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Biochemical Features, Metabolism and Medical Importance of Sclerostin: A Review Article

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Abstract

Sclerostin is a glycoprotein that was encoded by the SOST gene and crucially described as a key regulator in bone metabolism and skeletal homeostasis. The original discovery provided an insight into how Wnt/β-catenin pathway inhibitor, sclerostin regulates bone formation through osteoblasts and their activities while giving information concerning regulation of bone resorption. Besides this basic physiological function, many studies have revealed that Sclerostin was involved in metabolic, vascular, and immunological pathways thus emphasized clinical interests in such diseases as osteoporosis or cardiovascular disorders together with chronic kidney disease. Herein biochemical details and metabolic routes of Sclerostin besides its medical importance are discussed raising considerations about using it as a biomarker as well as therapeutic targeting. bone remodeling is an extremely complicated and dynamic process controlled by many biochemical factors with the central inhibitory role of sclerostin. At present, this protein occupies a unique place in the intersection of bone biology, systemic regulation, and clinical intervention-protein with high biomedical importance. Though further research on its structure, metabolism, and function would certainly lead to more therapeutic breakthroughs-the-more unveiling new dimensions about health and disease-this article attempts a review-in-ever modern-related-literature describing biochemical nature, metabolic control, and medical importance of sclerostin that make it highly relevant in skeletal as well as systemic physiology.

Keywords: Sclerostin; *SOST* gene; Bone metabolism; Osteoporosis

Introduction

Bone is dynamic tissue. It plays an essential role in structural support, movement, and protection of vital organs plus mineral homeostasis for humans and other vertebrates. Bone does not remain as a static framework. Remodeling occurs on a continuous basis over the entire life span through tightly controlled mechanisms involving bone resorption by osteoclasts and bone formation by osteoblasts (Boyle et al., 2003). Hence, remodeling is constantly going on; there has to be some balance between these two activities. The process, therefore, ensures that the skeleton retains its strength or integrity while also providing enough quantities of calcium and phosphate needed for various metabolic activities. Bone remodeling deregulation results in diseases like osteoporosis, osteopetrosis as well as other skeletal pathologies that fall under metabolic bone diseases. Consequently, understanding the molecular and biochemical factors controlling this process occupies a major focus in skeletal biology plus medicine (Florencio-Silva et al., 2015).

Bone remodeling is orchestrated by the action of systemic hormones, local growth factors, and multiple intracellular signaling pathways. Among these, the canonical Wnt/β-catenin pathway has come to be appreciated as a major mechanism about the regulation of bone mass (Baron & Kneissel, 2013). Wnt signaling promotes bone formation by way of encouraging osteoblast proliferation, differentiation, and survival; decreased function means reduced bone mass when signaling is inhibited. This pathway is extracellularly modulated by many antagonists that include Dickkopf proteins, secreted frizzled-related proteins (SFRPs), and sclerostin. These are negative regulators of bone formation; therefore, they could provide an exciting future for therapeutic intervention in bone diseases (Maeda et al., 2013).

It is within this perspective that sclerostin has come to significant attention over the last two decades as the major osteocyte-derived protein inhibitor of bone formation. It was first discovered in studies of rare genetic disorders such as sclerosteosis and Van Buchem disease - high bone mass diseases caused by loss-of-function mutations in the SOST gene encoding sclerostin, then quickly appreciated as an important regulator of bone metabolism (Balemans 2001). The identification of sclerostin initiated the most insightful detail regarding molecular pathways that would be a regulator for bone formation and swung therapeutic strategies toward osteoporosis and other metabolic bone diseases. Sclerostin inhibition opened a validated therapeutic approach evidenced already with the development and clinical validation on the market of monoclonal antibodies like romosozumab increasing bone mass and decreasing risk for fracture in osteoporotic patients (McClung et al., 2014).

Sclerostin is a glycoprotein; it comes mainly from osteocytes-these are the bone cells of which there exist many populations and generations that serve as mechanosensors within the matrix of bone. Osteocytes were most abundantly described to secrete sclerostin (Poole et al., 2005). Inhibiting the pathway for Wnt signaling by binding to the low-density lipoprotein receptor-related proteins LRP5/6, this sets up steoblastic differentiation and also bone formation-further blocking net anabolic pathways-extremely active in integrating mechanical load, hormonal effect, and molecular cellular cross-signaling in bone. Thus, synthesis of Sclerostin reduced by physical activity and mechanical loading but increased under conditions of unloading or immobilization-to link it with signaling mechanisms that control skeleton response to outside force (Robling et al., 2008). Thereby, systemic factors such as parathyroid hormone (PTH), estrogen, and glucocorticoids add another dimension controlling levels of Sclerostin: further placing its secretion within interactions between local networks at various hierarchies (Modder et al., 2011).

The metabolism of sclerostin—its expression, regulation, presence in serum circulation, and degradation—is a very important area with practical implications towards the development of biomarkers and understanding therapeutics. Sclerostin levels in serum have been proposed to indicate bone turnover, fracture risk, and treatment responses in interventions needing further validation for clinical applicability (Amrein et al., 2012). In addition, there is proof that sclerostin is expressed not only by bone but also by other tissues—perhaps its known function within the vascular system—it has a role in vascular calcification. So, already increasing the medical importance attached to sclerostin outside skeletal pathology through cardiovascular health plus metabolic disease (Wójcik-Piotrowicz et al., 2021).

Medically speaking, sclerostin is being regarded as both a biomarker and therapeutic target. The clinical

development of anti-sclerostin antibodies in the treatment of osteoporosis does validate the basic research on this protein for translation. This happens amid fears related to side effects, particularly on the aspect of cardiovascular risk related to inhibition of sclerostin (Cosman et al., 2016). To optimize therapy and reduce risks, therefore, an understanding of sclerostin at the biochemical level and systemic function should be better understood. It may act beyond osteoporosis; conditions such as chronic kidney disease-mineral bone disorder (CKD-MBD), rheumatoid arthritis, and vascular calcification put more importance on it in biomedical research (Cejka et al., 2011).

Biochemical features and metabolism of sclerostin

Sclerostin is a glycoprotein encoded by the SOST gene. It acts as a secreted antagonist against the Wnt/β-catenin signaling pathway and thus comes to play in bone homeostasis (Poole et al., 2005). Discovered only recently—within the early 2000s—sclerostin has rapidly developed high interest within musculoskeletal biology. This was not merely on account of its primary function in bone remodeling but also based on putative systemic functions stretching across vascular physiology, metabolism, and inflammatory pathways (van Bezooijen et al., 2007). Biochemical characterization and definition of metabolic control over sclerostin are required toward working out clinical relevance and therapeutic potential.

Guide to Understanding Sclerostin in Biochemistry

Sclerostin is a glycoprotein weighing 22 kDa and comprising about 190 amino acids with two cysteine-knot-like motifs known as CTCK that are important in maintaining its stability and in receptor-binding activities (Winkler et al., 2003). A high level of affinity binding presented by the cysteine-rich structure to low-density lipoprotein receptor-related proteins 5 and 6 (LRP5/6) presents the co-receptors for the canonical Wnt pathway. When bound by sclerostin, LRP5/6 can no longer be activated by Wnt ligands to elicit downstream β-catenin signaling and therefore per se forms an inhibitor of osteoblast proliferation and differentiation (Li et al., 2005).

The fold of sclerostin has now been resolved at the atomic level by X-ray crystallography, confirming its adoption of a cystine-knot fold that is highly conserved among other growth factors and inhibitors (Veverka et al., 2009). The compactness imparts extracellular stability to the molecule. Extracellular stability is further imparted by post-translational modifications, such as glycosylation, which lead to abundant secretion and may enable osteocytes to secrete it efficiently since osteocytes are believed to be the major source of sclerostin in bone tissue (Lewiecki, 2014).

The SOST gene maps to chromosome 17q12-q21 and is controlled at the level of transcription by several pathways. Major regulatory elements include the van Buchem disease deletion region enhancer that controls osteocyte-specific SOST expression (Balemans et al., 2002). Mutation or deletion within this region will precipitate pathogenic conditions like Sclerosteosis and van Buchem disease, on the one hand, due to inadequate expression or total absence of the expression of sclerostin, on the other hand, characterized by high bone mass.

Several factors modulate the expression of the SOST gene. Mechanical loading strongly regulates sclerostin as a negative regulator; in fact, it is mechanical strain that reduces its expression to promote bone formation (Robling et al., 2008). Conditions of unweighting the skeleton such as immobility or space flight increase the level of sclerostin making bone resorption (Spatz et al., 2012). Much hormonal influence occurs. Parathyroid hormone (PTH) acts by suppressing the transcription of sclerostin, thereby relating its anabolic effect on bone with the activation of Wnt signaling (Keller & Kneissel, 2005). Other hormones include glucocorticoids that upregulate the expression of sclerostin which partly explains osteoporosis induced by glucocorticoids (O'Brien et al., 2014)

Sites of Production Sclerostin is mainly produced by osteocytes. Osteocytes are the fully matured osteoblasts that get trapped inside the bone matrix. Osteocytes constitute more than 90% of the whole population of bone cells and are believed to be mechanosensors that control bone remodeling by releasing signaling molecules among which sclerostin appears to be the most important (van Bezooijen et al., 2004).

Beyond bone, recent findings suggest that sclerostin is expressed in extra-skeletal tissues with lower levels though. Some studies have found its expression in the kidney, vasculature, and cartilage; thus, it has wider functions in mineral metabolism and vascular health (Clarke & Drake, 2013). This systemic presence has led researchers to study sclerostin as a potential biomarker

for cardiovascular disease, chronic kidney disease (CKD), and diabetes mellitus (Evenepoel et al., 2015).

Sclerostin primarily acts as an inhibitor of the Wnt/β-catenin signaling pathway. The Wnt pathway is necessary for osteoblast proliferation, differentiation, and survival. When there is no inhibition of Wnt signaling, β-catenin accumulates in the cytoplasm then moves to the nucleus where it can activate osteogenic genes (Baron & Kneissel, 2013). Binding to LRP5/6 makes sclerostin a Wnt pathway inhibitor because it blocks the binding sites for Wnt ligands, which increases signaling through β-catenin and results in reduced osteoblast activity and bone formation (Li et al., 2005). Besides, sclerostin also inhibits bone morphogenetic protein, BMP signaling though the aspect is less pronounced compared to its regulation of Wnt signaling (van Bezooijen et al., 2007).

Circulating Levels and Metabolism

Sclerostin serum levels reflect the net effect of bone formation and bone resorption activities. In healthy adults, normal serum concentrations range between 20 and 60 pmol/L but can vary with age, sex, or condition of the skeleton (Mödder et al., 2011). It has a relatively short half-life in circulation because anything that is rapidly cleared or degraded most probably through renal excretion. Conditions where the patient is suffering from CKD will always find elevated levels; hence support for kidney involvement in sclerostin metabolism (Cejka et al., 2011).

Age and sex also influence circulating levels. With increasing age, Sclerostin presents more in the circulation with advancing ages thereby accompanying reduced bone formation with advancing ages (Amrein et al., 2012). Just like higher serum concentrations of men than women probably due to difference in bone mass and hormonal regulation. It underscores how much more complex the regulation of sclerostin metabolism is under normal and abnormal conditions (Ardawi et al., 2012).

Physiological Roles Beyond Bone

Though bone remodeling remains the main site of action, sclerostin has been implicated in wider physiological contexts:

Vascular Biology: Sclerostin was identified within atherosclerotic plaques; higher levels are related to vascular calcification. This finding suggested that it may play a regulatory role in vascular mineralization (Claes et al., 2013).

Kidney Function: Serum levels of sclerostin are markedly elevated in patients with CKD, due to impaired clearance and probably increased production either from bone or vascular tissue (Evenepoel et al., 2015).

Energy Metabolism: New studies conducting on the relation between sclerostin and glucose metabolism indicated evidence that higher sclerostin may be correlated with insulin resistance and obesity (Kim et al., 2015).

This means that the metabolism of sclerostin goes beyond skeletal tissues and describes it as a multifunctional regulator of both bone physiology and general body physiology.

Pathophysiological Implications

Dysregulation in the expression or metabolism of sclerostin plays a role in several diseases. The genetic mutations in SOST function loss lead to two conditions—sclerosteosis and van Buchem disease—where high bone mass is maintained through unregulated Wnt signaling (Balemans et al., 2002). More typical, however, is increased expression of sclerostin in cases of osteoporosis wherein reduced bone formation further enhances the condition's already extremely deleterious effects on bone fragility (Lewiecki, 2014).

In CKD, increased circulating sclerostin has been implicated in the pathogenesis renal osteodystrophy and vascular calcification making it a potential biomarker and therapeutic target (Cejka et al., 2011). In metabolic disorders, it is through maladjusted sclerostin that seemingly perturbed interactions between bone and energy metabolisms take place; however, this area requires further studies (Kim et al., 2015).

Therapeutic Targeting of Sclerostin

The understanding of sclerostin as a negative regulator of bone formation has led to the synthesis of antibodies against sclerostin. Romosozumab is a humanized monoclonal antibody that has shown results in increasing bone mineral density and decreasing the risk of fractures in postmenopausal osteoporosis (Cosman et al., 2016). When sclerostin is blocked from performing its

inhibitory function, the Wnt pathway signaling strength is increased thereby promoting bone formation with a net effect being more on formation than resorption. This gives sclerostin very high value in terms of biochemistry and metabolism for study not only in bone biology but potential off-target effects in the cardiovascular and metabolic systems (McClung et al., 2018).

Clinical Importance of Sclerostin

Sclerostin, glycoprotein by the SOST gene, has recently come to light as a very important regulator of bone homeostasis and skeletal health. Apart from the well-established fact that it acts as an inhibitor in the Wnt/β-catenin signaling pathway and thereby helps keep osteoblast activity under check, increasing evidence primarily relates sclerostin to several diverse clinical conditions; for example, osteoporosis and fracture risk, chronic kidney disease or cardiovascular disorder, metabolic bone diseases, and possible therapeutic interventions. The growing clinical relevance in medicine places it at dual importance both as a diagnostic biomarker and therapeutic target.

Sclerostin and Bone Health

The most well-studied aspect of sclerostin is bone metabolism and skeletal strength. Sclerostin, predominantly secreted by osteocytes-the most abundant cells of bone-secretes activity leading to the inhibition of one pathway when promoting resorption by upregulating osteoclastogenic signaling. In healthy physiology, this would be to maintain balance between bone formation and breakdown (Drake & Clarke, 2019).

Osteoporosis is strongly associated with increased circulating sclerostin levels. Multiple studies provided a positive correlation between serum sclerostin and bone loss with increasing age, particularly in postmenopausal women and elderly men making sclerostin both a predictive marker for the risk of developing osteoporosis and an attractive target for new drugs (Amrein et al., 2012).

The finding of rare genetic diseases like sclerosteosis and van Buchem disease also caused by loss-of-function mutations in the SOST gene further underscores its clinical relevance. Individuals from these conditions present the pathology with high bone mass due to no or reduced sclerostin activity. It thus formed a basis from which sclerostin inhibitors could be developed as the anabolic therapies for osteoporosis (Balemans et al., 2001).

Sclerostin as a Biomarker of Fracture Risk

Beyond bone mineral density (BMD), sclerostin is now being studied as a biomarker of fracture risk. Higher serum sclerostin has been associated with increased risk of hip and vertebral fractures, aside from the effects of BMD. This has advanced the notion that circulating levels represent not just bone mass but include microarchitectural quality and remodeling activity (Arasu et al., 2012). Most importantly, studies note sex- and age-related differences in sclerostin levels. Men normally show higher serum concentrations than women and levels increase with age. These demographic variations may assist clinicians to particular subgroups of a higher propensity for fracture risk and thus develop prevention strategies (Modder et al., 2011).

Sclerostin in Chronic Kidney Disease (CKD)

CKD and ESRD patients manifest significantly increased sclerostin levels, hence putatively reflecting the degree of derangements in mineral metabolism and skeletal health. Increased circulating sclerostin is most commonly associated with a CKD-mineral and bone disorder (CKD-MBD) pathology in which abnormal bone turnover mediates not only fractures but also vascular calcification as well as mortality (Cejka et al., 2011).

Serum sclerostin levels in CKD patients correlate more with vascular stiffness and arterial calcification than with any other factors, pathology possible related between bone and vascular systems. This puts Sclerostin in the middle of renal disease, skeletal fragility, and enhanced risks of cardio-vascular pathology (Viaene et al., 2013).

Cardiovascular Implications of Sclerostin

The role of sclerostin in life is beyond the skeleton. Several studies conducted have indicated that there is sclerostin expression in VSMCs of calcified arteries (Clarke, 2019). This proves to mean that it takes part in controlling a process and pathway playing as an inhibitor of Wnt signaling, which limits vascular calcification.

High circulating sclerostin has paradoxically associated both with increased vascular calcification and reduced cardiovascular mortality depending on study design and population under consideration. This will indicate that sclerostin can be an agent eliciting protection in vascular biology while at the same time working as a marker of

pathology. Therapeutically, the implications are profound. While anti-sclerostin antibodies do confer the benefit of skeletal health, there still remains a concern relating to vascular calcification whether it will be positive or negative. Continuous post-marketing surveillance of these therapies will deliver meanwhile very welcomed (Evenepoel et al., 2015).

Sclerostin in Metabolic Disorders

Sclerostin also regulates metabolism outside the bone. Emerging evidence relates sclerostin levels to type 2 diabetes mellitus (T2DM), obesity, and insulin resistance. High concentrations of sclerostin in obese and diabetic patients have been described; results correlate it with increased fat mass and inverse with sensitivity to insulin (Gaudio et al., 2012).

One postulation is that Sclerostin-mediated inhibition of the Wnt signaling pathway could extend its effects beyond just controlling osteoblastogenesis to include adipocyte differentiation thus linking bone with energy metabolism. This underscores the plausibility of sclerostin as a biomarker for metabolic bone disease and possible mediator of skeletal fragility in diabetes (Wang et al., 2018).

Sclerostin in Cancer and Other Diseases

Increasing proof shows that changed sclerostin levels might help cancer grow. Some studies point to a role in bone spread, especially in breast and prostate cancers where sclerostin might affect the tumor-bone environment (Winkler et al., 2018). Also, diseases like rheumatoid arthritis and ankylosing spondylitis show faulty sclerostin control, tying it to harmful bone changes in immune system diseases (Appel et al., 2009).

Therapeutic Targeting of Sclerostin

Major clinical breakthrough includes the development of monoclonal antibodies against sclerostin. Among them is romosozumab, which falls in prescription for postmenopausal osteoporosis and helps increase BMD, decrease fracture risk, as well as stimulate bone formation (Cosman et al., 2016).

Yet possible negative effects on the heart have made people worry, with some studies showing a higher chance of heart attacks and strokes (. So picking the right patients and checking their risks are still important for safe treatment use. The success of anti-sclerostin treatment shows how basic biochemical knowledge can turn into new medical approaches. But it also highlights the need for constant watching for unexpected whole-body impacts (Saag et al., 2017).

Future Directions and Clinical Translation

Great strides notwithstanding, several questions regarding the clinical relevance of sclerostin remain unaddressed. Some of these key questions that should dominate future research efforts are:

1. Standardizing assays to measure serum sclerostin in such a way that results from different studies become comparable.
2. Further elucidation of the nature of the causal relationship between sclerostin and vascular calcification.
3. Its potential role as a biomarker in metabolic and inflammatory diseases.
4. Long-term safety surveillance of anti-sclerostin therapies.
5. As knowledge grows, sclerostin steps out from being just a special bone sign and turns into a many-system bio mark and treatment aim with use in hormone study, kidney care, heart study, and cancer care.

Conclusion

Biochemical and metabolic characteristics place sclerostin at the heart of bone remodeling while new systemic functions are being discovered for the glycoprotein. From a structural point of view, Sclerostin accommodates a motif that enables it to bind Wnt co-receptors with high efficiency; therefore, it has strong influences on osteoblast activity and bone formation. Its gene is regulated by mechanical, hormonal, and pathological signals and its metabolism involves both bone-specific and systemic pathways. The expression of this glycoprotein in vascular and metabolic scenarios suggest general modulating effects. All these aspects bring this molecule into the limelight clinically as a biomarker and therapeutic target in bone and systemic diseases. Sclerostin has a central clinical function that goes well beyond its classic pathway of bone formation inhibition. Increased serum levels are associated with osteoporosis and the risk for fracture, CKD-MBD, vascular calcification, diabetes, and some cancers. Diagnostic biomarker and therapeutic target; indeed,

anti-sclerostin therapies have already revolutionized the treatment of osteoporosis. However, it does have effects on systems particularly on the cardiovascular system and caution is required therein. In summary, sclerostin is where bone biology meets systemic health to give new vistas in personalized medicine and holistic patient care.

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