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INIVITED REVIEW

Regulatory mechanisms of sclerostin expression during bone remodeling

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Abstract

Osteocytes are embedded in bone matrices and are connected to each other to respond to mechanical loading on bone. Recent studies have demonstrated the roles of mechanical loading in bone accrual. Bone responds to mechanical loading by decreasing the expression of sclerostin, an inhibitor of Wnt/β-catenin signals, in osteocytes. This increases bone mass because the activation of Wnt/β-catenin signals in bone microenvironments promotes bone formation and suppresses bone resorption. Thus, in recent years, sclerostin have attracted increasing attention in bone metabolism. However, the regulatory mechanism of sclerostin expression during bone remodeling has not been fully elucidated. In this review, we summarized the regulation of bone formation and resorption by Wnt signals, a Wnt/β-catenin signal inhibitor sclerostin, and molecular mechanisms by which the expression of sclerostin is suppressed by mechanical loading and parathyroid hormone. We also discuss a possibility that osteoclasts suppress the expression of sclerostin during bone remodeling, which in turn, promote bone formation. The effectiveness of an anti-sclerostin antibody with anti-dickkopf-1 antibody for increasing bone mass was discussed.

Keywords Sclerostin · Bone remodeling · Osteocytes · Osteoblasts · Osteoclasts

Introduction

Bone is continuously remodeled throughout life to maintain plasma calcium homeostasis and prevent the accumulation of old bone. Osteoclasts resorb bone, and new bone is then formed by osteoblasts to replace the amount of bone resorbed. This is called bone remodeling, and bone mass is kept constant by balanced bone remodeling due to the coupling between bone resorption and formation [1, 2]. An imbalance between bone resorption and formation leads to either a low bone mass or a high bone mass [1].

Osteoclasts differentiate from osteoclast precursors, monocyte–macrophage lineage cells, by stimulation by receptor activator of NF-κB ligand (RANKL) and macrophage colony-stimulating factors (M-CSF) [3–5]. RANKL and M-CSF bind to receptor activator of NF-κB (RANK) and c-fms, respectively. Both receptors are expressed in osteoclast precursors. Osteoprotegerin (OPG), a decoy receptor of RANKL, is expressed by osteoblasts and osteocytes. OPG interferes with the interaction between RANKL and RANK, which in turn, inhibits osteoclast differentiation [6, 7].

OPG-knockout (KO) mice exhibited increased bone resorption due to excess osteoclast differentiation and activity [8, 9]. In addition, the activity of bone formation markers, such as serum alkaline phosphatase, and bone formation parameters were also increased [8, 10], suggesting that bone formation was also enhanced in OPG-KO mice even though bone mass was decreased. When these mice were treated with the anti-bone-resorbing drug bisphosphonate, bone formation was markedly suppressed in association with the suppression of bone resorption [10]. These results demonstrated that bone resorption is linked to bone formation by factors facilitating the transition from bone resorption to formation, the so-called coupling factors.

Several factors have been found to act as coupling factors between bone resorption and formation [1, 2]. Transforming growth factor beta (TGF-β) and insulin-like growth factor I (IGF-I) are embedded in bone matrices during bone formation [11, 12]. These cytokines are released from bone

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matrices during bone resorption and they then induce the migration of osteoblast precursors to bone resorption sites. Osteoclast-derived factors, such as cardiotrophin-1 (CT-1), Wnt10b, sphingosine-1-phosphate, BMP-6, collagen triple-helix repeat-containing 1, and platelet-derived growth factor (PDGF)-BB, were reported to directly act on osteoblast lineage cells, and promote the differentiation of osteoblasts and bone formation [13–17]. EphrinB2, expressed by osteoclasts, also promotes the differentiation of osteoblasts through EphB4 receptors [18].

Osteocytes reportedly produce several Wnt ligands including Wnt1 [19] and Wnt/β-catenin signal inhibitor sclerostin [20]. The loss-of-function mutations of the *SOST* gene (encoding sclerostin) cause osteosclerosis with abnormal high bone mass, suggesting that bone formation is usually suppressed by sclerostin through the inhibition of Wnt/β-catenin signals to achieve normal bone development. However, it is not fully examined whether osteoclast-derived factors also act on osteocytes to inhibit the expression of sclerostin, which in turn, promote bone formation.

In this review, we introduced roles of Wnt signals in bone formation and regulatory mechanism of sclerostin expression by PTH. We would like to propose a possibility that osteoclasts suppress the expression of sclerostin during bone remodeling, which in turn, promote bone formation [21]. In addition, we discussed the effects of anti-Dkk-1 and anti-sclerostin antibodies on bone accrual.

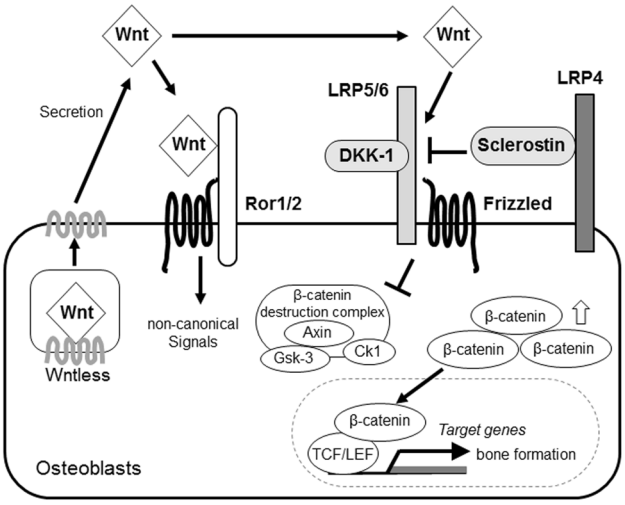

Fig. 1 Wnt signals. Wnt ligands activate β-catenin-dependent canonical and -independent non-canonical signals. Wntless, an 8-pass transmembrane protein, is necessary for Wnt secretion. Wntless-deficient cells failed to secrete all Wnt ligands. Wnt ligands bind to the receptor complex of frizzled and LRP5/6, and inhibit the activity of β-catenin destruction complexes. This leads to cytosolic accumulation and nuclear translocation of β-catenin. Nuclear β-catenin together with TCF/LEF induces the transcription of the target genes. Sclerostin and Dkk-1 bind to LRP5/6, and inhibit Wnt/β-catenin signals. Binding of sclerostin to LRP4 is required for the inhibitory action of sclerostin. Wnt ligands such as Wnt5a binds receptor complex of frizzled and Ror1/2, which in turn activates β-catenin-independent non-canonical signals

Regulation of bone formation by Wnt/β-catenin signals

Wnt ligands activate β-catenin-dependent canonical and -independent non-canonical signaling pathways [22] (Fig. 1). Canonical and non-canonical Wnt signals regulate bone formation and resorption [23]. At present, 19 Wnt ligands have been identified in humans and mice [22]. Wnt ligands, such as Wnt1, Wnt5a, Wnt7b, and Wnt10b, reportedly regulate bone formation [19, 24–27].

Analysis of mice having gain-of-function and loss-of-function mutations of β-catenin in mature osteoblasts revealed that Wnt/β-catenin signals markedly increase bone mass due to the decreased bone resorption without affecting bone formation [28]. This study has shown that activation of Wnt/β-catenin signals in mature osteoblasts promotes OPG expression, thereby inhibiting osteoclastogenesis. Ten years later, mice expressing dominant active form of β-catenin in osteocytes (DA-β-catenin Ocy mice) reportedly exhibited high bone mass associated with increased bone resorption and formation [29]. Similar to mice expressing constitutively active form of β-catenin in mature osteoblasts [28], the expression of OPG was increased in those mice. The expression of RANKL was also increased in DA-β-catenin Ocy mice, thereby increasing bone resorption. These findings suggest that osteocytes as well as osteoblasts play a critical role in bone anabolic action of Wnt/β-catenin signals although the mechanism by which the expression of RANKL was increased in DA-β-catenin Ocy mice remains to be elucidated.

Non-canonical Wnt signals impact bone resorption. Non-canonical Wnt5a binds to its receptor Ror2 in osteoclast precursors and promotes the expression of RANK, which in turn increased RANKL-induced osteoclast formation [24]. Wnt5a-Ror2 signals also promote bone-resorbing activity of osteoclasts through small GTPase Rho-Pkn3-c-Src signaling axis [30]. In contrast to Wnt5a, Wnt16 reportedly activated canonical Wnt signals in osteoblastic cells and non-canonical signals in osteoclast precursors [31]. Wnt16-deficient mice exhibited low cortical but not trabecular bone mass [31]. Osteoblastogenesis is normal in those Wnt16-deficient calvaria-derived osteoblasts in cultures. Treatment of osteoblastic MC3T3-E1 cells with Wnt16 increased the expression of OPG through the Wnt/β-catenin signals. Furthermore, Wnt16 inhibited RANKL-induced osteoclast formation by suppression of NF-κB and NFATc1 signals [31]. These results suggest that Wnt16 inhibits RANK signals in osteoclast precursors

and induces the expression of OPG in osteoblasts, which in turn, inhibits osteoclast formation.

Wntless (Wls), an 8-pass transmembrane protein, is required for the secretion of Wnt ligands [32, 33] (Fig. 1). Therefore, Wnt ligands cannot be secreted from Wls-deficient cells. Both canonical and non-canonical Wnt signals are inactivated in those cells. As several kinds of Wnt ligands are secreted from osteoblasts, Wls-deficient osteoblasts are useful to analyze the roles of osteoblast-derived Wnt ligands in bone formation. Osteoblast-specific Wls-conditional knockout (cKO) mice exhibit a marked decrease in trabecular bone and cortical bone [34]. Histomorphometric analysis revealed a significant reduction of the bone formation rate in Wls-cKO mice [34]. Furthermore, the expression of osteoblast marker genes, such as Runx2 and Osterix, as well as the Wnt target gene Axin2 was significantly decreased in Wls-deficient osteoblasts [34]. Mineralization was also decreased in these cells. These findings suggested that Wnt ligands secreted from osteoblast lineage cells are important for osteoblast differentiation and bone formation.

Low-density lipoprotein receptor-related protein (LRP) 5/6 functions as a co-receptor for Wnt/β-catenin signals. Analysis of loss-of-function and gain-of-function mutations in the Lrp5 gene demonstrated that Wnt/β-catenin signals promote osteoblast differentiation and increase bone mass [35]. Furthermore, Osterix failed to be expressed by β-catenin-deficient perichondrial cells or periosteal cells [36, 37]. Thus, Wnt/β-catenin signals are necessary for osteoblast differentiation and bone formation.

Roles of Wnt inhibitors in bone formation

The SOST gene is a responsible gene for osteosclerosis and van Buchem disease. A loss-of-function mutation in the SOST gene causes sclerosteosis with an abnormal increase in bone mass [38, 39]. A homozygous 52-kb non-coding deletion (ECR5 region) of the SOST gene causes Van Buchem disease, which presents the same clinical features as sclerosteosis [40]. The ECR5 region in the SOST gene is a bone-specific enhancer of sclerostin expression in osteocytes [41]. Sclerostin, a glycoprotein secreted from osteocytes, binds to the first two YWTD-EGF repeat domains of LRP5/6 and inhibits Wnt/β-catenin signals [42]. Similar to sclerosteosis, Sost-KO mice exhibited high bone mass with a marked increase in bone formation [43]. Bone resorption parameters such as serum TRAP5b and the number of osteoclasts remained unchanged, indicating that the deficiency of sclerostin does not affect osteoclast formation. This finding suggests that sclerostin is not strongly involved in osteoclast formation during developmental process. Furthermore, administration of anti-sclerostin neutralizing antibody reportedly promoted bone formation and increased bone mass [44, 45]. These findings suggest that sclerostin inhibits Wnt/β-catenin signals and suppresses bone formation (Fig. 1).

LRP4 is reportedly required for the inhibitory action of sclerostin (46). Two mutations in the *LRP4* gene (R1170W and W1186S) have been found in patients with sclerosteosis [46]. Sclerostin failed to bind these *LRP4* mutants and inhibit Wnt/β-catenin signals in cells expressing these mutants. These findings indicated that LRP4 bound to sclerostin to facilitate the inhibitory action of sclerostin. Osteoblast-specific *Lrp4* cKO mice ($Lrp4^{flox/flox}$; osteocalcin-cre mice) exhibited a high bone mass with increased bone formation [47, 48]. These findings strongly indicate that LRP4 facilitates the inhibitory action of sclerostin in vivo.

Dickkopf-1 (Dkk-1) is also an inhibitor of Wnt/β-catenin signals. Dkk-1 binds to LRP5/6 receptors and a transmembrane protein kremen, and the complex of Dkk-1, kremen, and Lrp5/6 internalizes from cell surfaces, thereby inhibiting Wnt/β-catenin signals [49]. Dkk-1 is highly expressed in bone tissue. Mice having heterozygous deletion of the Dkk-1 gene exhibited increased bone mass [50], whereas Dkk-1 transgenic mice exhibited decreased bone mass [51]. Bone resorption markers such as urine deoxypyridinoline and the number of osteoclasts remained unchanged in those mice, suggesting that Dkk-1 is not strongly involved in osteoclast formation during developmental process [50]. Furthermore, administration of an anti-Dkk-1 neutralizing antibody reportedly increased bone mass by promoting bone formation [52]. These findings demonstrate that Wnt/β-catenin signals in bone are tightly regulated by Dkk-1 and bone-specific sclerostin.

Effects of mechanical loading on the sclerostin expression

Osteocytes sense changes in bone fluid flow caused by mechanical loading, and are involved in the increase and maintenance of bone mass [53]. Loading in upper limbs reduced the expression of sclerostin and Dkk-1 in ulna-loading model mice [54]. In contrast, unloading increased the expression of sclerostin in the lower limbs of tail-suspended mice and then decreased bone formation [55]. Bone formation failed to decrease in the unloaded lower limbs of Sost-KO mice [55]. Furthermore, transgenic mice expressing human sclerostin in osteocytes exhibited the suppression of mechanical loading-induced bone formation [56]. These findings revealed that mechanical loading suppresses the expression of sclerostin in osteocytes, which in turn, promotes bone formation.

Periostin is a secreted extracellular matrix protein expressed in the periosteum and periodontal ligaments [57]. Periostin (encoded by the Postn gene)-KO mice developed

osteoporosis and periodontitis [58]. Mechanical loading also reportedly induced the expression of periostin and suppressed sclerostin expression [59]. Bonnet et al. [59, 60] analyzed the expression of sclerostin in osteocytes and the bone mass of cortical bone in Postn-KO mice treated with PTH or mechanical loading. In Postn-KO mice, administration of PTH or mechanical loading failed to decrease the expression of sclerostin, and the bone mass in cortical bone was not increased. In contrast, administration of an anti-sclerostin neutralizing antibody increased the bone mass in cortical bone of Postn-KO mice. Therefore, administration of PTH or mechanical loading increased the expression of periostin in the periosteum, and the increased periostin reduced the expression of sclerostin, which in turn, promoted bone formation in cortical bone (Fig. 2). These results suggest a new function of periostin as a suppressor of sclerostin expression. The mechanisms by which periostin suppresses the expression of sclerostin need to be clarified in the future.

Regulatory mechanism of sclerostin expression by PTH and IL-6 family cytokines

As described above, the down-regulation of sclerostin expression is considered to be an important step for bone accrual. Because the effect of PTH on the expression of sclerostin is well-studied, here we would like to introduce the inhibitory action of PTH in sclerostin expression. Intermittent administration of PTH increases bone mass [61, 62]. As PTH markedly suppresses the expression of sclerostin in osteocytes, the role of PTH in bone accrual is considered to be mediated, in part, by the inhibition of sclerostin expression [63, 64]. The 52-kb region (ECR5) containing the enhancer downstream of the Sost gene is important for bone-specific sclerostin expression [40] (Fig. 3). Myocyte enhancer factor (MEF) 2, a transcription factor, binds to the ECR5 region and induces the expression of sclerostin [65]. Stimulation of PTH in osteocytes reduced the recruitment

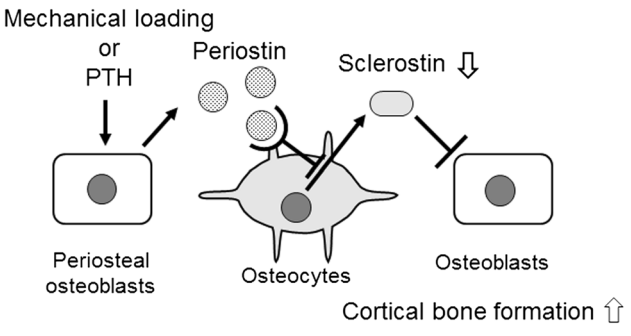

Fig. 2 Roles of periostin in the suppression of sclerostin expression. Periostin secreted from periosteal osteoblasts acts on osteocytes and inhibits the expression of sclerostin

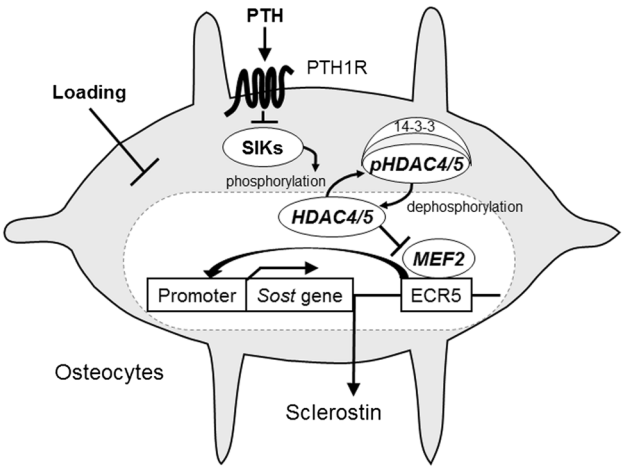

Fig. 3 PTH signals suppress the expression of sclerostin. MEF2 binds the ECR5 (enhancer region) of the Sost gene to induce the expression of sclerostin. Salt-induced kinases (SIKs) phosphorylate HDAC4/5 to promote complex formation of HDAC4/5 and 14-3-3, which in turn retains HDAC4/5 in the cytoplasm. PTH signals inhibit the kinase activity of SIKs, which in turn increases dephosphorylated HDAC in nucleus. Nuclear dephosphorylated HDAC inhibits the activity of MEF2

of MEF2 to the ECR5 region and decreased the expression of sclerostin [65].

The detailed roles of MEF2 in the expression of sclerostin have been proposed. Histone deacetylase (HDAC) 5 binds to MEF2 and suppresses the expression of sclerostin [66] (Fig. 3). The expression of sclerostin was enhanced in HDAC5-KO mice, which exhibited decreased bone formation [66], suggesting that HDAC5 suppresses the expression of sclerostin. Knockdown of HDAC5 enhanced the transcriptional activity of MEF2 and the expression of sclerostin. Taken together, the association of HDAC5 with MEF2 in osteocytes reduced the transcription activity of MEF2, and subsequently the expression of sclerostin. Recently, a further detailed mechanism was reported. Salt-inducible kinases (SIKs), which are a kinase for HDAC4/5 and cAMP-regulated transcriptional coactivators (CRTC) [67], were found to phosphorylate HDAC5 to promote the complex formation of HDAC5 with 14-3-3 proteins. 14-3-3 proteins are intracellular dimeric proteins involved in various biological events such as signal transductions. 14-3-3 retained HDAC5 in the cytoplasm [68, 69]. Stimulation of PTH suppressed the activity of SIKs and increased dephosphorylated HDAC4/5, which localizes to the nucleus. The nuclear HDAC4/5 forms a complex with MEF2 and inhibits the transcriptional activity of MEF2, which in turn, suppresses the expression of sclerostin [69] (Fig. 3). Furthermore, SIK inhibitors have been reported to promote bone formation. Of note, the suppression of SIK activity was demonstrated to increase the expression of RANKL via nuclear translocation of dephosphorylated CRTC 2 [69].

This suggests that SIK is also involved in osteoclastogenesis when osteoblast linage cells are stimulated by PTH. In the future, clarification as to whether SIKs and HDAC4/5 are involved in the mechanical loading-induced suppression of sclerostin expression is needed.

Roles of PTH1 receptor (PTH1R) in osteocytes in the expression of sclerostin have been examined using dentin matrix protein (DMP)-1-Cre: PTH1R conditional knockout mice. Powell et al. [70] prepared tamoxifen-inducible PTH1R cKO mice using DMP-1-CreERT2 mice. These PTH1R cKO mice exhibited low bone mass with the increased expression of sclerostin mRNA. The expression of Wnt target gene axin was decreased in bone tissues from those mice. These results suggest that PTH1R signals suppress the expression of sclerostin, which in turn, promotes bone accrual under physiological condition. In contrast to tamoxifen-inducible PTH1R cKO mice [70], PTH1R cKO mice using non-inducible DMP-1 Cre exhibited high bone mass with a modest decrease in bone resorption. These results suggest that PTH1R signal in osteocytes may not be involved in the suppression of sclerostin expression by PTH [71]. However, the expression of Wnt target genes such as Naked2 and Conexin 43 were decreased in those mice, suggesting that Wnt/β-catenin signals suppressed probably due to the increase in the expression of sclerostin. Furthermore, the anabolic action and the suppression of sclerostin expression by intermittent injections of PTH disappeared in those cKO mice [71], suggesting that PTH1R signals play an important role in anabolic action of PTH by the suppression of sclerostin expression. Those cKO mice exhibited the decreased expression of RANKL and the decrease in bone resorption marker serum CTX. These findings suggest that bone mass is increased due to the suppression of bone resorption in those cKO mice. The increased bone mass in those cKO mice might be due to cre recombinase activity during developmental process. Further studies are needed to clarify this point.

Recently, we found that osteoclast-derived leukemia inhibitory factor (LIF) suppresses the expression of sclerostin in UMR106 cells [21]. Therefore, we introduce effects of IL-6 family cytokines such as LIF, oncostatin M, and CT-1 on the expression of sclerostin. These IL-6 family members reportedly suppress the expression of sclerostin in cultured UMR106 cells [72]. Oncostatin M was reported to be abundantly expressed in osteoblasts [72]. Furthermore, administration of recombinant oncostatin M decreased the expression of sclerostin in wild-type mice [72]. IL-6 family cytokines such as IL-6 and oncostatin M reportedly induced the expression of RANKL to promote osteoclast formation in co-cultures of bone marrow cells with osteoblastic cells [5]. The treatment with oncostatin M also increased the expression of RANKL in osteoblastic cell line KUSA 4b10 cells [72]. These results indicate that osteoblast-derived oncostatin M suppresses the expression of sclerostin and increases that of RANKL to induce osteoclast formation during bone remodeling. They also suggest that osteoclast-derived CT-1 also suppresses the expression of sclerostin. However, it is unknown how CT-1 regulates the expression of sclerostin in vivo.

Roles of sclerostin in bone remodeling

During bone remodeling, several coupling factors are considered to link bone resorption with formation because bone resorption promotes bone formation [1, 2]. Excellent review articles describe roles of osteocytes in bone remodeling [73–75]. Osteocytes response to mechanical loading and PTH, and then decrease the expression of sclerostin, thereby promoting bone formation. Osteocytes also produce RANKL to induce bone resorption. Thus, osteocytes regulate bone remodeling.

As mentioned above, OPG-KO mice exhibited high bone turnover with increased bone resorption and formation. The expression of sclerostin was reportedly lower in OPG-KO mice [76]. However, the mechanisms have not been fully elucidated at the molecular level. We analyzed OPG-KO mice and found that osteoclasts promoted bone formation via the suppression of sclerostin expression in osteocytes [21]. Antibody array analysis and real-time PCR analysis demonstrated that mature osteoclasts abundantly expressed and secreted LIF [21]. LIF secreted from osteoclasts reduced the expression of sclerostin in osteocytes and cultured UMR106 cells [21]. Anti-LIF antibody, but not anti-oncostatin M antibody, neutralized the suppressive effects of osteoclast-conditioned medium on sclerostin expression in UMR106 cells [21], suggesting that osteoclast-conditioned medium contains enough LIF to suppress the expression of sclerostin. Furthermore, administration of the anti-RANKL antibody inhibited osteoclast differentiation and inhibited bone resorption in OPG-KO mice, and increased the expression of sclerostin by osteocytes [21]. Wnt/β-catenin signals in bone tissues were decreased in mice treated with the anti-RANKL antibody, which in turn, suppressed bone formation [21]. These results suggest that regulation of sclerostin expression by osteoclasts plays an important role in the coupling between bone resorption and formation (Fig. 4). A clinical study found that the administration of the anti-RANKL antibody reduced bone formation markers associated with the suppression of bone resorption markers [77, 78]. Moreover, administration of the anti-RANKL antibody increased the amount of sclerostin in serum [79, 80]. These clinical studies strongly suggested that bone resorption suppresses the expression of sclerostin, which in turn, promotes bone formation in humans. Thus, simultaneous administration of anti-sclerostin antibodies with RANKL antibodies

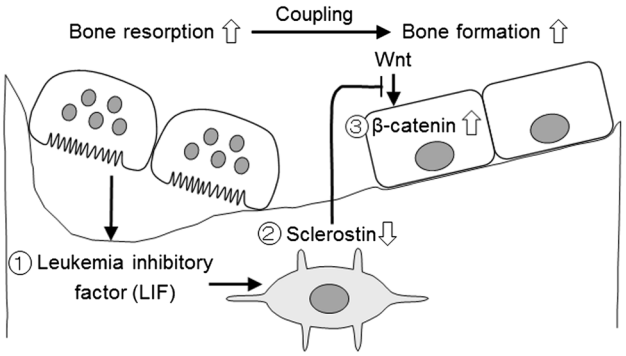

Fig. 4 LIF secreted from osteoclasts inhibits the expression of sclerostin in osteocytes. Osteocytes produce sclerostin, which inhibits Wnt/β-catenin signals in osteoblasts and suppresses excess bone formation. Osteoclasts secrete LIF (1) and inhibit the expression of sclerostin (2), which in turn, promotes bone formation through the activation of Wnt/β-catenin signals (3). Osteocytes are involved in the coupling between bone resorption and formation

maybe effective for keeping bone formation rate, because administration of anti-RANKL antibodies suppresses bone formation due to up-regulation of sclerostin expression. It is also important that the regulatory mechanisms of sclerostin expression by bone resorption be elucidated in more detail in the future.

Anti-sclerostin antibody and anti-DKK1 antibody

Recently, Witcher et al. [81] reported that conditional deletion of the Dkk-1 gene using DMP-1 Cre and treatment of wild-type mice with an anti-Dkk-1 antibody had negligible effects on bone accrual. Administration of the anti-Dkk-1 antibody increased the expression of sclerostin [81], suggesting that it is regulated by Wnt/β-catenin signals. This finding is consistent with the previous finding that genetic activation of β-catenin in osteocytes increases the expression of sclerostin in bone [82]. Thus, Wnt/β-catenin signals positively regulate the expression of sclerostin. Further studies are needed to clarify whether Wnt/β-catenin signals regulate the transcription activity of the *Sost* gene. Administration of the anti-Dkk-1 antibody to Sost-KO mice further enhanced bone formation even though Sost-KO mice exhibited high bone mass. The combined administration of anti-DKK-1 and anti- sclerostin antibodies markedly promoted bone formation. These results suggest that the increased expression of sclerostin by inhibition of Dkk-1 weakens the stimulatory effects of the anti-Dkk-1 antibody on bone formation. In addition, postnatal global deletion of the Dkk-1 gene reportedly caused high bone mass [83]. Of note, the expression of sclerostin was higher in these mice [83]. This also suggests that Wnt/β-catenin signals promote the expression of sclerostin. In contrast, treatment of ovariectomized rats with the anti-sclerostin antibody increased the expression of Dkk-1[83]. Administration of both anti-Dkk-1 and anti-sclerostin antibodies more markedly increased the bone volume than only Dkk-1 antibody or sclerostin antibody in fracture model rats [83]. In addition, administration of a bispecific antibody targeting sclerostin and Dkk-1 promoted fracture healing as compared with the anti-sclerostin antibody [84]. These results suggest that the inhibition of both sclerostin and Dkk-1 is useful for promoting bone formation compared with neutralizing either sclerostin or Dkk-1, and that the inhibition of sclerostin induces the expression of Dkk-1 because Dkk-1 is a target gene of Wnt/β-catenin signals.

Conclusion

In this review, we introduced the regulatory mechanism of sclerostin expression, roles of osteocytes in the coupling between bone resorption and formation, and the usefulness of sclerostin and Dkk-1 inhibition for bone accrual and fracture treatment. Osteoclasts secrete LIF and inhibit the expression of sclerostin, which in turn, promote bone formation through the activation of Wnt/β-catenin signals. Although recent studies established important roles of sclerostin in bone metabolism, several molecular mechanisms, such as the suppression of sclerostin expression by mechanical loading and LIF, remain to be elucidated. These issues will be solved in future studies, leading to the development of drugs for osteoporosis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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