Sclerostin regulation: a promising therapy for periodontitis by modulating alveolar bone

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Abstract

Periodontitis is one of the most prevalent epidemics affecting human health and life recently, and exploration of the pathogenesis and treatment of periodontitis has been valued by scholars. In recent years, sclerostin, a new factor on bone resorption and reconstruction caused by inflammation and mechanical stimulation, has been a research hotspot. This article summarizes the researches on sclerostin in periodontitis development in recent years. Among them, sclerostin has been shown to be a critical negative regulator of bone formation, thereby inhibiting bone remodeling in periodontitis development, and is closely associated with tooth movement. Besides, evidence indicates that the removal of sclerostin seems to reasonably protect the alveolar bone from resorption. Regulation of sclerostin expression is a novel, promising treatment for periodontitis and addresses several complications seen with traditional therapies; accordingly, many drugs with similar mechanisms have emerged. Moreover, the application prospect of sclerostin in periodontal therapy combined with orthodontic treatment is another promising approach. There are also a lot of drugs that regulate sclerostin. Anti-sclerostin antibody (Scl-Ab) is the most direct one that inhibits bone resorption caused by sclerostin. At present, drugs that inhibit the expression of sclerostin have been applied to the treatment of diseases such as multiple myeloma and osteoporosis. Therefore, the application of sclerostin in the oral field is just around the corner, which provides a new therapeutic bone regulation strategy in oral and general health.

Keywords: Sclerostin; Periodontitis; Orthodontics; Tooth movement; Mechanical forces; Adjunctive therapy

Introduction

As of 2016, severe periodontitis was the eleventh most prevalent epidemic disease in the world, which contributes to progressive alveolar bone destruction.[1] Basic periodontitis treatments include scaling, subgingival scaling, and root planning, which cannot eliminate the infection and possibly induced complications. In recent years, several adjunctive therapies such as anti-microbial therapy, host modulation therapy, laser therapy, and tissue engineering for tissue repair and regeneration have been studied to address and improve the issues associated with severe periodontitis. However, as they are all in the initial stage, more clinical trials and longer observation times are needed. New evidence has shown that sclerostin plays an important role in the progression of inflammation and tooth movement; anti-sclerostin antibody (Scl-Ab) is also claimed to be a novel therapeutic agent in oral disease.

Sclerostin, encoded by the *SOST* gene, is mainly secreted by mature osteocytes. It inhibits bone formation as it is an antagonist of the canonical Wnt pathway.[2] Sclerostin has previously been researched in several diseases such as osteoporosis, sclerosteosis, and van Buchem disease.[3-5] In recent years, increasing research has focused on the effects of sclerostin in periodontitis development. In the past few years, researchers have found that inflammation can induce sclerostin expression.[6,7] Some studies showed that removal of sclerostin decreased bone destruction, as well as moderately protected the alveolar bone from resorption to delay periodontitis progression.[8-10] This suggests that the loss of sclerostin has a positive impact in periodontitis progression. Meanwhile, current research has shown that the expression of sclerostin is influenced by mechanical force stimulation[11-14]; thus, sometimes, periodontitis can be induced during orthodontic treatment.[15] Further, orthodontic tooth movement has been demonstrated as biological bone remodeling induced by mechanical force. Most of all, sclerostin seems to be a potential target to develop the effect of periodontitis and orthodontic treatment even the whole oral treatment.

Scl-Ab has been confirmed to enhance bone strength, bone mass, bone formation, and implant fixation in a rat

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model.[16,17] Therefore, we can speculate that Scl-Ab can stimulate bone regeneration after periodontitis, even in case of periodontitis caused by orthodontic treatment. Scl-Ab has shown a positive, therapeutic role in many complications that cause periodontitis such as cigarette smoking,[18] hyperglycemia,[19] inflammatory factor,[20] advancing age,[21] estrogen deficiency,[22] and osteoporosis,[23,24] and are difficult to treat by traditional treatment methods such as orthodontics and tooth extraction. Therefore, further exploration of the role of Scl-Ab in periodontitis may be beneficial.

Sclerostin in Tooth Movement

Sclerostin is a gene located at position 11.2 on the long arm of chromosome 17 and was found to be almost exclusively produced by mature osteocytes. Sclerostin is considered a potent antagonist of the canonical Wnt signaling pathway, which is regarded as an important pathway in bone formation and loss and plays an important mechanosensory role in bone remodeling.[25-27] However, little is known regarding the pattern of sclerostin expression in alveolar bone during tooth movement and the underlying mechanisms of tooth movement in bone remodeling. Further, sclerostin expression regulates bone remodeling via the osteoprotegerin (OPG)/mitogen-activated protein kinase (MAPK), Wnt, and extracellular signal-regulated kinase (ERK)1/2-Runx2 pathways [Figure 1].[25,26,28-30] The most commonly studied biomarkers in periodontitis research include osteoclast-activating factors (eg, receptor activator of nuclear factor κB ligand [RANKL], osteogenic factors [OPGs], and related pathways MAPK).[31] Researchers have conducted many animal experiments, and immunohistochemical staining has shown down-regulation of OPG expression and up-regulation of ERK1/2-MAPK and RANKL expression in mice with periodontitis that cause inflammatory bone resorption. According to studies based on experimental animal models of periodontitis, sclerostin expression can be increased by inflammatory factors.[8,32] As inflammatory factors have an important effect on the progressive bone destruction that characterizes periodontitis and given that sclerostin has a crucial role in inflammatory bone resorption, it is reasonable to determine that sclerostin alteration can affect periodontitis progression.[8-10] In addition, ERK1/2-Runx2 signaling is also related to mechanical stimulation, which may account for the high incidence of periodontitis during orthodontic treatment.[33-35]

Recently, new research studies have explored the mechanism and impact factors of sclerostin expression in tooth movement. It is well proven that mechanical forces are responsible for bone remodeling during orthodontic tooth movement (via the regulation of bone mesenchymal stem cells to control bone regeneration) and tissue engineering applications.[36,37] Recent evidence has indicated that modulation of sclerostin levels, via activation of the Piezo1-Akt pathway and inhibition of Wnt/LRP5 and TSC1/mTORC1 signaling, appears to finely tune the regional and local osteogenesis coordinated by osteocytes in response to increased mechanical stimulation.[11-14,38] In addition, the expression of sclerostin increased when mechanical loading decreased and reduced when mechanical loading increased [Figure 2].[38-40] Therefore, sclerostin modulation seems to be a target to develop the effect of orthodontic treatment. Modest and severe periodontitis may cause pathologic tooth migration; therefore, the number of periodontitis patients seeking orthodontic treatment is on the rise. Furthermore, periodontitis-orthodontic therapy has become more popular among patients. However, orthodontic treatment can cause periodontitis and even exacerbate pathogenetic conditions.[15] Above all, modulating the expression of sclerostin may be a method to reduce inflammatory bone resorption and improve periodontitis caused by orthodontic treatment.

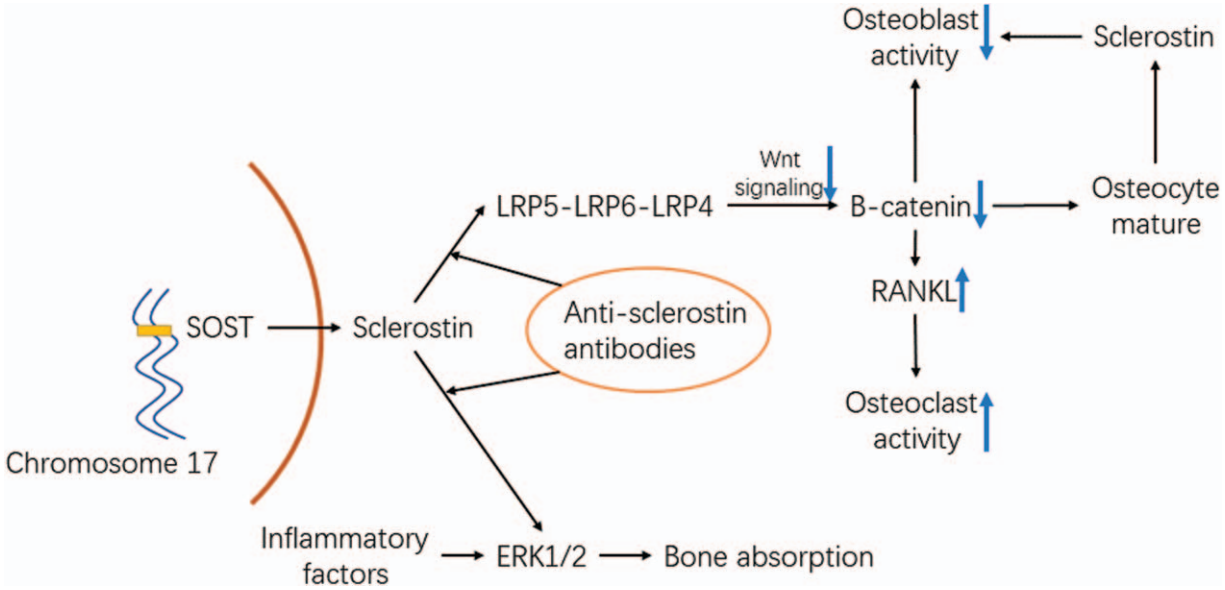

Figure 1: The mechanism of sclerostin in bone loss. Sclerostin increases osteoclast activity and decreases osteoblast activity during tooth movement via OPG/MAPK, Wnt pathway, and ERK1/2-Runx2 pathway. ERK: Extracellular signal-regulated kinase; RANKL: Receptor activator of nuclear factor κB ligand; OPG: Osteoprotegerin; MAPK: Mitogen-activated protein kinase.

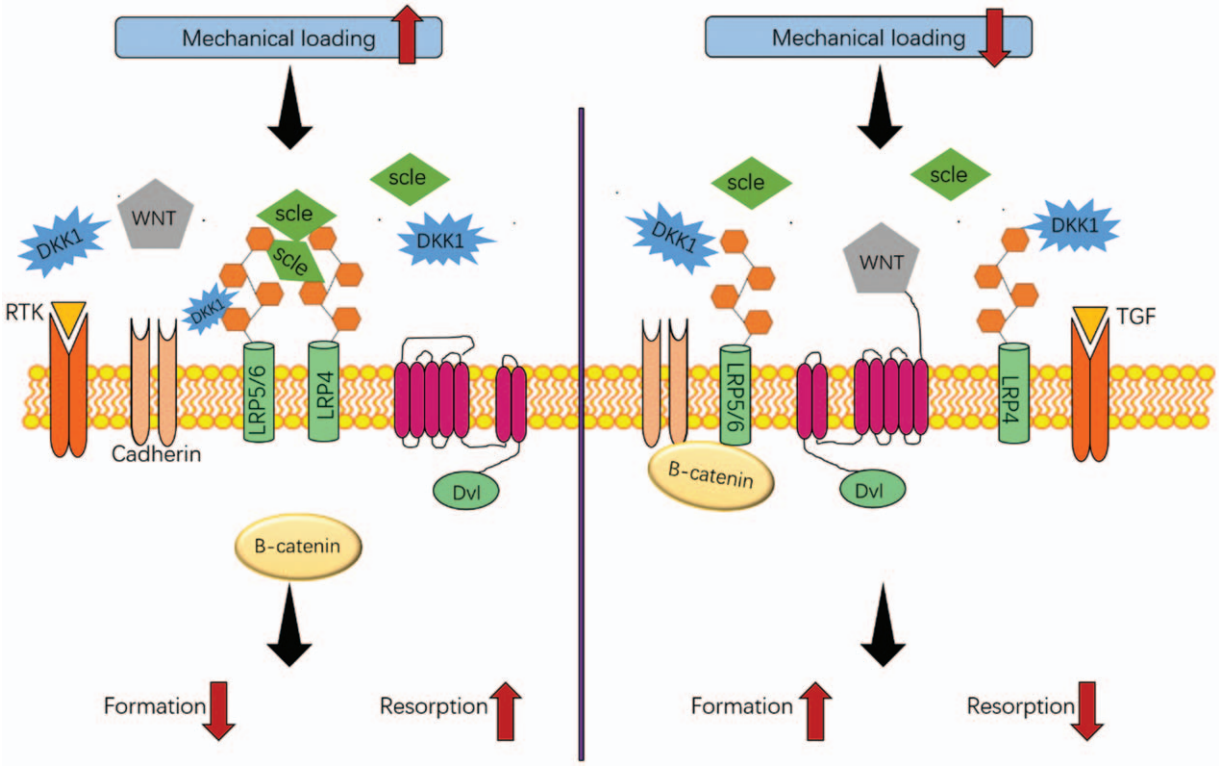

Figure 2: The relationship between sclerostin expression and mechanical forces. The expression of sclerostin is reduced when mechanical loading is increased and increased when mechanical loading is decreased. And the expression of sclerostin regulates bone formation and resorption via medicating the osteoblastic differentiation of bone mesenchymal stem cells. DKK1: Dickkopf 1; RTK: Receptor tyrosine kinase; Scle: Sclerostin; TGF: Transforming growth factor.

Periodontitis and Potential Therapies

Oral health is a critical element of general health. However, periodontitis affects more than 50% of adults, and 5% to 15% of the adult population suffer from advanced periodontitis.[41] The primary underlying cause of periodontitis is still controversial, but it is known to be associated with several factors such as tooth movement due to orthodontics and tooth extraction, cigarette smoking,[18] hyperglycemia,[19] inflammatory factor,[20] advancing age,[21] estrogen deficiency,[22,42] and osteoporosis.[23,24] These aspects hinder the cure of periodontitis.

Periodontitis is a chronic infectious disease caused by microorganisms in dental plaque. The most simple and effective traditional treatment is mechanical removal of local dental plaque. However, effective strategies to alleviate bone loss in periodontitis are still under research. Anti-resorptive agents such as bisphosphonates and denosumab are frequently used to inhibit bone resorption associated with osteoporosis and periodontitis.[43,44] However, these medications are associated with infrequent but potentially severe side effects such as osteonecrosis of the jaw.[45,46] Analogs of parathyroid hormone directly stimulate bone formation through parathyroid hormone type-1 receptors and regulation of osteocytic sclerostin expression.[47-49] Tumor necrosis factor-α antagonist inhibits expression of pro-inflammatory cytokines in periodontitis to attenuate alveolar bone loss and diminishes osteocytic RANKL and sclerostin expression in periodontitis to mediate bone formation.[50,51] WP9QY (W9) peptide, a RANKL-binding peptide, restores alveolar bone loss by inhibiting RANKL signaling to suppress osteoclastogenesis and attenuates sclerostin expression to enhance osteoblastogenesis. Thus, it is a potentially useful drug to prevent alveolar bone loss in periodontitis.[52] Resveratrol is a polyphenolic compound that can modulate the osteo-immune-inflammatory host response.[53,54] It has been shown to activate the Sirt1/AMPK and Nrf2/anti-oxidant defense pathways in inflamed gingival tissues and inhibit the expression of proinflammatory cytokines such as interleukin-1 and tumor necrosis factor-α,[53,55,56] suggesting that resveratrol therapy may positively influence periodontal bone loss, even in the presence of tobacco use.[57] Scl-Ab would be more effective as an adjuvant therapy to standard-of-care practice to reduce active inflammation in periodontitis owing to its modest effects and dual effect on bone, that is, increasing bone formation and decreasing bone resorption.[58,59] The majority of current research is based on the regulation of sclerostin expression, and Scl-Ab is one of the most critical and effective components.

Anti-Sclerostin Antibodies

Veverka *et al*[60] demonstrated that antibodies interact with loop 2 of sclerostin by interfering with sclerostin-mediated inhibition on Wnt-induced AXIN2 expression. Later, van Dinther *et al*[61] found that Scl-Ab reversed the inhibition effect of sclerostin on Wnt3a-induced activity. At present, although our understanding of this mechanism remains incomplete, we can conclude that Scl-Ab inhibits

the binding of sclerostin to LRP5/6, possibly forming the basis for a pathway for bone rebuilding.[61]

Many studies have found that sclerostin monoclonal antibody treatment could promote bone strength by increasing bone formation and decreasing bone resorption.[62-64] Therefore, more research about anti-sclerostin antibodies on several common clinical diseases have been carried out ever since. Osteoporosis is the mostly studied condition. Scl-Abs have been used in both clinical and preclinical studies of osteoporosis because of its positive effect on bone density, structure, strength, and fracture risk reduction. In 2018, an article summarized the latest evidence correlated with osteoporosis; in that, Romosozumab, a humanized Scl-Ab, was reported to increase bone formation, decrease bone resorption, increase bone mineral density, and reduce the incidence of vertebral fractures. It can be potentially introduced as a skeletal anabolic agent in clinical practice.[65,66] Further, Scl-Ab treatment was also studied in the context of multiple myeloma-induced bone loss prevention and tumor burden reduction and was regarded as a novel target.[67,68] In addition, Scl-Ab administration can enhance osseointegration and bone regeneration around bone implant and dental implants, which indicates a potential therapeutic approach to reduce the healing time and accelerate bone regeneration after implant placement.[69,70] Moreover, an animal experiment in 2018 proved that treatment with Scl-Ab significantly increased mandibular bone mass and alveolar height in wild-type mice.[63] Use of Scl-Ab is a prospective treatment method for bone absorption induced by periodontitis and other oral therapies like orthodontic or implant treatment.

Periodontitis-Orthodontic Treatment

Periodontally compromised patients often have maxillary anterior proclination with traumatic occlusion, rotations, and irregular spacing, and extrusion (pathologic migration). Therefore, more patients with periodontitis are turning to orthodontic therapy to alleviate or eliminate these symptoms. More dentists are attempting to evaluate the effect of periodontitis-orthodontic treatment, and most have noted that the method is beneficial for the repair of oral tissue function and esthetics.[71-74] The results showed that moderate orthodontic teeth movements may reconstruct the inter-proximal soft tissue, with esthetic improvement of the papillary level and resolution of periodontal defects. To conclude, periodontitis-orthodontic treatment is a potentially valuable treatment choice. However, the conflict between alveolar bone resorption caused by periodontitis and bone reconstruction required by orthodontic treatment remains to be solved.

The mechanosensor function of osteocytes is complex, in that it plays an important role in bone remodeling by regulating the sclerostin expression controlled by the *SOST* gene. Inflammatory factors in periodontitis lead to bone resorption in ERK1/2-Runx2 and Wnt pathway, signaling pathways are also related to mechanical stress, which may explain why periodontitis frequently occurs during orthodontic treatment. Some osteocyte proteins such as RANKL/OPG and interleukin-6 known to have mechanosensory roles are also signaling molecules that play key roles in inflammatory processes.[75-78] Sclerostin has been proven to regulate bone remodeling via the OPG/MAPK, WNT, and ERK1/2-Runx2 pathway and other potential mechanisms[25,26,28-30]; therefore, sclerostin regulation may be an effective therapeutic approach to balance bone resorption and remodeling during periodontitis-orthodontic treatment. This suggests that other cytokines may perhaps have similar dual roles in responding to conditions of loading/unloading and inflammation. The utility of Scl-Ab in osteoporosis treatment appears promising; hence, it is reasonable to assume that alveolar bone might be preserved by Scl-Ab against periodontitis in orthodontic treatment. Other drugs aimed at regulating the expression of sclerostin should also be researched in future.

Conclusion

There are several lines of ongoing research on sclerostin. Many of these are attempting to explore the mechanism of sclerostin-induced inhibition of osteogenesis (such as the inhibition of Wnt pathways) and to increase osteoclastic activity and number. And increasing research studied the influence of inhibiting sclerostin expression on bone formation, such as enhancing bone formation, bone mass, and bone strength. Several current drugs are based on the regulation of sclerostin expression to improve bone loss caused by periodontitis and systemic osteoporosis, and Scl-Ab is one of the most critical and effective agents discovered thus far. Researchers have studied the application of Scl-Ab for the prevention and treatment of osteoporosis, Paget disease, metastatic bone conditions, and conditions where cytokine over-activity leads to up-regulation in osteoclasts.

The latest finding suggests that Scl-Ab can be used in periodontitis or in orthodontic treatment. Moreover, Scl-Ab administration can enhance osseointegration and bone regeneration around dental implants. Furthermore, Scl-Ab has shown a positive, therapeutic role in many complications caused by periodontitis, and is difficult to treat by traditional treatment methods such as orthodontics and tooth extraction. Scl-Ab inhibits the production of sclerostin and thereby also inhibits the absorption of alveolar bone, which provides a better and promising therapy for periodontitis and other combined treatment methods. In particular, regulating the expression of sclerostin like Scl-Ab is a novel therapeutic bone regulation strategy for oral health and likely a future line for research for general health.

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Conflicts of interest

None.

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