclerostin's effects on cementoblasts

as an inhibitor of Wnt signaling [41]. Thus, more studies are required in the future.

In summary, sclerostin negatively regulates cementum formation, and the application of sclerostin antibody has shown a therapeutic potential in cementum regeneration for periodontal diseases. However, the specific mechanism of sclerostin's role in cementum formation still needs to be elucidated.

Sclerostin and Dentin

In addition to periodontal structures, sclerostin is also expressed by pulp cells and regulates the formation of dentin. Dentin is a calcified tissue surrounding the pulp where its formation is initiated by odontoblasts. As dentin formation continues throughout life, sclerostin is observed within odontoblasts and dental pulp cells during root development and reparative dentinogenesis [17-20]. In the late bell and cytodifferentiation stages during tooth development, sclerostin is expressed in odontoblasts in the tooth germs [20]. After tooth maturation, sclerostin shows a specific expression pattern in pulp cells. Expression levels of sclerostin was dramatically higher in senescent human dental pulp than in young human dental pulp [19]. In the injured pulp chamber, sclerostin can be found in the cells adjacent to the reparative dentin. In contrast, there is no sclerostin in the pulp chamber of non-injured teeth [17]. Additionally, reduced sclerostin expression is observed in odontoblasts beneath mechanically induced sclerotic dentin, whereas sclerostin is expressed extensively in the pulp of such teeth [18]. Altogether, these studies indicate sclerostin has a role in dentin development and reparative dentinogenesis in response to injury and mechanical stimuli.

As reported previously, sclerostin can inhibit dental pulp cell proliferation and odontoblastic differentiation, leading to a negative effect on dentinogenesis [19]. In consistency with this finding, although it is not significant, deletion of Sost led to smaller pulp chambers which is likely because of increased dentin formation in mice [26]. Under mechanical strain, upregulation of odontogenic differentiation markers, including Runx2, OCN, OPN and dentin sialophosphoprotein, was found in odontoblast-like cells that were induced from human dental pulp cells (hDPCs) with downregulated sclerostin expression. When sclerostin was overexpressed, the expression of these differentiation markers were attenuated [18]. In addition, the reparative dentinogenesis was dramatically hastened after pulpal injury in Sost null mice [17]. Thus, sclerostin's negative effects on reparative dentinogenesis were proven under different kinds of stimuli. Furthermore, sclerostin is believed to be involved in pulp senescence. In a study of senescence of hDPCs, overexpression of sclerostin in early-passage hDPCs caused increased the expression of cell-cycle regulators p16, p53 and p21, which led to decreased proliferation and odontoblastic differentiation. Additionally, sclerostin knockdown reversed the diminished odontoblastic differentiation in late passage hDPCs. This implies that the decreased sclerostin expression observed in senescent hDPCs may contribute to the impaired ability of odontoblastic differentiation through p16 and p53 signaling pathways [19].

To date, the effect of sclerostin on dentin has not been studied thoroughly. Along with the proliferation and odontoblastic differentiation, Wnt/β-catenin signals are regulated when sclerostin expression is modulated in hDPCs [19], indicating that Wnt/β-catenin pathway may have a part in sclerostin-regulated dentinogenesis. In summary, sclerostin functions as a negative regulator in dentin formation during tooth development as well as aging and reparative dentinogenesis. This suggests that sclerostin modulation is a possible solution for dentin regeneration and anti-aging although the mechanism and application of sclerostin would require further research.

POTENTIAL CLINICAL TRANSLATION OF SCLEROSTIN IN DENTISTRY

Sclerostin in Osseointegration

Initially described by Brånemark, osseointegration is defined as "a direct structural and functional connection between ordered, living bone and the surface of a load-carrying implant" [48,49]. On the basis of osseointegration, dental implants have developed into a reliable treatment option for patients with tooth loss. As osseointegration occurs, biological bonding between the dental implant and the surrounding bone tissue is ensured by activation of peri-implant osteogenesis, proving long-term stability for dental implants [50].

As an inhibitor for osteogenesis, sclerostin has a negative effect on osseointegration of the inserted implants. In animal models, increased sclerostin expressions were detected around implants with poor osseointegration and decreased bone volume. However, deficiency of Sost significantly enhanced osseointegration around the implants in ovariectomized mice [25,51]. Neutralizing sclerostin by systemic administration of sclerostin antibody has been verified to accelerate and enhance mechanical fixation of implants by promoting osseointegration in both long bone and peri-implant alveolar bone [52,53]. In ovariectomized osteoporotic rat models, sclerostin antibody treatment showed a significant effect on promoting implant fixation through enhancing bone-implant contact as well as improving trabecular bone volume and architecture [54]. Additionally, sclerostin antibody treatment completely negated the negative effect of polyethylene particles on implant fixation in rats. This suggests that sclerostin antibody has potential treatment effects on preventing peri-implant osteolysis and aseptic loosening of inserted implant [55]. To sum it up, targeting sclerostin in the bone surrounding the inserted implant by sclerostin antibody injection promotes osseointegration in animal experiments, which is likely to be a promising alternative for achieving long-term stability of the dental implants.

Sclerostin in Dental and Periodontal Inflammatory Diseases

Inflammation is a well-known factor associated with bone metabolism and leads to bone loss [56]. In the course of the inflammation, pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6) and interleukin-17 (IL-17) are activated and take part in regulation of bone metabolism [56]. By regulating the expression levels of osteocyte proteins, these pro-inflammatory cytokines affect biological functions of osteoblasts and osteoclasts. Sclerostin, as an osteocyte protein closely related to bone metabolism, is reported to be regulated by pro-inflammatory cytokine TNF-α *in vivo* and *in vitro* experiments [57-59]. Additionally, IL-1β and the combination of IL-1β, IL-6 and TNF-α are also reported to elevate sclerostin expression in osteocyte [60]. Thus, sclerostin acts as a critical bioactive factor to promote osteoclastogenesis during inflammatory bone loss.

Periodontitis is an inflammatory disease that targets the supporting structures around the teeth and leads to destruction

of these periodontal tissues [61]. Without treatment, periodontitis usually leads to progressive periodontal tissues loss, tooth mobility and subsequent tooth loss. The underlying cause of periodontitis is controversial, but the presence of periodontal pathogens such as *Porphyromonas gingivalis* has been verified as a necessary factor for periodontitis, while smoking and diabetes mellitus are regarded as risk factors [62].

During periodontitis, sclerostin is clearly related to periodontal bone resorption induced by inflammation. As a key factor in the development of periodontitis, *Porphyromonas gingivalis* lipopolysaccharide stimulates the release of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6, thus promotes sclerostin expression in periodontium and leads to periodontal bone resorption [63,64]. Experimental periodontitis in rats and mice confirmed that bone resorption occurred with increased osteocytic expression of sclerostin, while Sost deficiency resulted in decreased alveolar bone loss [24,65]. Clinical studies have also confirmed the results obtained in animals regarding sclerostin's involvement in alveolar bone resorption during periodontitis. In patients with chronic periodontitis, the mRNA and protein levels of Sost and pro-inflammatory cytokine TNF-α in periodontal tissues, as well as the circulating level of sclerostin and TNF-α in serum were increased when compared to healthy people [66]. Moreover, chronic periodontitis patients with smoking habit and/or diabetes mellitus showed higher expression of sclerostin and TNF-α in periodontal tissues than patients without these two risk factors [67]. While the association between sclerostin and smoking requires further investigation, the involvement of sclerostin in the development of diabetes mellitus-associated periodontitis have been confirmed by previous studies. Along with the up-regelation of sclerostin, patients with diabetes mellitus and periodontitis have an accumulation of advanced glycation end-products(AGEs, a major pathogenic factor in diabetes mellitus) in periodontal tissues which plays an important role in the occurrence of periodontitis [68,69]. *In vivo* studies have shown that AGEs elevated the expression level of sclerostin in osteocytes [63,70]. Altogether, AGEs accumulate in periodontal tissues and promotes the expression of sclerostin, leading to inflammatory bone resorption in periodontal tissues.

Above all, the involvement of sclerostin expressed in alveolar bone resorption during periodontitis and diabetes mellitus-associated periodontitis has been illustrated. For clinic application, sclerostin has been suggested as a reliable marker in diagnosis and clinical evaluation of periodontitis as sclerostin concentration in gingival crevicular fluid is significantly higher during chronic periodontitis and lower after treatment [71,72]. Also, researchers have applied anti-sclerostin therapy in mouse and rat models of periodontitis and have achieved positive results. Subcutaneous injection of sclerostin antibody significantly restored vertical alveolar bone mass and alveolar crest height following ligature-induced periodontitis in rats [73,74]. Also, blocking sclerostin function by intraperitoneally injecting sclerostin antibody in the periodontitis model of periostin-knockout (PKO) mice restored bone and PDL defects [75]. Pathologic changes were observed in the PKO mice within osteocytes. This might be closely linked to bone loss. Deletion of Sost or blocking Sost function by sclerostin antibody treatment attempts to prevent and restore osteocyte morphologies, which may be associated with improvement of bone loss in the PKO mice [75]. To sum it up, treatment with sclerostin antibody could restore alveolar bone loss during periodontitis in animals. Clinical trials are required to further confirm the effect of sclerostin antibody on periodontitis patients.

In the pulp, inflammation often happens due to the invasion of pathogens into mineralized dental tissues during dental caries or trauma [76]. Subsequently, odontoblasts and dental pulp cells produce numerous pro-inflammatory cytokines in pulp and activate inflammatory immune responses which is followed by reparative dentin formation. As mentioned before, sclerostin is secreted by odontoblasts and pulp cells and acts as a negative regulator of reparative dentin formation, making it a possible factor involved in reparative dentinogenesis during pulp inflammation. *In vivo*, it has been shown that lipopolysaccharide, a key factor in pulp infections, promotes the expression of sclerostin in odontoblasts [77]. Exogenous sclerostin increases LPS-induced productions of pro-inflammatory cytokines like IL-6, IL-8, and IL-1β in odontoblasts, while inhibits LPS-induced odontoblastic differentiation of dental pulp cells. This confirms the role of sclerostin in reparative dentinogenesis during pulp inflammation. Additionally, the mRNA level of Sost in dental pulp cells was decreased in the treatment with pro-inflammatory cytokine IL-1β [78], indicating sclerostin may act as a mediator between odontoblasts and dental pulp cells to coordinate pulpal inflammatory processes.

Sclerostin in Orthodontic Tooth Movement

Orthodontic tooth movement is a mechanical-biological coupling process which depends on the remodeling of periodontium. When an appropriate orthodontic force loads on the tooth, the tooth initially shifts within the PDL space. On the side receiving pressure, the PDL is compressed which causes a disturbance in the blood flow and local hypoxia. On the other side, the PDL is stretched, leading to an increase in blood flow [79-81]. The change of blood flow rapidly leads to an alteration of the oxygen tension and chemical environments in PDL by releasing inflammatory factors like prostaglandins and cytokines. The changes in PDL homeostasis affect cellular activities in the periodontium, resulting in different responses of the alveolar bone on different sides. Due to the differences in the activation of osteoblasts and osteoclasts, the tensile side mainly shows bone formation, while the compressed side displays bone resorption. Macroscopically, the tooth is moved in the alveolar bone after application of orthodontic force.

As mentioned before, sclerostin secreted by PDL cells and osteocytes is involved in alveolar bone remodeling induced by mechanical stimulation, which indicates sclerostin is likely a key factor during the orthodontic tooth movement processes. As the tooth shifts under orthodontic force, sclerostin expression in PDL cells is increased on both the compressed and tensile sides with no significant difference [82,83]. The increase in sclerostin in PDL cells in response to compressed force contributes to the *Sost* upregulation in osteocytes, as shown in an osteocyte-PDL coculture system [83]. In contrast, a different expression pattern has been shown in osteocytes of the compression and tension sides during orthodontic tooth movement. In rats, sclerostin expression in osteocytes rapidly decreased under orthodontic force and remained low during tooth movement on the tension side while increased and maintained high levels after orthodontic force application on the compression side [23]. Other studies have reported similar results with respect to this expression pattern of sclerostin [82-84]. The upregulation of sclerostin on compression side and downregulation on tension side are consistent with the pattern of bone remodeling during orthodontic tooth movement, in which bone is resorbed on the compression side but deposited on the tension side. In Sost KO mice, osteoclast activity in compression side was significantly reduced [23], strongly supporting the hypothesis that sclerostin is essential in osteocyte-controlled bone

remodeling during orthodontic tooth movement. Thus, it could be inferred that during orthodontic tooth movement, sclerostin expression is regulated differently in compression and tension side, leading to the occurrence of different bone remodeling patterns.

The mechanism why the expression of sclerostin in osteocytes is different between compression and tension sides is still controversial. In vitro experiments have shown that there was no difference in the effect of uniaxial tension and compression on sclerostin expression in murine long bone osteocyte Y4 (MLO-Y4) cells [23], eliminating the possibility that the types of forces are directly involved in sclerostin expression in osteocytes. In previous studies, osteoblasts cultured in a hypoxic environment showed a substantial decline in the levels of sclerostin transcription and expression [23,85]. Deficiency of von Hippel-Lindau (VHL) or proline hydroxylase-domain proteins (PHDs), regulatory factors of hypoxia-inducible factor, led to a decrease of sclerostin expression as well as promoted bone formation in mice [86,87], confirming the role of sclerostin in hypoxia-induced osteogenesis. This may be the reason for the upregulation of Sost in osteocytes and osteoblasts on the compression side during orthodontic tooth movement.

On the other hand, inflammatory factors also regulate periodontium remodeling during orthodontic tooth movement. TNF-α and IL-1β significantly increased on the compression side after orthodontic force was applied [57,58,81,88,89]. As shown in several studies, inflammatory factors induce osteoclastogenesis by increasing sclerostin expression in osteocytes [57-60], which may contribute to the high level of sclerostin in the compression side. A recent *in vivo* study showed that sclerostin-positive osteocytes on the compression side showed a significant reduction in TNF receptor-deficient mice after 6 days of orthodontic loading [90], indicating TNF-α plays a role in sclerostin regulation during orthodontic tooth movement. Further studies are required to illustrate the implication of TNF-α and other inflammatory factors in sclerostin regulation during this process.

Given the fact that mechanical forces regulate bone remodeling via regulation of sclerostin expression in PDL cells and osteocytes during orthodontic tooth movement, sclerostin is a potential target for modulating orthodontic treatment. One of the potential applications of sclerostin in orthodontics is to accelerate tooth movement, which is a long-term research hotspot for orthodontists. In orthodontic tooth movement, osteoclast-mediated bone resorption has a decisive role in increasing the efficiency of tooth movement. While surgical interventions have been studied extensively, nonsurgical interventions is easier to be accepted in clinical application [91]. In a recent study, sclerostin administration on the compression side promoted osteoclastogenesis without affecting the osteoblastic activity on the tension side in orthodontic tooth movement on rat [92], indicating sclerostin is promising to be a modulator for non-surgical acceleration of orthodontic tooth movement.

In addition, root resorption is a severe side effect of orthodontic treatment [93,94], which may cause tooth loss and exfoliation. During orthodontic tooth movement, the hyalinized tissues caused by a complete absence of the blood vessel in the PDL are removed by osteoclasts and odontoclasts, which are likely contributing to root resorption simultaneously [95]. Similar to osteoclastic bone resorption, root resorption is regulated by RANKL/OPG signaling. In response to mechanical forces, RANKL expression is enhanced in PDL cells and cementoblasts which activates odontoclastic differentiation and leads to root resorption [96-100]. As a key factor regulating biological behaviors of osteocyte-like cells, sclerostin was found to reinforce the resorption of cementum through elevating RANKL but inhibiting OPG expression [41,101]. Injection of sclerostin antibody significantly increased new cementum formation in rat models with periodontal defects, while no cementum formation was found in the control groups [46], showing the therapeutic potential of sclerostin in root resorption.

Summary and Perspectives

It has been shown that sclerostin is secreted by osteocytes, cementocytes, PDL cells, odontoblasts, and dental pulp cells. Sclerostin regulates the homeostasis of dental and periodontal hard tissue including alveolar bone, cementum and dentin. Based on the understanding of the functions of sclerostin in these oral tissues, extensive research has investigated the therapeutic effects of sclerostin modulation in formation and regeneration of oral tissues. In animal models, sclerostin modulation has been shown to be effective on recovering alveolar bone loss in periodontitis while promoting osseointegration in implant dentistry. In orthodontic tooth movement, sclerostin modulation is also an inspiration for clinical strategies to prevent and reverse root resorption, as well as accelerate tooth movement. Yet, there are several limitations for the application of sclerostin in oral diseases. First, the sclerostin antibody was injected subcutaneously in most animal studies. However, the effects of sclerostin antibody on global bone homeostasis were barely mentioned in these studies. It has been reported that local injection of sclerostin antibody showed limited regenerative effects on alveolar bone regeneration in experimental periodontitis when compared to subcutaneous injection [74]. Thus, the therapeutic effect of local application of sclerostin antibody is not clear yet, which limits its clinical application in oral diseases. Second, the potential side effects of sclerostin antibody cannot be ignored. Subcutaneous administration of Romosozumab, a humanized monoclonal sclerostin antibody approved by Food and Drug Administration (FDA) for clinical treatment of osteoporosis, has been reported to cause adverse events including hypersensitivity reactions and osteonecrosis in jawbone in clinical trials [102,103]. Thus, more studies are required to address the side effects of sclerostin antibody in clinical therapy for oral diseases.

To conclude, targeting on sclerostin is an emerging strategy for the treatment of dentin and periodontium-related diseases. Future studies are needed to investigate the therapeutic effects of local application of sclerostin and the potential side effects.

ACKNOWLEDGEMENT

This study was partially supported by the National Natural Science Foundation of China (81671024 and 81870803 to X.Han.).

REFERENCES

1. Brunkow ME, Gardner JC, Van Ness J, Paeper BW, Kovacevich BR, et al. (2001) Bone dysplasia sclerosteosis results from loss of the SOST gene product, a novel cystine knot-containing protein. Am J Hum Genet 68(3): 577-589.

2. Balemans W, Ebeling M, Patel N, Van Hul E, Olson P, et al. (2001) Increased bone density in sclerosteosis is due to the deficiency of a novel secreted protein (SOST). Hum Mol Genet 10(5): 537-543.

3. Kusu N, Laurikkala J, Imanishi M, Usui H, Konishi M, et al. (2003) Sclerostin is a novel secreted osteoclast-derived bone morphogenetic protein antagonist with unique ligand specificity. J Biol Chem 278(26): 24113-24117.

4. Veverka V, Henry AJ, Slocombe PM, Ventom A, Mulloy B, et al. (2009) Characterization of the structural features and interactions of sclerostin:

molecular insight into a key regulator of Wnt-mediated bone formation. J Biol Chem 284(16): 10890-10900.

5. Weidauer SE, Schmieder P, Beerbaum M, Schmitz W, Oschkinat H, et al. (2009) NMR structure of the Wnt modulator protein Sclerostin. Biochem Biophys Res Commun 380(1): 160-165.

6. Li X, Zhang Y, Kang H, Liu W, Liu P, et al. (2005) Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling. J Biol Chem 280(20): 19883-19887.

7. Delgado-Calle J, Sato AY, Bellido T (2017) Role and mechanism of action of sclerostin in bone. Bone 96: 29-37.

8. Glass DA, Bialek P, Ahn JD, Starbuck M, Patel MS, et al. (2005) Canonical Wnt signaling in differentiated osteoblasts controls osteoclast differentiation. Dev Cell 8(5): 751-764.

9. Tu X, Delgado-Calle J, Condon KW, Maycas M, Zhang H, et al. (2015) Osteocytes mediate the anabolic actions of canonical Wnt/beta-catenin signaling in bone. Proc Natl Acad Sci U S A. 112(5): E478-486.

10. Kogawa M, Khalid KA, Wijenayaka AR, Ormsby RT, Evdokiou A, et al. (2018) Recombinant sclerostin antagonizes effects of ex vivo mechanical loading in trabecular bone and increases osteocyte lacunar size. Am J Physiol Cell Physiol 314(1): C53-C61.

11. Kogawa M, Wijenayaka AR, Ormsby RT, Thomas GP, Anderson PH, et al. (2013) Sclerostin regulates release of bone mineral by osteocytes by induction of carbonic anhydrase 2. J Bone Miner Res 28(12): 2436-2448.

12. van Lierop AH, Appelman-Dijkstra NM, Papapoulos SE (2017) Sclerostin deficiency in humans. Bone 96: 51-62.

13. Stephen LX, Hamersma H, Gardner J, Beighton P (2001) Dental and oral manifestations of sclerosteosis. Int Dent J 51(4): 287-290.

14. van Bezooijen RL, Bronckers AL, Gortzak RA, Hogendoorn PC, van der Wee-Pals L, et al. (2009) Sclerostin in mineralized matrices and van Buchem disease. J Dent Res 88(6): 569-574.

15. Jager A, Gotz W, Lossdorfer S, Rath-Deschner B (2010) Localization of SOST/sclerostin in cementocytes in vivo and in mineralizing periodontal ligament cells in vitro. J Periodontal Res 45(2): 246-254.

16. Lehnen SD, Gotz W, Baxmann M, Jager A (2012) Immunohistochemical evidence for sclerostin during cementogenesis in mice. Ann Anat 194(5): 415-421.

17. Collignon AM, Amri N, Lesieur J, Sadoine J, Ribes S, et al. (2017) Sclerostin deficiency promotes reparative dentinogenesis. J Dent Res 96(7): 815-821.

18. Liao C, Ou Y, Wu Y, Zhou Y, Liang S, et al. (2019) Sclerostin inhibits odontogenic differentiation of human pulp-derived odontoblast-like cells under mechanical stress. J Cell Physiol 234(11): 20779-20789.

19. Ou Y, Zhou Y, Liang S, Wang Y (2018) Sclerostin promotes human dental pulp cells senescence. PeerJ 6: e5808.

20. Naka T, Yokose S (2011) Spatiotemporal expression of sclerostin in odontoblasts during embryonic mouse tooth morphogenesis. J Endod 37(3): 340-345.

21. Jonasson G, Skoglund I, Rythen M (2018) The rise and fall of the alveolar process: Dependency of teeth and metabolic aspects. Arch Oral Biol 96: 195-200.

22. Florencio-Silva R, Sasso GR, Sasso-Cerri E, Simoes MJ, Cerri PS (2015) Biology of bone tissue: Structure, function, and factors that influence bone cells. Biomed Res Int 2015: 421746.

23. Shu R, Bai D, Sheu T, He Y, Yang X, et al. (2017) Sclerostin Promotes Bone Remodeling in the Process of Tooth Movement. PLoS One 12(1): e0167312.

24. Kim JH, Lee DE, Cha JH, Bak EJ, Yoo YJ (2014) Receptor activator of nuclear factor-kappaB ligand and sclerostin expression in osteocytes of alveolar bone in rats with ligature-induced periodontitis. J Periodontol 85(11): e370-378.

25. Shu R, Ai D, Bai D, Song J, Zhao M, et al. (2017) The effects of SOST on implant osseointegration in ovariectomy osteoporotic mice. Arch Oral Biol 74: 82-91.

26. Kuchler U, Schwarze UY, Dobsak T, Heimel P, Bosshardt DD, et al. (2014) Dental and periodontal phenotype in sclerostin knockout mice. Int J Oral Sci 6(2): 70-76.

27. Chukkapalli SS, Lele TP (2018) Periodontal cell mechanotransduction. Open Biol 8(9): 180053.

28. Li M, Zhang C, Yang Y (2019) Effects of mechanical forces on osteogenesis and osteoclastogenesis in human periodontal ligament fibroblasts: A systematic review of in vitro studies. Bone Joint Res 8(1): 19-31.

29. Galea GL, Lanyon LE, Price JS (2017) Sclerostin's role in bone's adaptive response to mechanical loading. Bone 96: 38-44.

30. Xu Y, Wang L, Sun Y, Han X, Gao T, et al. (2016) Sclerostin is essential for alveolar bone loss in occlusal hypofunction. Exp Ther Med 11(5): 1812-1818.

31. Manokawinchoke J, Limjeerajarus N, Limjeerajarus C, Sastravaha P, Everts V, et al. (2015) Mechanical force-induced TGFB1 increases expression of SOST/POSTN by hPDL cells. J Dent Res 94(7): 983-989.

32. Ueda M, Goto T, Kuroishi KN, Gunjigake KK, Ikeda E, et al. (2016) Asporin in compressed periodontal ligament cells inhibits bone formation. Arch Oral Biol 62: 86-92.

33. Ueda M, Kuroishi KN, Gunjigake KK, Ikeda E, Kawamoto T (2016) Expression of SOST/sclerostin in compressed periodontal ligament cells. J Dent Sci 11(3): 272-278.

34. Men Y, Wang Y, Yi Y, Jing D, Luo W, et al. (2020) Gli1+ Periodontium Stem Cells Are Regulated by Osteocytes and Occlusal Force. Dev Cell 54(5): 639-654.

35. Liu M, Kurimoto P, Zhang J, Niu QT, Stolina M, et al. (2018) Sclerostin and DKK1 Inhibition Preserves and Augments Alveolar Bone Volume and Architecture in Rats with Alveolar Bone Loss. J Dent Res 97(9): 1031-1038.

36. Bosshardt DD, Selvig KA (1997) Dental cementum: the dynamic tissue covering of the root. Periodontol 2000 13(1): 41-75.

37. Cerrito P, Bailey SE, Hu B, Bromage TG (2020) Parturitions, menopause and other physiological stressors are recorded in dental cementum microstructure. Sci Rep 10(1): 5381.

38. Yamamoto T, Hasegawa T, Yamamoto T, Hongo H, Amizuka N (2016) Histology of human cementum: Its structure, function, and development. Jpn Dent Sci Rev 52(3): 63-74.

39. Zhao N, Foster BL, Bonewald LF (2016) The cementocyte- An osteocyte relative? J Dent Res 95(7): 734-741.

40. Zhao N, Nociti FH, Jr., Duan P, Prideaux M, Zhao H, et al. (2016) Isolation and functional analysis of an immortalized murine cementocyte cell line, IDG-CM6. J Bone Miner Res 31(2): 430-442.

41. Bao X, Liu Y, Han G, Zuo Z, Hu M (2013) The effect on proliferation and differentiation of cementoblast by using sclerostin as inhibitor. Int J Mol Sci 14(10): 21140-21152.

42. Zhang R, Yang G, Wu X, Xie J, Yang X, et al. (2013) Disruption of Wnt/beta-catenin signaling in odontoblasts and cementoblasts arrests tooth root development in postnatal mouse teeth. Int J Biol Sci 9(3): 228-236.

43. Kim TH, Lee JY, Baek JA, Lee JC, Yang X, et al. (2011) Constitutive stabilization of ss-catenin in the dental mesenchyme leads to excessive dentin and cementum formation. Biochem Biophys Res Commun 412(4): 549-555.

44. Nemoto E, Sakisaka Y, Tsuchiya M, Tamura M, Nakamura T, et al. (2016) Wnt3a signaling induces murine dental follicle cells to differentiate into cementoblastic/osteoblastic cells via an osterix-dependent pathway. J Periodontal Res 51(2): 164-174.

45. Aida Y, Kurihara H, Kato K (2018) Wnt3a promotes differentiation of human bone marrow-derived mesenchymal stem cells into cementoblast-like cells. In Vitro Cell Dev Biol Anim 54(6): 468-476.

46. Han P, Ivanovski S, Crawford R, Xiao Y (2015) Activation of the canonical wnt signaling pathway induces cementum regeneration. J Bone Miner Res 30(7): 1160-1174.

47. Nemoto E, Koshikawa Y, Kanaya S, Tsuchiya M, Tamura M, et al. (2009)

Wnt signaling inhibits cementoblast differentiation and promotes proliferation. Bone 44(5): 805-812.

48. Brånemark PI, Adell R, Breine U, Hansson BO, Lindstrom J, et al. (1969) Intra-osseous anchorage of dental prostheses. I. Experimental studies. Scand J Plast Reconstr Surg 3(2): 81-100.

49. Brånemark PI (1983) Osseointegration and its experimental background. J Prosthet Dent 50(3): 399-410.

50. Li J, Jansen JA, Walboomers XF, van den Beucken JJ (2020) Mechanical aspects of dental implants and osseointegration: A narrative review. J Mech Behav Biomed Mater 103: 103574.

51. Da Silva FL, Alves Maced CA, Peruzzo DC, Montalli VA, Duarte PM, et al. (2016) Preliminary findings on the role of sclerostin in the osseointegration process around titanium implants. Int J Oral Max Impl 31(6): 1298-1302.

52. Virdi AS, Liu M, Sena K, Maletich J, Mc Nulty M, et al. (2012) Sclerostin antibody increases bone volume and enhances implant fixation in a rat model. J Bone Jt Surg (Am) 94(18): 1670-1680.

53. Yu SH, Hao J, Fretwurst T, Liu M, Kostenuik P, et al. (2018) Sclerostin-neutralizing antibody enhances bone regeneration around oral implants. Tissue Eng Part A 24(21-22): 1672-1679.

54. Virdi AS, Irish J, Sena K, Liu M, Ke HZ, et al. (2015) Sclerostin antibody treatment improves implant fixation in a model of severe osteoporosis. J Bone Jt Surg (Am) 97(2): 133-140.

55. Liu S, Virdi AS, Sena K, Sumner DR (2012) Sclerostin antibody prevents particle-induced implant loosening by stimulating bone formation and inhibiting bone resorption in a rat model. Arthritis Rheum 64(12): 4012-4020.

56. Metzger CE, Narayanan SA (2019) The role of osteocytes in inflammatory bone loss. Front Endocrinol (Lausanne) 10: 285.

57. Baek K, Hwang HR, Park HJ, Kwon A, Qadir AS, et al. (2014) TNF-alpha upregulates sclerostin expression in obese mice fed a high-fat diet. J Cell Physiol 229(5): 640-650.

58. Kim BJ, Bae SJ, Lee SY, Lee YS, Baek JE, et al. (2012) TNF-alpha mediates the stimulation of sclerostin expression in an estrogen-deficient condition. Biochem Biophys Res Commun 424(1): 170-175.

59. Vincent C, Findlay DM, Welldon KJ, Wijenayaka AR, Zheng TS, et al. (2009) Pro-inflammatory cytokines TNF-related weak inducer of apoptosis (TWEAK) and TNFalpha induce the mitogen-activated protein kinase (MAPK)-dependent expression of sclerostin in human osteoblasts. J Bone Miner Res 24(8): 1434-1449.

60. Pathak JL, Bakker AD, Luyten FP, Verschueren P, Lems WF, et al. (2016) Systemic inflammation affects human osteocyte-specific protein and cytokine expression. Calcif Tissue Int 98(6): 596-608.

61. Listgarten MA (1986) Pathogenesis of periodontitis. J Clin Periodontol 13(5): 418-430.

62. Van Dyke TE, Sheilesh D (2005) Risk factors for periodontitis. J Int Acad Periodontol 7(1): 3-7.

63. Sakamoto E, Kido JI, Takagi R, Inagaki Y, Naruishi K, et al. (2019) Advanced glycation end-product 2 and Porphyromonas gingivalis lipopolysaccharide increase sclerostin expression in mouse osteocyte-like cells. Bone 122: 22-30.

64. Jain S, Darveau RP (2010) Contribution of Porphyromonas gingivalis lipopolysaccharide to periodontitis. Periodontol 2000 54(1): 53-70.

65. Yang X, Han X, Shu R, Jiang F, Xu L, et al. (2016) Effect of sclerostin removal in vivo on experimental periodontitis in mice. J Oral Sci 58(2): 271-276.

66. Napimoga MH, Nametala C, da Silva FL, Miranda TS, Bossonaro JP, et al. (2014) Involvement of the Wnt-beta-catenin signalling antagonists, sclerostin and dickkopf-related protein 1, in chronic periodontitis. J Clin Periodontol 41(6): 550-557.

67. Miranda TS, Napimoga MH, Feres M, Marins LM, da Cruz DF, et al. (2018) Antagonists of Wnt/beta-catenin signalling in the periodontitis associated with type 2 diabetes and smoking. J Clin Periodontol 45(3): 293-302.

68. Zizzi A, Tirabassi G, Aspriello SD, Piemontese M, Rubini C, et al. (2013) Gingival advanced glycation end-products in diabetes mellitus-associated chronic periodontitis: an immunohistochemical study. J Periodontal Res 48(3): 293-301.

69. Sonnenschein SK, Meyle J (2015) Local inflammatory reactions in patients with diabetes and periodontitis. Periodontol 2000 69(1): 221-254.

70. Tanaka K, Yamaguchi T, Kanazawa I, Sugimoto T (2015) Effects of high glucose and advanced glycation end products on the expressions of sclerostin and RANKL as well as apoptosis in osteocyte-like MLO-Y4-A2 cells. Biochem Biophys Res Commun 461(2): 193-199.

71. Balli U, Aydogdu A, Dede FO, Turer CC, Guven B (2015) Gingival crevicular fluid levels of sclerostin, osteoprotegerin, and receptor activator of nuclear factor-kappaB ligand in periodontitis. J Periodontol 86(12): 1396-1404.

72. Rezaei Esfahrood Z, Yadegari Z, Veysari SK, Kadkhodazadeh M (2018) Gingival crevicular fluid levels of sclerostin in chronic periodontitis and healthy subjects. J Korean Assoc Oral Maxillofac Surg 44(6): 289-292.

73. Chen H, Xu X, Liu M, Zhang W, Ke HZ, et al. (2015) Sclerostin antibody treatment causes greater alveolar crest height and bone mass in an ovariectomized rat model of localized periodontitis. Bone 76: 141-148.

74. Taut AD, Jin Q, Chung JH, Galindo Moreno P, Yi ES, et al. (2013) Sclerostin antibody stimulates bone regeneration after experimental periodontitis. J Bone Miner Res 28(11): 2347-2356.

75. Ren Y, Han X, Ho SP, Harris SE, Cao Z, et al. (2015) Removal of SOST or blocking its product sclerostin rescues defects in the periodontitis mouse model. Faseb J 29(7): 2702-2711.

76. Farges JC, Alliot-Licht B, Renard E, Ducret M, Gaudin A, et al. (2015) Dental Pulp Defence and Repair Mechanisms in Dental Caries. Mediators Inflamm 2015: 230251.

77. Liao C, Wang Y, Ou Y, Wu Y, Zhou Y, et al. (2019) Effects of sclerostin on lipopolysaccharide-induced inflammatory phenotype in human odontoblasts and dental pulp cells. Int J Biochem Cell Biol 117: 105628.

78. Janjic K, Samiei M, Moritz A, Agis H (2019) The Influence of Pro Inflammatory Factors on Sclerostin and Dickkopf-1 Production in Human Dental Pulp Cells Under Hypoxic Conditions. Front Bioeng Biotechnol 7(430): 430.

79. Dutra EH, Nanda R, Yadav S (2016) Bone Response of Loaded Periodontal Ligament. Curr Osteoporos Rep 14(6): 280-283.

80. Isola G, Matarese G, Cordasco G, Perillo L, Ramaglia L (2016) Mechanobiology of the tooth movement during the orthodontic treatment: a literature review. Minerva Stomatol 65(5): 299-327.

81. Li Y, Jacox LA, Little SH, Ko CC (2018) Orthodontic tooth movement: The biology and clinical implications. Kaohsiung J Med Sci 34(4): 207-214.

82. Nishiyama Y, Matsumoto T, Lee JW, Saitou T, Imamura T, et al. (2015) Changes in the spatial distribution of sclerostin in the osteocytic lacuno-canalicular system in alveolar bone due to orthodontic forces, as detected on multimodal confocal fluorescence imaging analyses. Arch Oral Biol 60(1): 45-54.

83. Odagaki N, Ishihara Y, Wang Z, Ei Hsu Hlaing E, Nakamura M, et al. (2018) Role of Osteocyte-PDL Crosstalk in Tooth Movement via SOST/Sclerostin. J Dent Res 97(12): 1374-1382.

84. Matsuda K, Haga-Tsujimura M, Yoshie S, Shimomura-Kuroki J (2014) Characteristics of alveolar bone associated with physiological movement of molar in mice: a histological and histochemical study. Odontology 102(1): 98-104.

85. Genetos DC, Toupadakis CA, Raheja LF, Wong A, Papanicolaou SE, et al. (2010) Hypoxia decreases sclerostin expression and increases Wnt signaling in osteoblasts. J Cell Biochem 110(2): 457-467.

86. Loots GG, Robling AG, Chang JC, Murugesh DK, Bajwa J, et al. (2018) Vhl deficiency in osteocytes produces high bone mass and hematopoietic

defects. Bone 116: 307-314.

87. Stegen S, Stockmans I, Moermans K, Thienpont B, Maxwell PH, et al. (2018) Osteocytic oxygen sensing controls bone mass through epigenetic regulation of sclerostin. Nat Commun9(1): 2557.

88. Kim JH, Kim AR, Choi YH, Jang S, Woo GH, et al. (2017) Tumor necrosis factor-alpha antagonist diminishes osteocytic RANKL and sclerostin expression in diabetes rats with periodontitis. PLoS One 12(12): e0189702.

89. Lee TY, Lee KJ, Baik HS (2009) Expression of IL-1beta, MMP-9 and TIMP-1 on the pressure side of gingiva under orthodontic loading. Angle Orthod 79(4): 733-739.

90. Ohori F, Kitaura H, Marahleh A, Kishikawa A, Ogawa S, et al. (2019) Effect of TNF-alpha-Induced Sclerostin on Osteocytes during Orthodontic Tooth Movement. J Immunol Res : 9716758.

91. Huang H, Williams RC, Kyrkanides S (2014) Accelerated orthodontic tooth movement: molecular mechanisms. Am J Orthod Dentofacial Orthop 146(5): 620-632.

92. Lu W, Zhang X, Firth F, Mei L, Yi J, et al. (2019) Sclerostin injection enhances orthodontic tooth movement in rats. Arch Oral Biol 99: 43-50.

93. Massler M, Malone AJ (1954) Root resorption in human permanent teeth. Am J Orthod 40(8): 619-633.

94. Motokawa M, Sasamoto T, Kaku M, Kawata T, Matsuda Y, et al. (2012) Association between root resorption incident to orthodontic treatment and treatment factors. Eur J Orthod. 34(3): 350-356.

95. Brezniak N, Wasserstein A (2002) Orthodontically induced inflammatory root resorption. Part I: The basic science aspects. Angle Orthod 72(2): 175-179.

96. Yamaguchi M, Aihara N, Kojima T, Kasai K (2006) RANKL increase in compressed periodontal ligament cells from root resorption. J Dent Res 85(8): 751-756.

97. Matsuda Y, Motokawa M, Kaku M, Sumi H, Tanne K, et al. (2017) RANKL and OPG expression: Jiggling force affects root resorption in rats. Angle Orthod 87(1): 41-48.

98. Fukushima H, Kajiya H, Takada K, Okamoto F, Okabe K, et al. (2003) Expression and role of RANKL in periodontal ligament cells during physiological root-resorption in human deciduous teeth. Eur J Oral Sci 111(4): 346-352.

99. Rego EB, Inubushi T, Kawazoe A, Miyauchi M, Tanaka E, et al. (2011) Effect of PGE (2) induced by compressive and tensile stresses on cementoblast differentiation in vitro. Arch Oral Biol 56(11): 1238-1246.

100. Minato Y, Yamaguchi M, Shimizu M, Kikuta J, Hikida T, et al. (2018) Effect of caspases and RANKL induced by heavy force in orthodontic root resorption. Korean J Orthod 48(4): 253-261.

101. Wijenayaka AR, Kogawa M, Lim HP, Bonewald LF, Findlay DM, et al. (2011) Sclerostin stimulates osteocyte support of osteoclast activity by a RANKL-dependent pathway. PLoS One 6(10): e25900.

102. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, et al. (2016) Romosozumab treatment in postmenopausal women with Osteoporosis. N Engl J Med 375(16): 1532-1543.

103. Amri N, Djole SX, Petit S, Babajko S, Coudert AE, et al. (2016) Distorted patterns of dentinogenesis and eruption in Msx2 null mutants: Involvement of Sost/Sclerostin. Am J Pathol 186(10): 2577-2587.