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# The Effects of Sclerostin on the Immune System

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## Abstract

**Purpose of Review** We reviewed recent progress on the role of sclerostin (SOST) and its effects on the immune system in order to summarize the current state of knowledge in osteoimmunology, in regard to hematopoiesis, lymphopoiesis, and inflammation.

**Recent Findings** Changes in sclerostin levels affect distinct niches within the bone marrow that support hematopoietic stem cells and B cell development. Sclerostin's regulation of adipogenesis could also be important for immune cell maintenance with age. Surprisingly, B cell development in the bone marrow is influenced by *Sost* produced by mesenchymal stem cells and osteoblasts, but not by osteocytes. Additionally, extramedullary hematopoiesis in the spleen and increased pro-inflammatory cytokine levels in the bone marrow are observed in global *Sost*<sup>-/-</sup> mice.

**Summary** In addition to changes in bone marrow density, sclerostin depletion affects B lymphopoiesis and myelopoiesis, as well as other changes within the bone marrow cavity that could affect hematopoiesis. It is therefore important to monitor for hematopoietic changes in patients receiving sclerostin-depleting therapies.

**Keywords** Wnt · Wnt antagonists · Hematopoiesis · Immunology · Cell differentiation · Osteoimmunology

## Introduction

Sclerostin (SOST) is an important regulator of bone homeostasis and is secreted by several cell types, in particular osteocytes (mature mineralized bone cells (OCYs)). This expression inhibits the bone formation through blocking canonical Wnt signaling in osteoblasts (OBs) and preventing OB maturation into OCYs (1–4). In mice and humans, inhibition of SOST through gene-targeting or monoclonal antibodies results in enhanced Wnt signaling in OBs and increased bone mass (5, 6). A human monoclonal antibody against sclerostin, Romosozumab, was developed by Amgen and UCB Pharma to treat osteoporosis. This is relevant for hematopoietic development and maturation, as canonical Wnt signaling between adult hematopoietic stem and progenitor cells (HSPC) and OBs is as an important regulator of hematopoietic stem cell

(HSC) maintenance, self-renewal, and differentiation in the bone marrow microenvironment (7–9).

Romosozumab binds to *SOST* to inhibit its activity and leads to increased bone formation in mice and humans (10, 11). Global approval was first awarded to Japan in January of 2019 for the treatment of osteoporosis. The success of Romosozumab is clearly evident with an associated 73% lower risk of new vertebral fractures in postmenopausal women after treatment in Phase III clinical trial “Fracture Study in Postmenopausal Women with osteoporosis” (FRAME, NCT01575834). There is a dramatically positive benefit of treatment with Romosozumab on bone mineral density (BMD), which produces a decreased fracture risk in postmenopausal women. However, this population of patients is also at higher risk for respiratory, urogenital, and gastrointestinal infections and is susceptible to autoimmune disease and mortality, resulting from these challenges to the immune system (12). Hematopoiesis and the bone are elegantly intertwined, and manipulation of one can have drastic effects on the other; it is therefore imperative that the immune system of patients receiving Romosozumab be monitored closely.

The effects of SOST on bone homeostasis, and the close proximity and interaction of the bone with hematopoietic cells in the bone marrow, has led to several investigations of the role that SOST has on hematopoiesis and immune cell development (13–15••). In this review article, we provide an

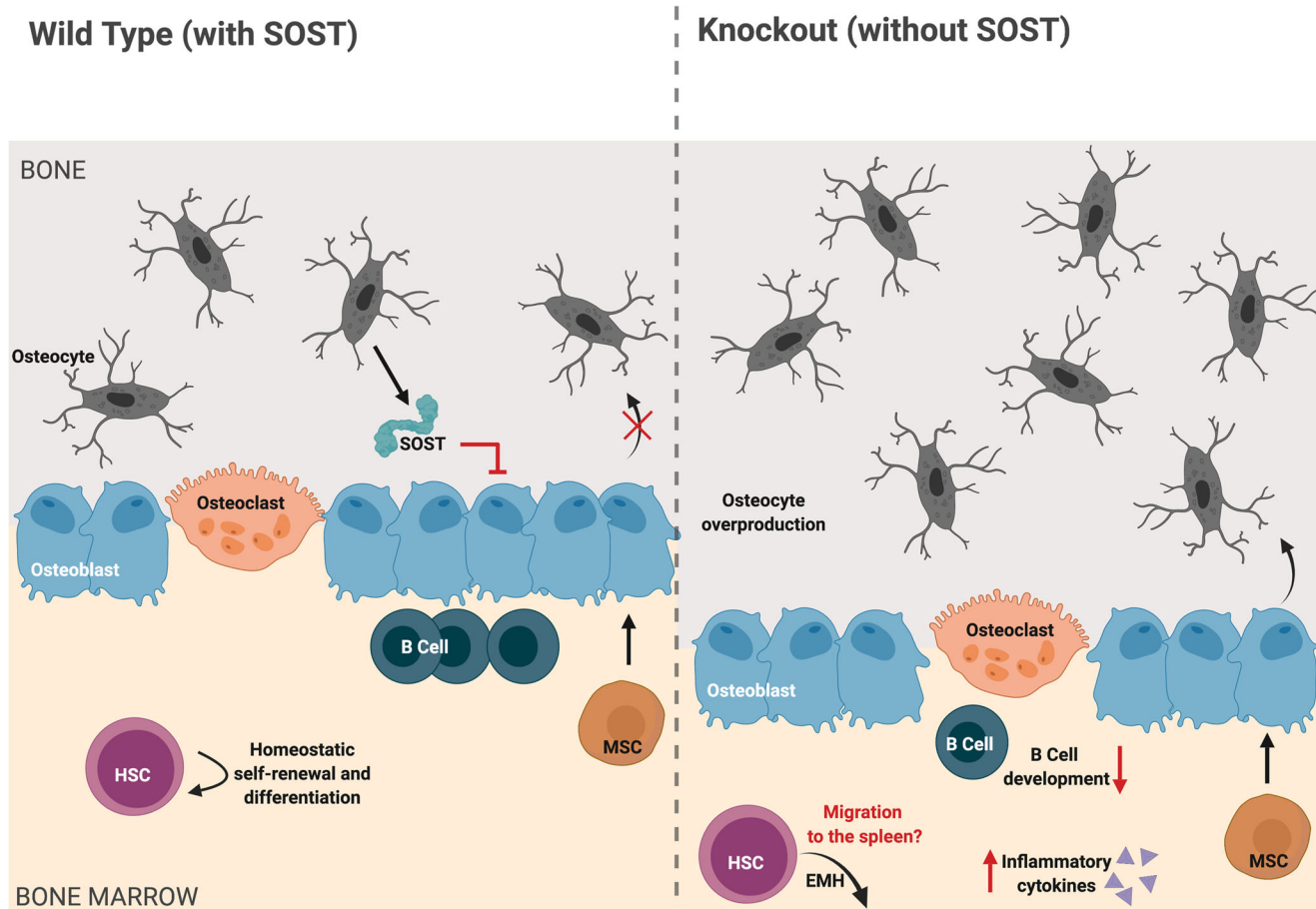
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**Fig. 1** Graphical illustration of the changes in the bone that are caused by loss of sclerostin, and their effects on cells of the immune system. Left: under wild type homeostatic conditions, osteocyte production from mesenchymal stem cells is normal, producing stable levels of sclerostin to control the maturation of osteoblasts to osteocytes. Hematopoietic stem cells and B cell development are supported by niches in the bone marrow

cavity. Right: when sclerostin is globally deleted or reduced, osteocyte production is dysregulated, leading to increased bone mass and decreased bone marrow volume and cellularity. Within the sclerostin-deficient bone marrow, we have collected evidence of inflammation, defective B cell development, and possible hematopoietic stem cell migration to the spleen. This figure was created with [BioRender.com](https://www.biorender.com)

overview of hematopoiesis within the bone marrow niche, a summary of previous and recent findings describing changes in hematopoiesis and immune cell development in studies of mouse models of sclerostin-deficiency, and ideas for future investigations.

### The Bone Marrow Niches that Support Hematopoietic Stem Cells and B Cell Development

It is widely accepted that crosstalk between cells of the bone microenvironment and hematopoietic cells affects each other’s behavior (16, 17). HSC self-renewal, quiescence, migration, and differentiation is regulated by the cellular and molecular interactions between the stem cells and its local microenvironment (18, 19). For adult mammalian HSCs, there are two main stem cell niches: the *endosteal niche*, which is located where the bone and bone marrow (BM) meet, and the

*perivascular niches*, which contains blood vessels that are located more central within the BM cavity. In addition to hematopoietic cells, the BM contains non-hematopoietic cells, loosely termed bone marrow stromal cells (BMSCs), which are critical for HSC maintenance and differentiation. BMSCs are located in close proximity to HSCs and cells of differentiated blood lineages. BMSCs include mesenchymal stem cells (MSCs), osteoblasts (OBs), and endothelial cells (ECs), amongst others. All of these play distinct roles in HSC maintenance and differentiation. HSC behavior and fate are also influenced differently by other cell types, such as adipocytes, endothelial cells, and macrophages in the bone marrow microenvironment (20, 21). In addition, elegant studies combining tissue-specific knockout mice, imaging, and functional assays of hematopoiesis and immune development provided important details about the BM microenvironment that support early B cell progenitors. In particular, within the BM, perivascular stromal cells, osteoprogenitor cells, osteoblasts, and osteocytes are critical B cell “niches,” providing CXCL12, SCF,

IL7, and IGF for B cell progenitors (20–25). In addition, other factors, such as oxygen levels within the BM are key influencers of hematopoietic stem cells and B cell progenitor survival and maintenance, via preferred energy metabolism pathways. In the BM, B cell progenitors are localized in the relatively hypoxic perisinusoidal regions of the marrow (26, 27). Osteocytes are bone-matrix embedded cells throughout the bone that communicate with hematopoietic, endothelial, and other bone cell types via their canaliculi network. Several studies demonstrate the role of osteocytes in the regulation of B cell development (14, 15, 28, 29, 30). However, the molecular mechanisms that regulate crosstalk between hematopoietic and these different niche cells in the bone are incompletely understood.

### Sclerostin and Lymphoid Cells

Studies in global *Sost*<sup>-/-</sup> mice (31) revealed *Sost*'s influence on the regulation of immune cell development. Wnt signaling is enhanced in the absence of *Sost*, and Wnt signaling has been implicated in the maintenance of hematopoietic stem cells and during B cell development (32). Therefore, it was hypothesized that hematopoiesis would be altered in *Sost*<sup>-/-</sup> mice. Cain et al. found that the numbers of hematopoietic progenitors was unaffected in *Sost*<sup>-/-</sup> mice. However, B lymphocyte development was severely affected. B cell numbers were diminished, and B lymphocyte apoptosis increased in the *Sost*<sup>-/-</sup> bone marrow (14). Reciprocal bone marrow transplantation experiments demonstrated that the impaired B cell development in *Sost*<sup>-/-</sup> mice was due to a B cell-extrinsic (i.e., microenvironmental) mechanism. Analysis of the microenvironment revealed that expression of CXCL12, a critical B cell growth factor, was reduced in *Sost*<sup>-/-</sup> bone marrow stromal cells. These studies revealed a novel role of SOST on B cell development in the bone marrow (16). As SOST is expressed primarily by osteocytes in the bone, these data suggested that osteocytes were an important regulator of B cell development. However, using conditional *Sost* knockout mice (*Sost*<sup>iCOIN/iCOIN</sup>, MGI:5544793), Yee et al. recently demonstrated that osteoblasts and mesenchymal stem cells also express *Sost*, and that *Sost* in specific osteolineage cells differentially contribute to B cell development (15). Remarkably, B cell development was unaffected by the deletion of *Sost* in osteocytes (using *Dmp1-Cre*). Surprisingly, MSC-specific deletion of *Sost* (using *Prx1-Cre*) and OB-specific deletion of *Sost* (using *Col1-Cre*) reduced total numbers of B cells in the BM. However, MSC-specific *Sost* influences proper transitions through B cell developmental stages. In contrast, *Sost* in OBs and OCYs do not appear to regulate B cell precursors and immature B cell subsets (15).

The role of SOST on B cell development was further confirmed indirectly by studies of mice in which the von-Hippel-

Lindau (*Vhl*) gene was deleted specifically in osteocytes (28). *Vhl* is a gene in the hypoxia response signaling pathway. In *Vhl*-knockout mice, hypoxia-inducible factor 1 $\alpha$  (Hif1 $\alpha$ ) is stabilized. Evidence in the literature supports both positive and negative effects of hypoxia and Hif1 $\alpha$  on *Sost* expression. *Sost* expression is positively regulated by the direct binding of Hif1 $\alpha$  to the SOST promoter (33). In contrast, enhanced Hif1 $\alpha$  expression in osteocytes decreased sclerostin expression (34), and osteoblast-specific deletion of *Vhl* results in Hif1 $\alpha$  activation with concomitant reduction in *Sost*-positive osteocytes (35). Osteocyte-specific *Vhl*-conditional knockout mice (*Dmp1-Cre;Vhl*<sup>fl/fl</sup>) (herein abbreviated *Vhl*cKO) (36), display decreased *Sost* expression (28). In addition, *Vhl*cKO mice and *Sost*<sup>-/-</sup> mice both display high bone mass and impaired B cell developmental phenotypes, but the effects are more severe in the *Vhl*cKO. For example, we have observed no differences in the frequency and number of mature B lymphocytes in the spleens of global *Sost*<sup>-/-</sup> mice, whereas peripheral B cells are significantly reduced in the *Vhl*cKO spleens (Chicana and Manilay et al., unpublished results). Functional analysis of B cells in *Sost*<sup>-/-</sup> mice support the conclusion that B cell responses to T-dependent antigens may be altered (37), but functional B cell responses to antigens in *Vhl*cKO mice require further investigation. In any case, these findings imply that patients receiving sclerostin-depleting therapies for osteoporosis might suffer from defects in B cell developmental and function. We are unaware if these changes occur in humans, as these data are not reported in recent reports of the Romosozumab clinical trial results (38). Given our observations in *Sost*-deficient mice, it would be interesting to add analysis of peripheral blood B cells and antibody titers after vaccinations in patients receiving Romosozumab and other sclerostin-depleting drugs.

### Sclerostin and Inflammation

It is still not fully understood how the bone marrow microenvironment influences changes in long-term hematopoietic stem cell (LT-HSC) behavior. It is widely accepted that *Sost*-deficiency increases the bone mass; however, there are limited data as to how this change influences the bone marrow microenvironment. To investigate how the absence of *Sost* in the bone microenvironment affects hematopoietic differentiation, we performed transplantation of wild-type (WT) hematopoietic stem cells and progenitor cells (HSPCs) into global *Sost*<sup>-/-</sup> recipient mice. This demonstrated the *Sost*<sup>-/-</sup> bone marrow niche favors myeloid differentiation in WT  $\rightarrow$  *Sost*<sup>-/-</sup> chimeras when compared with WT  $\rightarrow$  control chimeras (Donham et al., manuscript in preparation). Inflammation in the BM can be characterized by rapid mobilization and overproduction of myeloid lineages as well as decreased production of lymphoid cells (39). Analysis of *Sost*<sup>-/-</sup> mice revealed

an increase in TNF $\alpha$  in the BM, as well as upregulation of several other pro-inflammatory cytokines in the BM, perhaps in an attempt to upregulate *Sost* expression (Donham and Manilay et al. unpublished data). TNF $\alpha$  suppresses HSC activity during an inflammatory response (40) and is produced predominantly by activated macrophages. TNF $\alpha$ 's involvement in decreasing B lymphopoiesis is also documented (41●). Further research is needed to assess if the increased myelopoiesis in *Sost*<sup>-/-</sup> mice results in overproduction of activated macrophages. Using an osteoarthritis mouse model, Chang et al. recently demonstrated that *Sost* expression in the bone is upregulated by TNF $\alpha$  after injury (42●), further linking sclerostin and the processes of inflammation in the bone.

In addition to changes in the bone marrow cytokines and cellular composition, inflammation causes changes in the spleen such as extramedullary hematopoiesis (EMH) (43). *Sost*<sup>-/-</sup> mice display splenomegaly, and evidence of EMH, including increases in erythroid and myeloid production in the spleens (Donham et al. unpublished data). To our knowledge, extramedullary hematopoiesis has not been monitored in humans harboring inactivating *Sost* mutations, despite their having a similar bone marrow cavity occlusion phenotypes to that seen in *Sost*<sup>-/-</sup> mice, (44–46). Our studies of *Sost*<sup>-/-</sup> mice indicate that anti-sclerostin treatment in patients may alter developmental hematopoiesis in the bone marrow and spleen, and this could lead to complications for patients with impaired immune systems, such as the elderly. This is important as the primary recipient population for osteoporotic therapies are patients over the age of 50.

## Future Directions

### Comparison of Bone Marrow Microenvironments and Roles of Sclerostin in Different Bone Types

The bone marrow plays a key role in HSC maintenance and functionality, and it is found in numerous bones throughout the body, which vary in structure and cellular maintenance. Common sites used to study the bone marrow niche are calvaria, femurs, tibia, and vertebrae. Whether the bone marrow microenvironment from different bone types can lead to differences in BM function is a point of debate. Certainly, the development of marrow adipose tissue (MAT) in the long bones and vertebrae occurs within different time frames, which could affect the composition and frequency of non-hematopoietic and hematopoietic cells within the marrow during development (47). Comparison of bone marrow in calvaria and femurs demonstrated that they contain distinct HSC niches (48). However, analysis of 8 different bone types, suggested that BM harvest from a single bone is representative of the rest of the BM present in a mouse (49). Sclerostin is

generally expressed by osteocytes in all bone types, and sclerostin is detected in the serum, so studies to determine if sclerostin production from a particular bone or tissue has endocrine effects would be very interesting. Genetic tools that delete the *Sost* gene in specific cell types, such as *Prx1*-Cre, which is activated in the limb bones but not in the vertebrae (15●●), could help to reveal endocrine versus paracrine effects of SOST on bone marrow niches.

### Sclerostin, Adipose Tissue, and Immunity

Fairfield et al. first demonstrated a link between sclerostin and the regulation of the bone marrow adipose tissue development (50●●). Treatment of primary BM-MSCs with recombinant SOST increased adipocyte differentiation, and treatment of the 3T3-L1 cell line with osteocyte-conditioned media also increased adipocyte differentiation, showing a direct effect of osteocyte-produced SOST on BM adipogenesis. In addition, *Sost*<sup>-/-</sup> mice display reduced BM adipose tissue (BMAT) at 6 weeks of age, and treatment of wild-type mice with sclerostin antibody reduced BM adiposity. These results were confirmed by Li et al., who demonstrated that sclerostin antibody treatment reversed the increase in marrow adiposity observed in ovariectomized rabbits (51). The reduced BM adipose tissue observed by Fairfield et al. and Li et al. is contradictory to the observation of decreased B cell development in the BM of *Sost*<sup>-/-</sup> mice (14), since increased BM adiposity of the bone marrow is correlated with a decrease in B cell development in mice, rabbit, and humans (47, 52). Our observation of increased concentrations of inflammatory cytokines in the BM of *Sost*<sup>-/-</sup> mice would also be unexpected, if BM adipose tissue is reduced in the absence of *Sost*. Taken together, these papers suggest that osteocytes and BM adipocytes play direct roles in the maintenance of HSCs and B cell development, and that *Sost* is an important regulator of these cellular interactions in the bone. Further studies are necessary to identify the effects of constitutive marrow adipose tissue (cMAT) and regulated marrow adipose tissue (rMAT) on cellular metabolism during hematopoiesis (53), and whether cMAT and rMAT are differentially regulated by *Sost*. Since MSCs are a common progenitor of both adipocytes and osteocytes, it is also possible that SOST acts directly at the level of the MSC. It is tempting to speculate that deletion of *Sost* could affect MSC maintenance and function, which, in turn, could affect HSCs and B cells within the bone marrow niches (27), independently of the status of the BM adiposity and bone mass.

## Conclusion

Successful clinical trials have led to the approval of the sclerostin antibody Romosozumab for the treatment of



osteoporosis patients. Despite the promising effect on bone mass of this treatment, there is concern because defects in the immune development were identified in *Sost*-deficient mice. Increases in pro-inflammatory cytokines in the bone marrow of these mice as well as extramedullary hematopoiesis highlight the need for further exploration into the effects that inhibition of sclerostin has on bone marrow homeostasis. Monitoring of the three hallmarks of hematopoietic aging, anemia, thrombopoiesis, and immunosenescence, may be an important future clinical consideration for monitoring patients of Romosozumab.

**Authors' Roles** Drafting and revising manuscript: CD and JOM; approving final version of manuscript: JOM.

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### Compliance with ethical standards

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards and institutional approvals.

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

**Human and animal rights and informed consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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