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Sclerostin - The Silent Bone Breaker

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Review

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ABSTRACT

A disparity between host defense and periodontopathogens leads to periodontitis, which is an inflammatory disease of the periodontium of high prevalence. The dysregulated host immune response brought on by the disease's ongoing progression may result in tissue and bone destruction, which ultimately leads to tooth loss. Interpretation of bone metabolism has enhanced as a result of the identification of sclerostin and its function as a bone mass regulator. Primarily, osteocytes express sclerostin, an SOST gene known to inhibit formation of bone. The canonical Wnt pathway involved in bone homeostasis, is significantly suppressed by Sclerostin. It is thought to result in resorption of bone by altering the ratio of OPG and RANKL. Characteristics, mode of action and significance of sclerostin in periodontal diseases are discussed in this review.

Key words: Sclerostin, RANKL, SOST, Periodontitis, Osteocytes, Osteoclasts, Alveolar bone.

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Introduction

Bone destruction is a hallmark of periodontal disease. Bone is a highly dynamic and active tissue that constantly renews itself in response to nutritional, mechanical and hormonal factors and a balance between the related processes of bone formation by osteoblasts and bone resorption by osteoclasts is necessary to maintain bone homeostasis.[1]

In general, GBR[2] which could be invasive, results in potential surgical concerns, and autologous or allogeneic bone transplants are frequently used in alveolar bone reconstructive therapy.[3] Periodontal regenerative medicine would benefit from treatments that can enhance bone formation, bone quality and increase bone volume with minimal invasion in order to satisfy this requirement.[4]

Developments in the field of research in medicine have identified a bone matrix glycoprotein known as sclerostin, which is produced primarily by mature osteocytes and is critical in the regulation of bone homeostasis.[1] It has a detrimental impact on bone formation and is known to be a potent antagonist of the Wnt signalling pathway.[5]

Sclerostin was discovered as a result of research on two rare bone diseases van Buchem disease and sclerosteosis, both which have higher bone mineral density and bone formation induced as a result of skeleton sclerosis.[6] It is produced by osteocytes, as OPG and RANKL and inhibits bone formation by competitively binding to LRP 5/6, reducing its ability to combine with Wnt proteins, which blocks the activation of the Wnt/β-catenin pathway. RANKL is a receptor of OPG which downregulates bone resorption and is a primary regulator of osteoclast differentiation and activation.[7] Sclerostin initially was considered to have anabolic properties but has shown to play a role in bone catabolism according to recent research.[8]

Structure of Sclerostin

The DAN/Cerebrus family of glycoproteins includes the 190-residue secreted glycoprotein sclerostin. It is a three-loop structure surrounding a cysteine knot with a long and highly flexible C- and N-terminal arms. Four extremely conserved cysteine residues make up the cystine-knot motif, which then forms two intra-chain disulfide bonds that generally have 8-14 residues. Additionally, sclerostin has a core that binds a semi-flexible loop and heparin, which blocks Wnt signalling.[1]

In order to give the protein a structured core, loops 1 and 3 have cysteine knots at their bases and additional disulfide bonds at their tips. Loops 1 and 3 have a substantial hydrophobic patch that could be a protein interaction site. Loop 2 is a binding site for antibodies also known as the "target site". The binding site for LRP 5 is located on loop 3. In monomeric form, sclerostin weighs between 27 - 28 kDa.[9,10]

Regulation and Expression of Sclerostin

Sclerostin has been discovered in chondrocytes and osteoclasts in addition to being primarily secreted by osteocytes. Sclerostin has been identified in bone, bone marrow, cartilage, aorta, pancreas, kidneys, and liver.[11,12,13]

Age, Mechanical stimulation, vitamin D, estrogen levels, PTH, PGE2, TGF-β, glucocorticoids, as well as other factors, affect the synthesis of sclerostin. According to numerous studies, Mechanical loading impacts SOST expression. Mechanical regulation of sclerostin under loading and unloading conditions was investigated by Robling et al. In both rats and mice, sclerostin synthesis was upregulated in a loading model and downregulated in an unloading model. Additional animal studies have shown that transgenic mice's osteocytes lose sclerostin when subjected to mechanical loading.[1]

Age is associated with higher serum sclerostin levels. Age-related impairments in bone formation is the cause of this increase. Circulating sclerostin levels are known to drop with estrogen, and its synthesis is enhanced by oestrogen deficiency. Sclerostin synthesis was found to be greater in men compared to women and serum levels were markedly lowered in postmenopausal women who received estrogen therapy.[14,15]

Sclerostin and vitamin D both inhibit the Wnt pathway. In patients with vitamin D deficiency, a reduction in serum levels of sclerostin was seen following vitamin D therapy. Dawson-Hughes *et al*. found that serum sclerostin levels were increased in healthy older men, in response to vitamin D and calcium treatment in comparison to women.[16,17]

Osteoprogenitor cell proliferation and differentiation are well-known to be regulated by prostaglandin E2. A significant reduction in SOST expression occurs through cyclic AMP, BMP signalling and EP2 receptor Ptger2. PGE2 thus inhibits sclerostin, stimulating the Wnt signalling pathway (18). Expression of sclerostin is downregulated by PTH. Runx2, which breaks down into prosteosomes in the presence of PTH, upregulates expression of SOST and PTH inhibits SOST expression by cyclic AMP/PKA pathway activation.[19,20,21]

Sclerostin production in osteocytes is increased by an increase in glucocorticoids. Prednisolone-treated mice exhibited increased SOST expression, indicating the involvement of glucocorticoids in inhibiting formation of bone mediated by the Wnt pathway. According to Thiele *et al*. serum levels of sclerostin were upregulated in mice after glucocorticoid administration but reduced in human mesenchymal stem cells and people on glucocorticoid therapy.[22,23]

Sclerostin's Biological Aspects

The Wnt signalling pathway is directly inhibited by sclerostin which prevents Wnt from attaching to LRP 5 and LRP 6. As a result, degradation of β-catenin is blocked, antagonising the Wnt/β-catenin pathway. Interaction between sclerostin and LRP 4, fosters sclerostin's antagonistic effects on Wnt/β-catenin signalling. Osteoblasts and bone formation are thought to be negatively regulated by sclerostin by affecting the differentiation and proliferation of osteoblast and inhibits mineralisation of osteoblasts. Additionally, there is suppression of osteoblastogenesis that causes the apoptosis of osteoblastic cells. It inhibits Wnt signalling, which promotes an unbalanced bone turnover. Along with inhibiting formation of bone, it also promotes resorption of bone. Sclerostin's ability to trigger bone resorption has thus been established.[1,24,25]

Sclerostin Distribution Within Oral Tissues

Recent research has demonstrated that expression of sclerostin in oral tissues along with alveolar bone osteocytes are found in odontoblasts, cementocytes, periodontal ligament cells (PDLCs), dental pulp stem cells (DPSCs) and in GCF as well. The diverse manner in which sclerostin is expressed in oral cells and tissues has revealed the ability of sclerostin to regulate dental homeostasis.[26,27,28]

Sclerostin has also shown to be expressed in mouse and human cementocytes. Deficiency of SOST gene seen in mice also causes thickening of the buccal and lingual cementum, reflecting the reduction in cementogenesis caused by sclerostin. Another study conducted on mice showed the lack of production of sclerostin during early stages of cementogenesis. At four weeks it was expressed in the apical cellular cementum, with an increased expression at eight weeks. This finding raises the possibility of the involvement of sclerostin in regeneration and maintenance of homeostasis of cementum.[29,30,31]

The Relationship Between Sclerostin and Periodontal Disease

Recent research shows that sclerostin regulates the alveolar bone catabolism and anabolism, which could lead to periodontitis. Inhibition of sclerostin could restore the morphology of the periodontal ligament and increase alveolar bone mass. According to a study, increased expression of sclerostin and RANKL was associated with increased formation of osteoclast and a decrease in the formation of osteoid in rats with ligature-induced periodontitis.

Sclerostin expression is decreased with an increase in osteoid formation, which emphasises the significance of sclerostin and RANKL in causing loss of bone.[32,33]

For formation of periodontal ligament, periostin is a crucial matrix protein. Periodontal ligament integrity is lost due to periostin deficiency, which also causes loss of alveolar bone, inflammation of periodontal tissue, formation of periodontal pocket, along with other periodontitis-like manifestations. [33]

Periostin and periodontal homeostasis are regulated by the regulatory role of sclerostin.[34] It is expressed more strongly in gingival tissues and GCF of periodontitis patient according to *in vivo* studies. Patients with periodontitis have been reported to have elevated GCF and salivary levels of RANKL. In addition, periodontitis patients' crevicular fluid contains higher levels of sclerostin, which may provide to be a more accurate indicator of the disease's diagnosis or prognosis than RANKL. Patients with chronic periodontitis showed an increase in sclerostin in gingival biopsies and peri-implantitis patients were also found to have increased levels of sclerostin in their PICF.[35,36]

Based on an *in vitro* study by Wijenayaka *et al*., exogenous administration of recombinant sclerostin

increased the production of RANKL. This suggests that sclerostin may promote osteoclastogenesis through RANKL. Additionally, sclerostin-induced osteocyte development has been linked to higher resorptive activity. Sclerostin has anti-anabolic properties, but it also causes pathogenic bone loss in periodontitis due to inflammation-induced sclerostin expression.

It was also evaluated how NSPT affected the production of sclerostin. Following NSPT, Balli *et al*. found reduction in the sclerostin levels in GCF, which showed an improvement in clinical parameters.[37] Patients with chronic periodontitis had 1.6 times higher levels of sclerostin expression than at baseline, but Beiler *et al*. found no significant difference between salivary sclerostin levels prior to and following NSPT.[38]

Role of Sclerostin in Dental Implantation

Dental implants are a credible procedure to replace missing teeth. For dental implants to successfully osseointegrate after placement, sufficient bone density at the edentulous ridge is essential. Accelerating regeneration of alveolar bone to reduce healing time of implant and uphold enduring stability is a challenge for stable osseointegration.[39,40] For clinicians, the treatment and prevention of peri-implant diseases are becoming more pivotal.

Sclerostin levels in patients with periimplantitis are higher in comparison to patients with perimucositis and healthy peri-implant tissues and the region around inflamed implants have significantly higher levels of sclerostin, according to results from *in vivo* studies. These finding raise a possibility that sclerostin could be a useful biomarker for peri-implantitis.[41,10]

Conclusions

Early discovery of root resorption and accurate documentation of the patient's history are essential steps for successful management, prognosis, outcome of root resorption, and treatment at the appropriate time, which will prevent tooth loss. With the current advancement of sophisticated imaging methods, such as cone-beam computed tomography, which is an effective screening method for confirming the existence of root resorption, and bioceramic-based endodontic materials, which allows for the extension of the limits for tooth conservation, the treatment of root resorption has become more predictable and successful.

Clinical studies are necessary to understand the etiology and pathogenesis of the various root resorption types. In addition, a deeper understanding of this area is essential since root resorption diagnosis and management can be difficult for clinicians and result in misdiagnosis.

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