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Developments in sclerostin biology: regulation of gene expression, mechanisms of action, and physiological functions

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Abstract

The *SOST* gene, which encodes the protein sclerostin, was identified through genetic linkage analysis of sclerosteosis and van Buchem's disease (VBD) patients. Sclerostin is a secreted glycoprotein that binds to the Low-density lipoprotein Receptor-related Proteins (LRP) 4, 5, and 6 to inhibit Wnt signaling. Since the initial discovery of sclerostin, much understanding has been gained into the role of this protein in the regulation of skeletal biology. In this article, we discuss the latest findings in the regulation of *SOST* expression, sclerostin mechanisms of action, and the potential utility of targeting sclerostin in conditions of low bone mass.

Keywords

Sclerostin; *SOST*; skeleton; osteoporosis; osteocyte; sclerosteosis; Wnt; Lrp

Introduction

The *SOST* gene and sclerostin protein were identified in the study of sclerosteosis and van Buchem's disease (VBD). Sclerosteosis and VBD are rare, autosomal recessive bone disorders that present as generalized osteosclerosis and hyperostosis of the skeleton. The skeletal manifestations are most pronounced in the skull and mandible, where enlargement of the jaw and facial bones leads to facial paralysis and hearing loss. Sclerosteosis, but not VBD, is associated with gigantism and hand abnormalities. The similarity in radiological findings between sclerosteosis and VBD led to the hypothesis that the two diseases are caused by mutations to the same gene [1]. Linkage analysis of families affected by sclerosteosis and VBD revealed that the disease-causing mutations were located on

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chromosome 17q12-q21 [2, 3]. Sclerosteosis results from a mutation to *SOST* leading to premature termination of the sclerostin protein [4] [5]. Accordingly, sclerosteosis patients do not exhibit detectable serum sclerostin [6]. In contrast, VBD results from a 52 kb deletion 35 kb downstream of the *SOST* gene [7]. This deletion leads to decreased expression of *SOST* and VBD patients exhibit low levels of serum sclerostin. The fact that VBD patients maintain detectable sclerostin protein expression may explain the less severe phenotype when compared to sclerosteosis patients [8].

In the decade following the initial discovery of sclerostin, much insight was gained into the role of this protein in bone metabolism. Sclerostin is a secreted, cysteine-knot protein sharing homology with the Differential screening-selected gene Aberrative in Neuroblastoma (DAN) domain family [5], and functions as an antagonist to the Wnt signaling pathway. Canonical Wnt signaling is initiated by Wnt proteins binding to the Frizzled transmembrane receptor and the LRP co-receptor on target cells. Receptor activation causes disruption of the GSK-3β/β-catenin destruction complex, resulting in β-catenin accumulation and nuclear transport where it interacts with transcription factors to stimulate expression of Wnt target genes [9, 10]. Consistent with the high bone mass (HBM) phenotype evident with decreased or ablated *SOST* expression [4, 7, 5], activating or inactivating mutations to LRP5 result in HBM [11, 12] or low bone mass [13], respectively, in humans and mice. The human bone phenotypes associated with mutations to the Wnt signaling pathway have made this pathway an attractive target for the treatment of low bone mass [14].

In this review, we discuss the latest findings in the regulation of *SOST* expression, the molecular mechanism of sclerostin actions, and the physiological roles of sclerostin. In addition, we discuss the results of pre-clinical trials investigating sclerostin monoclonal antibodies as a therapy for low bone mass.

Regulation of *SOST* expression

During embryonic skeletal development, *Sost* is expressed in the osteogenic front of the calvarial bone and the periostea of the mandibulae and limb buds. *Sost* expression in these regions is consistent with the locations of the skeletal phenotypes of patients lacking sclerostin protein [15]. In adult animals, sclerostin is primarily expressed and secreted by osteocytes and other terminally differentiated cell types embedded within mineralized matrices (cementocytes, hypertrophic chondrocytes) [16, 17].

Expression of *SOST* has been noted in human kidney, lung, heart, and pancreas; however, sclerostin protein is not evident in these samples [18]. In 2003, Kusu, et al. reported that *Sost* expressing cells co-localized with matrix metalloproteinase (MMP)-9 expression in the developing skeleton, suggesting osteoclastic *Sost* expression [19]. We have shown that early osteoclast precursors express sclerostin, and this is rapidly down-regulated during differentiation [20]. More recently, our lab has found that osteoclasts derived from aged mouse bone marrow express and secrete sclerostin [21].

Expression of the *SOST* transcript is controlled by the *SOST* proximal promoter and the distal enhancer region, ECR5. Runx2 and osterix (OSX), two transcription factors essential

to osteoblast differentiation [22], bind to the proximal *SOST* promoter and contribute to *SOST* gene expression [23, 24]. Mutation of the Runx2 binding site in the proximal promoter results in an approximate 80% decrease in activation of a *SOST* promoter reporter [23]. OSX expression increases *SOST*-promoter activation, and OSX knockout mice exhibit a 47-fold down-regulation of *Sost* expression [24]. *Sost* expression in the developing skeleton closely parallels the expression of OSX [15]. Taken together, these data suggest that sclerostin may have a role in regulating osteoblast differentiation and bone formation downstream of Runx2 and OSX.

Recent publications show that the *SOST* proximal promoter is subject to epigenetic regulation. Delgado- Calle, et al., found that a CpG-rich region spanning −471 to −227 base pairs of the *SOST* proximal promoter showed differential methylation between osteoblasts and osteocytes. While this region was hypermethylated in osteoblasts, the region was hypomethylated in osteocytes. *In vitro* methylation of the *SOST* proximal promoter led to a significant decrease in reporter activity [25]. The authors showed that this methylation affected protein binding to the *SOST* proximal promoter and treatment of osteoblasts with the de-methylating agent AzadC significantly increased *SOST* expression [25, 26]. Consistent with a role for methylation of this region in influencing transcription factor binding and *SOST* gene expression, Yang, et al., demonstrated that a region between −260 and −106 base pairs was critical for OSX-induced *SOST* promoter reporter activity *in vitro*. Mutation of the GC rich element in the proximal promoter significantly reduced OSX-induced activation of the *SOST* promoter reporter [24].

AzadC increased the responsiveness of the *SOST* promoter to bone morphogenetic protein (BMP)-2 [25, 26] and AzadC-stimulated *SOST* expression was decreased with canonical BMP signaling inhibition. This suggests that once the *SOST* promoter is de-methylated, factors within the microenvironment such as BMPs play an additional role in modulating *SOST* expression [26]. Knockout of osteoblast lineage BMP receptor BMPR1a during embryonic development led to a significant decrease in *Sost* expression and undetectable sclerostin protein in osteoblasts and osteocytes. Mouse embryos expressing constitutively active BMPR1a exhibited significant increases in *Sost* expression, confirming BMP influences on *Sost* expression [27]. Papanicolaou, et al., demonstrated that *Sost* expression in immature MLO-A5 osteocytes was increased by treatment with BMP-2, -4 or -6, consistent with data that the proximal promoter becomes hypomethylated as osteoblasts mature to osteocytes; however mature MLO-Y4 osteocyte *Sost* expression is not responsive to BMP treatment [28].

The distal enhancer region ECR5 is a 255-base pair sequence located within the 52-kb non-coding region deleted in VBD. Deletion of this enhancer region alone results in a significant decrease in *Sost*-positive osteocytes, highlighting the importance of ECR5 for robust *Sost* expression. These mice exhibit a HBM phenotype, consistent with the HBM phenotype found in VBD [29]. Interestingly, using ECR5 LacZ and GFP reporter mice, Collette, et al., showed that ECR5 is sufficient to drive osteoblast and osteocytespecific gene expression in neonatal mice independently of the *Sost* proximal promoter; however the proximal promoter was required for high expression of the reporter in adult osteocytes [29]. The ECR5 region contains a MEF2 response element which binds to the MEF2 transcription factors. Deletion

of this element significantly impairs ECR5 reporter activity *in vitro*. *Sost* expression was reduced in the UMR osteoblastic cell line by siRNA knockdown of MEF2A, C, and D, or by expression of dominant negative MEF2C [30]. Knockout of MEF2C in the osteoblast/osteocyte lineage abolished ECR5 reporter expression and resulted in a HBM phenotype similar to the ECR5 knockout mice, suggesting that MEF2C is the main transcription factor responsible for ECR5-dependent *Sost* expression [29].

The ECR5 region is essential for positive regulation of *SOST* expression by TGF-β. TGFβ-1, -2, and -3, and ActivinA increase *Sost* expression, whereas inhibition or knockdown of the TGFβ Type I receptors Alk4/5 decrease *Sost* expression in the UMR106.01 osteoblast cell line. TGFβ-1 stimulated reporter activity in UMR106 cells expressing the ECR5 promoter reporter alone or in combination with the *SOST* proximal promoter. In contrast, TGF-β failed to induce reporter activity in cells transfected with the human *SOST* proximal promoter reporter alone. Deletion of either the SMAD2/3 or MEF2 binding sites in the ECR5 region prevents TGF-β-induced ECR5 reporter activity, suggesting that TGF-β stimulates *SOST* expression through SMAD and MEF2 dependent mechanisms [31]. There are reports of SMAD proteins acting as co-modulators for MEF2 transcription factors, and this mechanism remains under investigation [31, 32].

Parathyroid hormone (PTH) suppresses *SOST* expression through the ECR5 enhancer region, independent of the *SOST* proximal promoter. The PTH-responsiveness of ECR5 region is mediated by the MEF2 response element [30]. PTH binds to the PTH receptor (PTHR)-1 leading to the activation of cAMP/PKA, PKC, and calcium pathways. Keller, et al., used pharmacological agents to activate the individual second messenger pathways downstream of PTHR-1. The data showed that suppression of *SOST* expression occurred following activation of the cAMP/PKA pathway, whereas activation of PKC or calcium signaling pathways led to little to no inhibition of *SOST* expression. These data led to the conclusion that PTH suppresses *SOST* expression through activation of the cAMP/PKA pathway [33]. PGE2 also suppresses *SOST* expression through cAMP production, but, in contrast to PTH, the suppression of *SOST* expression by PGE2 is independent of MEF2C or MEF2D [34]. PGE2-mediated suppression of *SOST* expression is dependent on de novo protein synthesis, whereas the PTH-mediated suppression of *SOST* expression is not [33], supporting diverse mechanisms by which the cAMP/PKA pathway regulates *SOST* expression.

Mechanism of Action

Sclerostin shares homology with the DAN family, which includes Wise, CCN, Dan, VWF, Norrin, Mucin, and Slits [35]. The crystal structure of sclerostin was reported by Veverka, et al. In contrast to other cysteine-knot containing proteins, the N- and C-terminal arms of sclerostin are unstructured and flexible, and sclerostin does not appear to multimerize [36]. Because several DAN family members bind to BMP ligands, it was initially speculated that the effects of sclerostin on bone were due to inhibition of the BMP pathway [35]. Several early reports suggested that this speculation was correct. Sclerostin coprecipitated with BMP-5 and -6 *in vitro* and competed with the BMP type I and II receptors for BMP binding. Additionally, sclerostin protein impaired BMP-6 induced SMAD phosphorylation in

mesenchymal C3H10T1/2 cells [37]. A separate group found that sclerostin bound to BMP-6 and -7, inhibiting induction of ALP activity in MC3T3 osteoblastic cells [19].However, in contrast to these data, van Bezooijen, et al., found that sclerostin was unable to block BMP-4 induced SMAD phosphorylation in murine pre-osteoblastic KS483 cells and failed to inhibit BMP/SMAD-dependent promoter reporter activity. Unlike classic BMP antagonists, the effect of sclerostin to inhibit BMP bioactivity was dependent on the assay used. BMP-stimulated alkaline phosphatase (ALP) activity was not inhibited in C2C12 cells, and sclerostin did not affect BMP-induced morphological changes in fetal mouse metatarsals. Sclerostin not only antagonized ALP when added with BMP-6, but also when added 24 hours after BMP-6 addition, suggesting that sclerostin may antagonize a BMP-induced factor [16]. Further evidence that sclerostin does not act as a BMP antagonist came from genetic studies. Deletion of the BMP inhibitor Gremlin (Grem)-1 leads to defects in limb development. If sclerostin also acted as an antagonist to BMP signaling, it would be thought that transgenic (Tg) *SOST* could rescue the phenotype of Grem-1 knockout mice. Tg *SOST* exacerbated the phenotype of the Grem-1 knockout, suggesting that Grem-1 and sclerostin are not acting in the same molecular pathway [38].

In addition to the inhibition of BMP signaling, there is evidence that certain DAN family members alter Wnt signaling. Wise, which shares 38% amino acid identity with sclerostin, acts as an extracellular inhibitor of Wnt8 in a context dependent manner [39]. Collette, et al., provided genetic evidence that sclerostin acts as an inhibitor of the Wnt signaling pathway. Using a BatGal Wnt signaling reporter mouse, the authors showed that ectodermal expressed *SOST* suppressed Wnt signaling ventrally and dorsally in E10.5 Wnt reporter mouse embryos. In a model of limb development, Lrp6 knockout forelimbs have severe limb defects, which are partially rescued by *SOST* deletion. Tg *SOST* in combination with heterozygous deletion of Lrp6 recapitulated the phenotype of homozygous Lrp6 deletion, providing further evidence that *SOST* and Lrp6 are components of the same pathway [38].

It is now known that sclerostin inhibits Wnt signaling by binding to the transmembrane Wnt co-receptors LRP5 and 6 [40]. Leupin, et al., used an unbiased tandem affinity purification proteomics approach to identify sclerostin interaction partners. In this study, the authors identified interactions of sclerostin with LRP5 and 6, as well as LRP4 [41]. LRP5 and 6 are six bladed β-propeller containing proteins that act as co-receptors for Wnt proteins with members of the Frizzled receptor family [42]. Sclerostin binds to the first β-propeller domain, E1, of LRP5 and 6 [43]. Sclerostin binding to LRP6 is prevented by an anti-sclerostin antibody [35]. The gain of function mutations to LRP5 and 6 that cause HBM in humans disrupt the binding of sclerostin to the LRP extracellular domain [35, 44], making these proteins resistant to sclerostin-mediated inhibition of Wnt signaling [35]. Consistent with the data that sclerostin does not inhibit BMP signaling, Leupin, et al. found no interaction of sclerostin with BMP proteins under any testing condition [41].

Holdsworth, et al., reported the crystal structure of the N-terminal region of LRP5, and revealed that sclerostin binding was mediated by the central core, loop 2 region of sclerostin, and did not involve the N- or C-terminal flexible arm regions. Further, the authors demonstrated the importance of the NXI motif within loop 2 of sclerostin for interacting with LRP5 and 6, but not with LRP4 [42]. The NXI motif, in which “X” is Ala, Ser, or Trp,

is found in several Wnt signaling inhibitors that bind to LRP5 and 6, including the DKK proteins and Wise [43]. Wnt1, but not Wnt3a or Wnt9b, binding to LRP5 could be blocked through a peptide derived from the loop2 region of sclerostin, suggesting different binding mechanisms for Wnts to LRP5 and 6. Despite not impairing Wnt9b binding, the loop2 peptide of sclerostin impaired Wnt9b induced Wnt signaling [42].

LRP4 interacts with sclerostin directly, and facilitates the inhibitory effects of sclerostin on Wnt1/βcatenin signaling. Silencing of LRP4 prevents sclerostin-mediated inhibition of *in vitro* osteoblast mineralization. Similarly to mutation of other components of the Wnt signaling pathway, mutation of LRP4 in humans leads to skeletal phenotypes. The LRP4 mutations, R1170W and W1186S, located on the E3 propeller domain disrupt sclerostin binding, and lead to a bone overgrowth, sclerosteosis-like phenotype [41].

Physiological functions

The skeletal phenotypes of sclerosteosis and VBD patients, as well as stimulation of *SOST* expression by transcription factors essential for osteoblast differentiation, suggest that sclerostin has a role in regulating bone formation [23]. Exogenous sclerostin inhibits the differentiation of osteoblastic cultures as assessed by alkaline phosphatase activity and mineralization [16, 37, 45]. Sclerostin has also been shown to induce osteoblast apoptosis [45]. Because sclerostin is thought to be specifically expressed by osteocytes, sclerostin is viewed as a negative feedback signal to counter further bone formation.

Regulation of *SOST* expression in osteocytes is a mechanism by which these cells respond to mechanical load. Mechanical load improves bone mass and strength by stimulating bone formation on surfaces undergoing high strain. Both the *SOST* transcript and sclerostin protein are reduced by mechanical loading, with greater mechanical strain stimulus being associated with a larger reduction in *SOST* expression [46]. Trangenic expression of *SOST* significantly reduced loading-induced bone formation [47]. Mechanical unloading leads to decreased bone formation and bone loss. Lin, et al., showed that unloaded femurs have elevated *SOST* expression compared to loaded femurs, and *SOST* knockout mice were resistant to mechanical unloading-induced bone loss [48]. Effects of mechanical signals on *SOST* expression has also been reported *in vitro* [28, 49]. A recent study suggests that mechano-regulation of *Sost* expression occurs through TGF-β signaling in osteocytes. Loss of sensitivity to TGF-β with dominant-negative TGFβRII prevented the anabolic effect of mechanical load and prevented mechano-regulation of *SOST* [50], supporting TGF-β mediation of mechanical load influences on osteocyte *SOST* expression.

It is well known that advancing age correlates with impaired bone formation [51]. Modder, et al. reported that serum sclerostin levels increased significantly with age in men and women. While sclerostin levels positively correlated with total body bone mineral content (TBBMC) in elderly subjects, the authors noted that this is likely due to a higher number of osteocytes present. Importantly, for any particular TBBMC, serum sclerostin was higher in elderly subjects compared to young subjects. These observations lead to the speculation that higher sclerostin levels contribute to impaired bone formation with age [52]. As mentioned earlier in this review, our lab has demonstrated that osteoclasts derived from aged-mouse

bone marrow express and secrete sclerostin, leading to decreased osteoclast-stimulated osteoblast mineralization. This mechanism may contribute to the decreased bone mass that is exhibited with age and warrants further investigation [21].

In addition to actions on osteoblasts, several studies have found roles for sclerostin in modulating osteocyte activities. Wijenayaka, et al., demonstrated that sclerostin increased RANKL expression by osteocytes, leading to an increased RANKL:OPG ratio. The increased RANKL:OPG ratio resulted in increased size and number of osteoclasts, as well as increased osteoclast resorption as demonstrated in co-culture of osteoclasts with osteocytes treated with sclerostin. This effect was prevented by the addition of OPG. The authors concluded that sclerostin may not only be anti-anabolic through its effects on osteoblasts, but may also have a catabolic effect through the promotion of osteoclast activity by osteocytes derived RANKL [53]. Additionally, sclerostin induces the expression of cathepsin K, TRAP, and carbonic anhydrase-2 in osteocytes, suggesting that sclerostin may have a role in osteocytic osteolysis of the extracellular matrix surrounding osteocytes to release mineral from bone [54].

The Wnt/β-catenin signaling pathway is functional in osteoclasts isolated from myeloma patients, as evidenced by the accumulation of Dishevelled-3 and β-catenin with Wnt3a treatment. However, disrupting Wnt signaling did not alter the differentiation, proliferation, or survival of osteoclasts [55]. In contrast to these data, our lab has found that osteoclasts express Lrp5 and 6, and osteoclast-specific deletion of Lrp5 and 6 or β-catenin in mice led to decreased bone volume and decreased trabecular bone. This data has been reported in a recent ASBMR abstract [56], and is substantiated by recent publications demonstrating that knockout of β-catenin in the early osteoclast lineage leads to decreased bone mass with increased osteoclast number and resorption activity *in vivo* [57–59]. Therefore, a potential role for sclerostin on osteoclasts should be investigated.

Intermittent PTH increases bone formation and is currently the only anabolic therapy approved for the treatment of osteoporosis. As discussed earlier, PTH decreases expression of *SOST* by osteocytes. Transgenic mice overexpressing *Sost* have a low bone mass phenotype with decreased bone strength, resulting from significantly decreased osteoblast activity and bone formation [37, 60]. Conversely, knockout of *Sost* leads to a progressive HBM phenotype. PTH induced bone formation is blunted in Tg *Sost* mice as well as *Sost* knockout mice, suggesting that PTH-induced bone formation is in part dependent on modulation of *Sost* expression [60].

Sclerostin is postulated to have other influences in addition to regulating bone metabolism. In a study published by Cain, et al., bone marrow isolated from *Sost* KO mice had depleted B cells due to elevated apoptosis at B cell development stages. In contrast to bone marrow B cells populations, spleen B cell function was normal. Wild type bone marrow transplant into *Sost* KO animals resulted in reduced bone marrow B cells, whereas *SOST* KO bone marrow transplant to wild type animals did not. The authors demonstrated that the levels of the pre-B cell growth stimulating factor CXCL12 is decreased in the *Sost* KO bone marrow. Expression of Wnt target genes were unchanged in the *SOST* KO B cells, suggesting that

Sost regulates the bone marrow environment that supports B cell development, perhaps through chemokine modulation [61].

Another area of research in which a role for sclerostin is being investigated is vascular calcification. A study by Claes, et al., found that chronic kidney disease patients with vascular calcifications exhibited higher serum sclerostin levels in univariate analyses. In a separate study, Bradenburg, et al. showed that hemodialysis patients with coronary artery and aortic valve calcifications had increased serum sclerostin. Of interest, the sclerostin was found to be produced locally to the calcification sites [62]. However, multivariate analyses by Claes, et al. revealed that higher serum sclerostin levels were associated with lower risk for vascular calcification, suggesting that sclerostin may be protective against vascular calcification [63]. The progression of aortic calcification is associated with increased risk of all-cause and cardiovascular mortality [64]. Therefore, while the role for sclerostin remains unclear, further investigation is warranted to determine the therapeutic potential of Wnt pathway modulators on vascular calcification [62].

The role of sclerostin in negatively regulating bone formation makes it an attractive target in the treatment of diseases of low bone mass. Carriers of the mutations associated with sclerosteosis and VBD exhibit lower serum sclerostin levels, with no disease characteristics; the carriers importantly exhibit increased BMD, protecting patients from fracture. The lack of phenotypes of sclerosteosis and VBD patients outside of the skeleton suggest that targeting sclerostin would lead to minimal off-target effects [8, 65].

In a rat model of ovariectomy-induced bone loss, five week-administration of sclerostin monoclonal antibody (Scl-AbII) not only prevented the bone loss induced by estrogen deficiency, but further increased bone mass and strength as compared to the non-ovariectomized controls [66]. A separate study using a humanized sclerostin-neutralizing monoclonal antibody (Scl-AbIV) on female cynomolgus monkeys found that two once-monthly treatments dose-dependently increased bone formation on trabecular, periosteal, endocortical, and intracortical surfaces. The treatment resulted in increased bone mineral content and bone mineral density (BMD) at several skeletal sites, as well as increased trabecular thickness and bone strength at the lumbar vertebrae in the highest dose group [67]. In a study investigating the use of sclerostin antibody to prevent immobilization/disuse bone loss in rats, under-loaded rats treated with sclerostin monoclonal antibody (Scl-Ab) significantly increased trabecular bone volume and thickness, mineralized surface, and bone formation, while decreasing eroded surface compared to under-loaded control animals [68]. These animal studies demonstrate the antibody-mediated blockade of sclerostin represents a promising approach for treatment of conditions of low bone mass, such as osteoporosis.

To date, two human studies have been published testing sclerostin monoclonal antibody treatments. The first-in-human study published by Padhi, et al., involved the administration of sclerostin monoclonal antibody AMG 785 (romosozumab) or placebo to 72 healthy subjects. AMG 785 was generally well tolerated and led to dose related increases in bone formation markers procollagen type 1 N-propeptide (P1NP), bone-specific ALP, and osteocalcin, with decreased bone resorption marker C-telopeptide (CTx).

The patients also exhibited significant increases in BMD at the lumbar spine and total hip compared with placebos on day 85 [69]. In the second, recently published report, the sclerostin monoclonal antibody blosozumab or placebo was administered to postmenopausal women. Similarly to the study by Padhi, et al., McColm, et al., reported dose-dependent increases in P1NP, bone-specific ALP, and osteocalcin, and decreased CTx. The lumbar spine BMD was significantly increased following administration of sclerostin monoclonal antibody [70]. These studies support further investigation into sclerostin monoclonal antibodies as anabolic treatments for conditions of low bone mass.

Conclusion

Many advances have been made in the study of sclerostin biology since the initial observation that mutations to *SOST* are responsible for the disease phenotypes of sclerosteosis and VBD. In a little over a decade since this observation, sclerostin has profoundly impacted the bone field and potentially provides a new osteoporosis therapy target. It is clear that regulation of *SOST* expression is a mechanism by which osteocytes respond to paracrine and endocrine signals to regulate bone formation and, potentially, bone resorption. Sclerostin inhibits Wnt signaling through interactions with the Wnt co-receptors LRP4, 5, and 6. Carriers of the sclerosteosis and VBD *SOST* mutations exhibit decreased serum sclerostin and increased BMD without disease symptoms, suggesting that targeting sclerostin would be a safe and effective way to treat conditions of low bone mass. While studies are ongoing, the pre-clinical animal and human trials testing sclerostin monoclonal antibodies have so far yielded promising results, increasing serum markers of bone formation, decreasing markers of resorption, and increasing BMD at several sites.

Acknowledgments

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