The role of sclerostin and dickkopf-1 in oral tissues – A review from the perspective of the dental disciplines [version 1; peer review: 2 approved]

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Abstract
Wnt signaling is of high relevance in the development, homeostasis, and regeneration of oral tissues. Therefore, Wnt signaling is considered to be a potential target for therapeutic strategies. The action of Wnt is tightly controlled by the inhibitors sclerostin (SOST) and Dickkopf (DKK)-1. Given the impact of SOST and DKK-1 in hard tissue formation, related diseases and healing, it is of high relevance to understand their role in oral tissues. The clinical relevance of this knowledge is further underlined by systemic and local approaches which are currently in development for treating a variety of diseases such as osteoporosis and inflammatory hard tissue resorption. In this narrative review, we summarize the current knowledge and understanding on the Wnt signaling inhibitors SOST and DKK-1, and their role in physiology, pathology, and regeneration in oral tissues. We present this role from the perspective of the different specialties in dentistry, including endodontics, orthodontics, periodontics, and oral surgery.

Keywords
Sclerostin, Dickkopf-1, Wnt Pathway, Regeneration, Periodontology, Endodontology
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**Introduction**

Research and development of novel treatment strategies for regenerative dentistry has become crucial to improve oral health due to the growing numbers of dental and maxillofacial problems which require treatment. Therefore, cell-therapy modalities, biologicals, and gene therapy approaches are in development with the aim to provide novel tools for the clinical demands (Dissanayaka et al., 2014; Fretwurst et al., 2018; Itoh et al., 2018; Kaigler et al., 2015; Nevins et al., 2005; Plonka et al., 2017; Taut et al., 2013). This research needs to be guided by an appropriate understanding of the cell biological mechanisms underlying pathological changes and regeneration in the oral tissue, including the periodontium and the dental tissue. Due to the major role of Wnt signaling and the respective regulators in development and healing, research in regenerative medicine and dentistry has evaluated the feasibility of targeting the pathway for therapeutic approaches (Florio et al., 2016; Heiland et al., 2010; Taut et al., 2013; Yu et al., 2018).

The Wnts comprise a family of at least 19 lipid-modified glycoproteins and short-range ligands. Wnts can activate canonical and non-canonical pathways of signaling in the cells (Mohammed et al., 2016; Tang et al., 2009; Yang et al., 2016). The canonical Wnt path involves the interaction of Wnt with frizzled (Fz) and low density lipoprotein receptor-related protein 5/6 (LRP5/6). Thereby β-catenin accumulation is induced leading to the translocation of β-catenin into the nucleus where target genes are activated (Mohammed et al., 2016; Tang et al., 2009; Yang et al., 2016) (Figure 1).

Wnt signaling regulates various cellular functions which include cell migration, proliferation, differentiation, apoptosis, and morphogenesis. Given this broad involvement of Wnt signaling it is not surprising that it has a key role in organ development, regeneration and homeostasis of tissues (Logan & Nusse, 2004; Sarkar & Sharpe, 2000; Seo et al., 2012). In the maxillofacial region, Wnt signaling modulates morphological patterns in tooth development including teeth number, shape, size, and positioning (Han et al., 2011; Kim et al., 2013; Kratochwil et al., 2002; Liu et al., 2008; Sarkar et al., 2000; Wang et al., 2009; Zhang et al., 2013). Maturation of dental mesenchyme into odontoblasts and cementoblasts is also modulated by Wnt signaling which highlights the relevance to dentistry (Janič et al., 2018; Zhang et al., 2013). Given this dominant role of Wnts, Wnt signaling needs to be tightly controlled involving inhibitors.

Sclerostin (SOST) and dickkopf-1 (DKK-1) are the primary inhibitors controlling the Wnt signaling pathways (Figure 1). These inhibitors can directly bind to LRP5/6 and inhibit the activation of LRP5- and LRP6-related signaling. Dkk-1 binds to a larger region on LRP5 and LRP6 extracellular surface and thereby can inhibit binding with other Wnts than SOST. (Ahn et al., 2011; Bourhis et al., 2010; Bourhis et al., 2011; Cheng et al., 2011; Florio et al., 2016; Li et al., 2005; van Bezooijen et al., 2004) Thereby SOST and DKK-1 play critical roles in the formation of hard tissue and associated diseases. SOST and DKK-1 are consequently considered potential therapeutic targets for regenerative approaches (Janič et al., 2018; Li et al., 2005; Semënov et al., 2005; Taut et al., 2013).

The glycoprotein SOST is mainly secreted by osteocytes, the mechanosensor cells of the bone, and has a major effect on bone and dental tissue (Kuchler et al., 2014; Pflanz et al., 2017; Saag et al., 2017; Taut et al., 2013; Winkler et al., 2003; Yu et al., 2018). In recent years, SOST production in oral tissues has gained more attention and led to in vitro and in vivo studies on the regulation of SOST (Pflanz et al., 2017; Taut et al., 2013; Yu et al., 2018). SOST production in mineralizing periodontal ligament cells is increased; this observation suggests that targeting of SOST might support periodontal regeneration. SOST has also been demonstrated to have a role in the dimension of the periodontal ligament (Kuchler et al., 2014). This further supports the hypothesis of a key role of SOST in oral tissues. DKK-1, another antagonist of Wnt signaling, modulates the dimension of oral tissues, including the periodontium and teeth (Bao et al., 2013; Jäger et al., 2010; MacDonald et al., 2007).

According to the findings of 10 years analysis of publications regarding SOST and DKK-1 in medical fields (Figure 2), it becomes evident that there is a growing set of literature on SOST

![Figure 1. Inhibition of Wnt signaling by sclerostin and dickkopf-1](image-url)
Within dentistry the majority of publications on SOST and DKK-1 is from the field of oral surgery. This review aims to provide a synopsis of the existing knowledge on the Wnt signaling inhibitors SOST and DKK-1 from endodontics, orthodontics, periodontics, and oral surgery perspectives.

**Endodontics perspective**

Research and developments in endodontics lead to the continuous improvement of the field, as the introduction of new techniques and biomaterials drive profound progress in endodontic clinical practice. In particular regenerative endodontics is an exciting dental specialty. Treatment protocols of infected root canals in immature teeth were established which allow continued apical closure and root maturation (Chueh & Huang, 2006; Huang, 2008; Huang et al., 2008). In these regenerative endodontic procedures, after treatment with ethylenediaminetetraacetic acid (EDTA) signaling factors embedded in the dentin matrix such as TGF-β are exposed and released into the canal space (Galler et al., 2017). These factors can guide the migration of dental pulp stem cells and support differentiation into odontoblast-like cells, leading to the production of mineralized matrix also termed reparative dentin (Nakashima et al., 1994; Rutherford et al., 1993; Sloan & Smith, 1999; Tziafas et al., 1998). Interestingly TGF-β has the capacity to induce SOST expression (Gruber et al., 2017; Manokawinchoke et al., 2015); therefore, it is possible that dentin conditioning can interfere with the regulation system of Wnt signaling (Gruber et al., 2017; Manokawinchoke et al., 2015).

Clinically applied regenerative protocols, such as revascularization, utilize the regenerative capacity of endogenous stem cells. During treatment, over instrumentation into the periapical tissues causes stem cells to migrate and enter into the canal system via the blood clot. This process leads to the treatment of immature teeth with
pulp necrosis by replacing dentin, root structures and pulp-dentin complex cells (Diogenes et al., 2016). However, revascularization can be accompanied by intracanal calcification (Song et al., 2017). It is unclear how Wnts and their inhibitors SOST and DKK-1 are involved in this process. Therefore, studies which investigate the regulation of SOST and DKK-1 in pulp cells and tissue under conditions which are present in the early phase of healing are of clear relevance (Janjić et al., 2018).

Results of Zhang et al. indicate that Wnt/β-catenin signaling is required for odontoblastic differentiation and also promotes proliferation of pre-odontoblasts and odontogenesis during root development (Zhang et al., 2013). Based on these findings, the integrity of Wnt/β-catenin signaling in odontoblasts is vital for proliferation and differentiation through root formation. Targeted deletion of β-catenin in odontoblasts leads to incomplete incisors and rootless molars. Furthermore, β-catenin deficiency disrupts the differentiation of odontoblasts and cementoblasts. (Zhang et al., 2013) Epithelial expression of DKK-1 or epithelium-specific inactivation of β-catenin causes abnormal tooth development at the early bud stage (Andl et al., 2002; Chen et al., 2009; Han et al., 2011). Mesenchyme-specific inhibition of β-catenin indicates the critical role of Wnt/β-catenin signaling in the potential mesenchymal odontogenic activation throughout early tooth growth (Chen et al., 2009).

After tooth development odontoblasts secrete dentin and the pulp chamber system narrows with age (Arana-Chavez & Massa, 2004; Foster et al., 2013; Lee et al., 2013; Sakai et al., 2010). While dentin gradually thickens, the pulp chamber space is reduced and a massive bone loss can be observed during aging. (Boskey & Coleman, 2010; Carvalho & Lussi, 2017; Gabet & Bab, 2011) In response to injuries and stress the formation of mineralized tissue by odontoblasts, also termed reparative dentinogenesis, is stimulated. The odontoblasts which are involved in this repair process are clearly responsive to Wnt (Zhao et al., 2018). SOST knockout mice demonstrate dramatically enhanced formation of reparative mineralized bridges and increased mineralization in dental pulp cells compared with wild-type mice (Collignon et al., 2017). These findings are related to an increased SOST expression in wild type cells. Further more these results show that SOST deficiency accelerates reparative dentinogenesis after pulp damage and therefore inhibition of SOST may provide a promising therapeutic strategy to improve the healing of injured pulps (Collignon et al., 2017).

Expression of DKK-1 is up-regulated in a rodent model of induced periapical lesions, suggesting that DKK-1 is involved in the inflammatory processes and bone resorption in periapical lesions (Zhang et al., 2014). Interestingly several potential therapeutic approaches rely on the modulation of Wnt signaling (Ishimoto et al., 2015; Lee et al., 2016; Zhao et al., 2018), including several plant-derived molecules. Baicalein promotes odontoblastic differentiation and angiogenesis of human dental pulp cells. It was suggested that via the inhibition of DKK-1 Baicalein can contribute to regenerative endodontics and dental pulp repair. (Lee et al., 2016).

Given the importance of hypoxia-induced signaling in the early phase of pulp healing we investigated the production of SOST and DKK-1 in dental pulp cells upon treatment with hypoxia or the hypoxia mimetic agent L-mimosine in monolayer, spheroid, and tooth slice cultures. Our results show that the response with regard to SOST and DKK-1 production depends on the culture model.

Taken together, the literature highlights a major role of SOST and DKK-1 in tooth development and as a potential target for regenerative strategies.

**Orthodontics perspective**

Orthodontic tooth movement is a result of external force applications to the teeth, an intervention which involves remodeling in dental and surrounding oral tissues, such as periodontal ligament, alveolar bone, and gingiva (Antoun et al., 2017; Krishnan & Davidovitch, 2006). The applied forces induce displacement of the teeth in the periodontal ligament space, thereby establishing sites where the tissue is compressed and sites were traction establishes (Antoun et al., 2017; Krishnan & Davidovitch, 2006). Thereby, modeling of the alveolar bone through the processes of bone resorption and bone formation is induced leading to clinical changes in the position of the tooth. (Krishnan & Davidovitch, 2006; Krishnan & Davidovitch, 2009; Reitan, 1967)

Mechanical forces can regulate the expression of SOST by osteocytes; for instance the expression of SOST is reduced when loading is increased, and increased when loading is decreased leading to an increase in bone formation or bone loss, respectively (Moustafa et al., 2012; Robling et al., 2008). This feature of SOST indicates that it is a crucial protein in bone formation under mechanical stimulation (Agholme et al., 2011; Mantila Roosa et al., 2011; Robling et al., 2008; ). Given that SOST is produced by osteocytes and cementocytes in alveolar bone and in cellular cementum, respectively, an involvement of SOST in tooth movement is likely (Jüger et al., 2010).

During orthodontic tooth movement, one of the essential processes is remodeling of the periodontal ligament. Periostin is one of the factors which increased in the periodontal ligament during initial stages of orthodontic tooth movement (Wilde et al., 2003), a matricellular protein and collagen-rich tissues which are highly expressed in periosteon under persistent mechanical stress (Horiuchi et al., 1999). Periodontal cells have shown to respond to these mechanical forces with an increase of TGF-β which can stimulate SOST (Gruber et al., 2017; Manokawinchoke et al., 2015). The increase in the levels of SOST in the compression side and the decrease in the tension side during tooth movement can be suggestive of an interplay between periostin from Sharpey’s fibres and SOST in alveolar bone during orthodontic therapy (Nishiyama et al., 2015).

Cementoblasts are highly differentiated cells from the mesenchymal lineage which generate cementum (Bosshardt, 2005). Diseases that influence bone characteristics often interfere with...
the properties of the cementum, which highlights the similarities of these tissues. Although SOST is expressed in both osteocytes and cementocytes in dental tissues (Jäger et al., 2010), it is still not clear if cementocytes can have similar mechanical stress sensing capacity as osteocytes. However, SOST which is released by osteocytes in the alveolar bone may affect the function of cementoblasts. This process might be modulated upon orthodontic treatment. Research on the role of SOST can also help to understand the impact of therapeutics on the periodontium. Strontium supports differentiation of cementoblasts (Bao et al., 2014) with one possible underlying mechanism being that strontium decreases the production of SOST. Thus, strontium was proposed for regenerative approaches to support cementum production in cases of root resorption. (Bao et al., 2014) However, if SOST or DKK-1 can serve effectively as targets for orthodontic approaches and cementum repair requires further studies.

**Periodontics perspective**

Periodontitis is an inflammatory disease of the teeth-supporting tissues, has a multifactorial etiology. The inflammation created by specific microorganisms extends deep into the tissues and causes the destruction of the tooth supporting connective tissue and alveolar bone. This progressive process leads to the pathological impairment of collagen fibres, loss of periodontal ligament and alveolar bone recession (Armitage, 2004; Highfield, 2009; Pihlstrom et al., 2005). Evaluation of SOST and DKK-1 in chronic periodontitis patients showed that both of these inhibitors were up-regulated in the periodontal tissues of these subjects (Napimoga et al., 2014).

There are hints from animal studies that inflammation can not only trigger bone resorption, but also decrease bone formation. This anti-anabolic effects seem to be mediated by increased levels of DKK-1 (Heiland et al., 2010). In vitro models of oral soft tissue augmentation suggest that DKK-1 is also increased in oral soft tissue wound healing (Agis et al., 2014). Thus, Wnt inhibitors can play a major role in pathological processes and regeneration in the periodontal tissue. Although periodontitis can be treated in early stages, mostly because of the chronic entity of problem, it is diagnosed in the advanced phase of destruction of the periodontal ligament and the prognosis of maintaining the teeth are poor. Conventional regenerative approaches use biomaterials of natural or synthetic origin as filler for the defect thereby aiding the host to replace lost periodontal tissue and bone. While these interventions can stimulate tissue repair and stop the destruction of the periodontium, methods to achieve full regeneration are still the focus of research (Hernández-Monjaraz et al., 2018).

The blocking of Wnt signaling impairs the periodontal ligament and alveolar bone (Lim et al., 2014), while enhancing Wnt signaling by SOST knock out stimulates alveolar bone formation and reduces the width of periodontal ligament (Kuchler et al., 2014). Expression of SOST by cementocytes suggests that these cells may regulate cell activity on the cementum surface (Bao et al., 2013; Lehnen et al., 2012). TGF-β can increase the production of SOST in fibroblasts from periodontal ligament and gingiva (Gruber et al., 2017). This mechanism seems to be involved in the impact of mechanical loading on mineralized tissue formation in the periodontal ligament (Manokawinchoke et al., 2015). Deletion of SOST leads to more cellular cementum, in parallel to more dramatically increased alveolar bone deposition (Kuchler et al., 2014). Blocking SOST by application of a SOST-specific antibody enhances healing of alveolar bone in experimental periodontitis (Chen et al., 2015; Liu et al., 2018; Taut et al., 2013). In addition, it was reported that reduced SOST in periostin knock-out mice can re-establish periodontal ligament and alveolar bone (Rangiani et al., 2016; Ren et al., 2015). This evidence supports that targeting of SOST is a feasible approach for periodontal therapy.

Dental cementum is a mineralized hard tissue on the surface of root dentin and present either in acellular or cellular form. Defective cementum results in periodontal breakdown, tooth dysfunction, and finally leads to tooth loss. Cementogenesis is a key element in the process of periodontal tissue regeneration (Bosshardt, 2005; Kao & Fiorellini, 2012). SOST was detected only in cementocytes of cellular cementum in the late stages of cementum development (Lehnen et al., 2012). SOST levels in cementocytes increased in periodontal ligament cultures, following mineralization treatment (Jäger et al., 2010). Interestingly, in periodontal ligament cells Baicaline can promote osteoblastic differentiation involving Wnt/β-catenin signaling (Chen et al., 2017). DKK-1 significantly reversed the effects of Baicalene on human periodontal ligament cells (Chen et al., 2017). It is possible that this mechanism can be exploited in regenerative approaches.

The here presented literature supports the significant effects of SOST and DKK-1 in the periodontium system and periodontal diseases. As a result, they could be the main targets in future periodontics regenerative therapies.

**Oral surgery perspective**

The alveolar bone supports the tooth in the maxilla and mandible and is characterized by continuous and rapid remodeling in response to mechanical forces (Javed et al., 2010; Pagni et al., 2012). Thereby alveolar bone continuously adapts to functional load. If this mechanical stimuli is lacking the alveolar bone undergoes a resorptive process (Einhorn & Gerstenfeld, 2015; Pagni et al., 2012; Sodek & McKee, 2000). Following trauma due to overloading or surgery bone has the capacity to regenerate. While long bone healing occurs by endo-chorial ossification, alveolar bone healing typically occurs without histological cartilage formation (Devlin et al., 1997). The success of oral surgery procedures, such as implants, depends on the proper healing of alveolar bone and strategies which stimulate bone regeneration (Lin et al., 2011). Thus understanding the cell and molecular biological background of bone healing is clearly of clinical relevance.

In bone, SOST is mainly secreted by osteocytes and represents a key modulator of bone homeostasis (Brunkow et al., 2001; van Bezooijen et al., 2004). The importance of SOST in bone formation is illustrated by sclerosteosis, a rare autosomal recessive disorder with a loss-of-function mutation in SOST (Sebastian & Loots, 2018; Yavropoulou et al., 2014). Further evidence comes from Van Buchem Disease, which is characterized by a noncoding deletion which removes a SOST-specific regulator.
Thus, it is very likely that SOST regulates the...oral tissue homeostasis throughout life (Florio et al., 2016; Heiland et al., 2010; Witcher et al., 2018). Major sources of Wnt inhibitors are the mechanosensors of the bone, the osteocytes (Moustaﬁa et al., 2012; Odagaki et al., 2018; Robling et al., 2008). Cells from oral tissue including cementocytes can modulate Wnt signaling by these inhibitors and mice deficient of SOST or DKK-1 have highlighted the important role in the oral tissue (Jäger et al., 2010; Lehnen et al., 2012). Based on this knowledge concepts to antagonize inhibitors Wnt signaling have been developed to support oral tissue regeneration (Taut et al., 2013; Yu et al., 2018). The future will reveal the capacity of these strategies which target these Wnt signaling inhibitors for regenerative therapy in dentistry. Given the interplay of SOST and DKK-1, a bidirectional approach which targets both SOST and DKK-1 locally has high potential (Florio et al., 2016).

**Data availability**

No data is associated with this article.

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**References**

Agholme F, Isaksson H, Li X, et al.: Anti-sclerostin antibody and mechanical loading appear to influence metaphyseal bone independently in rats. Acta Orthop. 2011; 82(5): 628–632. [PubMed Abstract] [Publisher Full Text] [Free Full Text]

Agis H, Collins A, Taut AD, et al.: Cell population kinetics of collagen scaffolds in ex vivo oral wound repair. PLoS One. 2014; 9(11): e112680. [PubMed Abstract] [Publisher Full Text] [Free Full Text]

Ahn VE, Chu ML, Choi HJ, et al.: Structural basis of Wnt signaling inhibition by Dickkopf binding to LRPS/6. Dev Cell. 2011; 21(5): 862–873. [PubMed Abstract] [Publisher Full Text] [Free Full Text]

Andl T, Reddy ST, Gadadpura T, et al.: WNT signals are required for the initiation of hair follicle development. Dev Cell. 2002; 2(5): 643–653. [PubMed Abstract] [Publisher Full Text]

Antoun JS, Mei L, Gibbs K, et al.: Effect of orthodontic treatment on the periodontal tissues. Periodontol 2000. 2017; 74(1): 140–157. [PubMed Abstract] [Publisher Full Text]

Arana-Chavez VE, Massa LF: Odontoblasts: the cells forming and maintaining dentine. Int J Biochem Cell Biol. 2004; 36(8): 1367–1373. [PubMed Abstract] [Publisher Full Text]

Armitage GC: Periodontal diagnoses and classification of periodontal disease. J Periodontol. 2010; 81(1): 47–56. [PubMed Abstract] [Publisher Full Text]

Aydin C, Baylar C, Ceylan G, et al.: Comparison of two different periodontal implant systems. Acta Odontol Scand. 2011; 69(6): 374–379. [PubMed Abstract] [Publisher Full Text]

Balemans W, van Bezooijen R, Stoica M, et al.: Anti-sclerostin antibody and mechanical loading appear to influence metaphyseal bone independently in rats. Acta Orthop. 2011; 82(5): 628–632. [PubMed Abstract] [Publisher Full Text] [Free Full Text]

...
Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling. J Biol Chem. 2005; 280(20): 19883–19887.

Wnt signaling regulates homeostasis of the periodontal ligament. J Periodontol. 2014; 85(6): 707–717.

Sclerostin is involved in controlling tooth size. J Dent Res. 2017; 96: (6): 751–759.

Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling. J Biol Chem. 2005; 280(20): 19883–19887.

Wnt signaling regulates homeostasis of the periodontal ligament. J Periodontol. 2014; 85(6): 707–717.

Sclerostin and DKK1 inhibit Wnt/β-catenin signaling. J Dent Res. 2012; 91(7): 597–608.

Sclerostin regulates bone mass and gene expression dynamics during bone healing and osteointegration. J Periodontol. 2011; 82(11): 1457–1472.

Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling. J Biol Chem. 2005; 280(20): 19883–19887.

Wnt signaling regulates homeostasis of the periodontal ligament. J Periodontol. 2014; 85(6): 707–717.

Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling. J Biol Chem. 2005; 280(20): 19883–19887.

Wnt signaling regulates homeostasis of the periodontal ligament. J Periodontol. 2014; 85(6): 707–717.

Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling. J Biol Chem. 2005; 280(20): 19883–19887.

Wnt signaling regulates homeostasis of the periodontal ligament. J Periodontol. 2014; 85(6): 707–717.

Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling. J Biol Chem. 2005; 280(20): 19883–19887.

Wnt signaling regulates homeostasis of the periodontal ligament. J Periodontol. 2014; 85(6): 707–717.

Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling. J Biol Chem. 2005; 280(20): 19883–19887.

Wnt signaling regulates homeostasis of the periodontal ligament. J Periodontol. 2014; 85(6): 707–717.
mesenchymal progenitors requires functional canonical Wnt/beta-catenin signalling. J Cell Mol Med. 2009; 13(8B): 2448–2464. PubMed Abstract | Publisher Full Text | Free Full Text

Taut AD, Jin Q, Chung JH, et al.: Sclerostin antibody stimulates bone regeneration after experimental periodontitis. J Bone Miner Res. 2013; 28(11): 2347–2356. PubMed Abstract | Publisher Full Text

Tziatas D, Alvanou A, Papadimitriou S, et al.: Effects of recombinant basic fibroblast growth factor, insulin-like growth factor-II and transforming growth factor-beta 1 on dog dental pulp cells in vivo. Arch Oral Biol. 1998; 43(6): 431–444. PubMed Abstract | Publisher Full Text

van Bezooijen RL, Bronckers AL, Gortzak RA, et al.: Sclerostin in mineralized matrices and van Buchem disease. J Dent Res. 2009; 88(6): 569–574. PubMed Abstract | Publisher Full Text

van Bezooijen RL, Roelen BA, Visser A, et al.: Sclerostin is an osteocyte-expressed negative regulator of bone formation, but not a classical BMP antagonist. J Exp Med. 2004; 199(6): 805–814. PubMed Abstract | Publisher Full Text | Free Full Text

Wang XP, O’Connell DJ, Lund JJ, et al.: Apc inhibition of Wnt signaling regulates supernumerary tooth formation during embryogenesis and throughout adulthood. Development. 2009; 136(11): 1939–1949. PubMed Abstract | Publisher Full Text | Free Full Text

Wilde J, Yokozeki M, Tanai K, et al.: The divergent expression of periostin mRNA in the periodontal ligament during experimental tooth movement. Cell Tissue Res. 2003; 312(3): 345–351. PubMed Abstract | Publisher Full Text | Free Full Text

Winkler DG, Sutherland MK, Geoghegan JC, et al.: Osteocyte control of bone formation via sclerostin, a novel BMP antagonist. EMBO J. 2003; 22(23): 6267–6276. PubMed Abstract | Publisher Full Text | Free Full Text

Witcher PC, Miner SE, Horan DJ, et al.: Sclerostin neutralization unleashes the osteoanabolic effects of Dkk1 inhibition. JCI Insight. 2018; 3(11): pii: 98673. PubMed Abstract | Publisher Full Text | Free Full Text | Free Full Text

Yarropoulou MP, Xygonakis C, Lolou M, et al.: The sclerostin story: from human genetics to the development of novel anabolic treatment for osteoporosis. Hormones (Athens). 2014; 13(4): 323–337. PubMed Abstract | Publisher Full Text

Yorgan TA, Schinke T: Relevance of Wnt signaling for osteoanabolic therapy. Mol Cell Ther. 2014; 2: 22. PubMed Abstract | Publisher Full Text | Free Full Text

Yu SH, Hao J, Fretwurst T, et al.: Sclerostin-Neutralizing Antibody Enhances Bone Regeneration Around Oral Implants. Tissue Eng Part A. 2018; 24(21–22): 1672–1679. PubMed Abstract | Publisher Full Text

Zhang R, Huang S, Wang L, et al.: Histochemical localization of Dickkopf-1 in induced rat periapical lesions. J Endod. 2014; 40(9): 1394–1399. PubMed Abstract | Publisher Full Text

Zhang R, Yang G, Wu X, et al.: Disruption of Wnt/beta-catenin signaling in odontoblasts and cementoblasts arrests tooth root development in postnatal mouse teeth. Int J Biol Sci. 2013; 9(3): 228–236. PubMed Abstract | Publisher Full Text | Free Full Text

Zhao L, Shim JW, Dodge TR, et al.: Inactivation of Lrp5 in osteocytes reduces young’s modulus and responsiveness to the mechanical loading. Bone. 2013; 54(1): 35–43. PubMed Abstract | Publisher Full Text | Free Full Text

Zhao Y, Yuan X, Liu B, et al.: Wnt-Responsive Odontoblasts Secrete New Dentin after Superficial Tooth Injury. J Dent Res. 2018; 97(9): 1047–1054. PubMed Abstract | Publisher Full Text | Free Full Text
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Current Referee Status: ✓ ✓

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This manuscript is a review paper on sclerostin and dickkopf-1 impacts on dentistry. The authors made good publication search work, and reviewed the expressions and biological functions of sclerostin and DKK-1 in each parts of tooth and surrounding tissues. Furthermore, the authors explored the correlation between SOST and DKK-1 and various pathologies. More importantly, the treatment pathways to target SOST and DKK-1 were discussed profoundly. The only flaw is the lack of SOST and DKK-1 in enamel formation, which does not affect the merits of this paper.

Is the topic of the review discussed comprehensively in the context of the current literature? Yes

Are all factual statements correct and adequately supported by citations? Yes

Is the review written in accessible language? Yes

Are the conclusions drawn appropriate in the context of the current research literature? Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** periodontal regeneration and dental implant researches

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Francisco Javier Rodríguez-Lozano

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The manuscript fits into the aim of the journal. The manuscript is well written and the results presented interesting.

I would like to know the search strategy. Inclusion/exclusion criteria.

Minor aspects:

Endodontic perspective: "Given the importance of hypoxia-induced signaling in the early phase of pulp healing we investigated the production of SOST and DKK-1 in dental pulp cells upon treatment with hypoxia or the hypoxia mimetic agent L-mimosine in monolayer, spheroid, and tooth slice cultures". Citation?

Periodontic Perspective: "Dental cementum is a mineralized hard tissue on the surface of root dentin and present either in acellular or cellular form. Defective cementum results in periodontal breakdown, tooth dysfunction, and finally leads to tooth loss." I recommend adding a reference.

Finally, I recommend re-writing the conclusion without citations

Is the topic of the review discussed comprehensively in the context of the current literature? Yes

Are all factual statements correct and adequately supported by citations? Yes

Is the review written in accessible language? Yes

Are the conclusions drawn appropriate in the context of the current research literature? Yes

Competing Interests: No competing interests were disclosed.

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