



Sclerostin, bone morphogenetic protein, Wnt and the lung: a potential role beyond bone metabolism?

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Abstract: Sclerostin is a secreted glycoprotein encoded by the SOST gene. Mutation to SOST are responsible for sclerosis of the skeleton leading to Van Buchen disease and sclerosteosis. Sclerostin has been hence described as a negative regulator of bone mineralization. Molecular studies revealed that sclerostin decreased osteoblasts differentiation and activity via inhibition of the bone morphogenetic protein (BMP)-induced canonical Wnt pathway. Recently, sclerostin has been described to be expressed not exclusively in the bone but in other tissue and organs such as smooth muscle cells of the vasculature and lung. Attenuation and de-regulation of BMP and Wnt pathways are very well described in pulmonary hypertension (PH), a condition where increased pulmonary vascular resistance leads to remodelling of the vascular wall with narrowing or occlusion of the vessel lumen and ultimately right heart failure. Here we suggest a potential role of sclerostin in altering homeostasis of endothelial and smooth muscle cells of the pulmonary vessel wall, thereby contributing to the development and progression of PH.

Keywords: Sclerostin; lung; smooth muscle cells; endothelial cells (ECs)

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Introduction

Sclerostin

Sclerostin is a secreted glycoprotein, encoded by the SOST gene (1,2). SOST was identified by linkage analysis in patients with Van Buchen disease (MIM 269500) in 2001, a condition where sclerosis of the skeleton occurs with progressive bone mass increase (3-5). It has been shown, that a homozygous mutation in the SOST or in the enhancer element (Chr 17p21)—which drives SOST expression—is responsible for the skeletal sclerosis (6). Sclerostin has been hence described as a negative regulator of bone growth and mineralization, and the human genetic phenotype was confirmed in animal models. Over-expression of SOST in

mice causes strong osteopenia (7,8), while SOST knock-out mice develop sclerosis of the skeleton mirroring the human disease (9). As indicated by the strong phenotype induced by the lack or over-expression of SOST, sclerostin is extremely abundant in osteocytes, where it activates bone resorption (10).

Sclerostin: mechanism of action in the bone

Bone morphogenetic protein (BMP) pathway

Sclerostin belongs to the differential screening-selected gene aberrant in the neuroblastoma (DAN) protein family (2,3). As the other DAN proteins such as gremlin or noggin, sclerostin presents a cysteine knot structure

which gives the possibility to antagonize BMP activity by competing with the BMP receptor (2). BMP signalling is constituted of BMP ligands (BMP2, 4 and 9) binding to BMP receptor type 1 (BMPRI) and BMP receptor type 2 (BMPRII) which in turn activate the transcription factor SMAD1 and 5 and hence downstream target genes (11). It was first reported that sclerostin exerts its negative effect on the bone by inhibiting BMP effect on osteoblasts (12). Later, it was discovered that sclerostin is actually not expressed by osteoblasts, but by osteocytes and once secreted it induces osteoblast apoptosis by inhibiting BMP6 induced signalling (8). It was also observed that the inhibitory effect of sclerostin on BMP was not direct but rather an indirect mechanism, suggesting that sclerostin may inhibit BMP signalling by interacting with an intermediate factor or pathway which in turn affects BMP signalling (10).

Wnt pathway

Wnt signalling consists of β -catenin-dependent (canonical) and -independent (non-canonical) pathways. In the β -catenin-dependent pathway, when there is no Wnt ligand, the cytoplasmic β -catenin is phosphorylated and therefore targeted for ubiquitination via proteasome-mediated proteolysis. When a Wnt ligand is present, it binds to LRP5/6 receptor and frizzled (FZD) co-receptor which leads to a stabilization of the cytoplasmic β -catenin. β -catenin then translocates into the nucleus and activates downstream target genes involved in cell proliferation and survival. The β -catenin-independent pathway is LRP5/6-independent and causes increased intracellular Ca^{2+} , activation of calcium-dependent proteins and the rearrangement of cytoskeleton, leading to cell proliferation and migration (13). More recently, sclerostin has been reported to bind to the receptor LRP5/6, sequestering it from the frizzled (FZD) co-receptor and thereby leading to inhibition of the wingless (Wnt) canonical pathway (14). In light of this study, van Bezooijen *et al.* have proposed and expanded the concept that sclerostin is an indirect antagonist of BMP signalling by showing that the BMP-inhibitory property of sclerostin lies in the modulation of Wnt pathway (15). The authors showed that sclerostin—by binding to LRP5/6—antagonizes Wnt ligand and inhibit BMP-induced activation of Wnt signalling, which is necessary for alkaline phosphatase activation during bone formation (15) (*Figure 1*).

Beyond the bone: focus on the lung

Pulmonary hypertension (PH): BMP and Wnt signalling

BMP and Wnt pathways are extremely important for bone remodelling, however, their expression and signalling are present in other organs and tissues as well, therefore their actions are not exclusively relevant for the bone. Interestingly, it has been shown that alterations on BMP and Wnt signalling can lead to pathological manifestations, such as PH (16). PH is a rare disease characterized by increased pulmonary vascular resistance which leads to remodelling of the smooth muscle and endothelial layer of the pulmonary arteries leading to narrowing or occlusion of the vessel lumen. As a consequence, the right ventricle of the heart is subjected to an excessive strain which ultimately causes right heart failure (17). The cause of PH is unknown, however the pathogenesis of PH have been often linked to abnormalities of the BMP and Wnt signalling (16). The BMP pathway is extremely important for maintaining the pulmonary vasculature homeostasis, and an attenuation of BMP signalling is a frequent observation in the PH pathogenesis (18,19). Loss of function mutations in BMPRII are associated with both hereditary and non-hereditary PH as well as in the animal models of the disease (19-21). It has been shown that BMP signalling is important on one hand for the survival of endothelial cell (EC) and on the other hand for counteracting the pro-proliferative effect of TGF- β on smooth muscle cell (SMC) of the lung vasculature (22,23). Attenuation of the BMP signalling would then leads to decreased survival of EC and hyper-proliferation of smooth muscle cells; both being hallmarks of PH pathogenesis (24).

The importance of BMP signalling in this aspect has also been proven by the findings that the DAN protein gremlin, acting as a BMP antagonist, is elevated in pulmonary arteries of PH patients and in animal models of PH (25,26). The inhibition of gremlin, by a blocking antibody, reversed the remodelling and the increased pulmonary pressure in the animal models of PH (27). These findings indicate that the action of BMP antagonists could explain the development of PH in the absence of BMPRII mutation.

The Wnt pathway has also been recently associated to PH development (28-30). Several studies reported activation of both Wnt canonical and non-canonical pathways in PH patients and in the corresponding monocrotaline and hypoxic animal models (31,32). The β -catenin protein levels

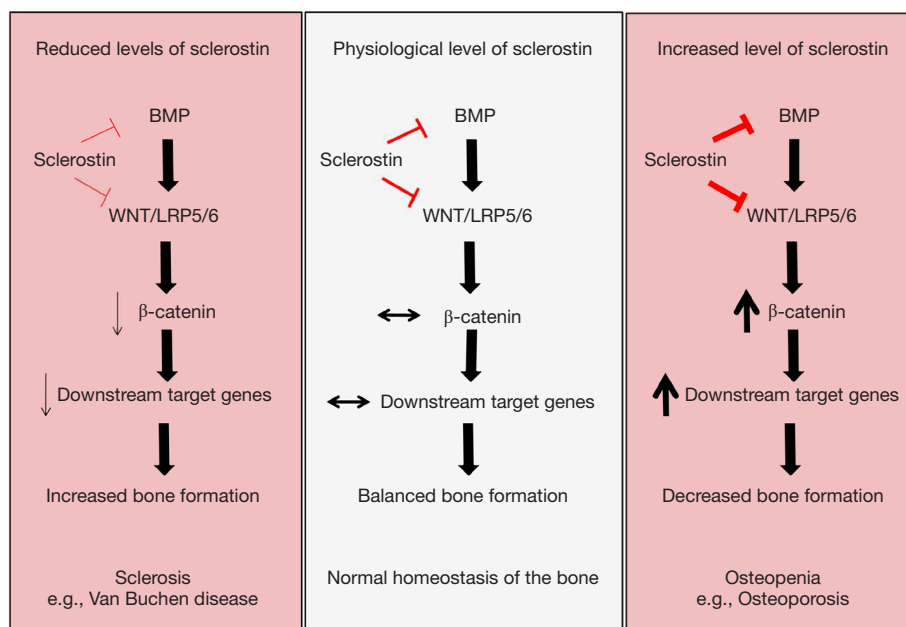


Figure 1 Summary of sclerostin action in the bone. Sclerostin has an effect on bone metabolism by inhibiting BMP and Wnt canonical pathways. The physiological level of sclerostin allows a balance between inhibition and activation of BMP and Wnt canonical pathway resulting in the normal homeostasis of the bone (middle) pathological decreased (left) or increased level (right) of sclerostin will perturbate the normal bone homeostasis resulting in sclerosis or osteopenia respectively. BMP, bone morphogenetic protein.

are elevated in the smooth muscle cells of PH patients, suggesting a pro-proliferative status of these cells (28). Additionally, similarly to the bone metabolism, recent studies have suggested that BMP and Wnt signalling are tightly interconnected during the pathomechanism of PH as well. It has been shown that the protective effect of BMP on EC survival is mediated via β -catenin activation (30). Additionally, a BMP-dependent activation of Wnt signalling has been shown to affect the proliferation and migration of pulmonary arterial SMC (33). These studies suggest that a molecule having potential to modulate both BMP and Wnt pathways, might influence the molecular mechanism governing altered homeostasis of the vascular cells in PH.

Expression of sclerostin: regulation and implications for the lung

Sclerostin has been discovered as an essential bone-related molecule, involved in bone remodelling and homeostasis (34).

However, recently it has been shown that sclerostin is not only confined to the skeletal compartment, but it is present in other organs as well. Expressional analysis revealed that sclerostin is expressed in the cartilage, liver,

kidney, heart and in the lung (3,35,36). Additionally, in the cardiovascular system, sclerostin has been detected in the aorta (36), specifically in the vascular SMC where it is often associated with vascular calcification (37). As sclerostin is a negative regulator of mineralization, sclerostin expression could be up-regulated to counteract the ongoing calcifying mechanisms. Importantly, expression studies have revealed that several factors important in the pathogenesis of PH affect sclerostin levels. In the bone, it has been shown that sclerostin expression is down-regulated by nitric oxide (NO) production. This evidence is particularly important in relation to the lung, where NO is one of the major messenger molecules for pulmonary vasodilation (38). However, in PH patients the endothelial production of NO is often impaired in the pulmonary vasculature, due to endothelial dysfunction (39). Therefore, the decreased vascular NO could be the cause of increased sclerostin levels in the PH pulmonary arteries. Additionally, expression of sclerostin is modulated by hypoxia and cytokines, such as IL-6 (40,41). Contrary to the systemic circulation, hypoxia induces vasoconstriction in the pulmonary vasculature (42). Hypoxic vasoconstriction is a necessary response in order to limit the circulation in

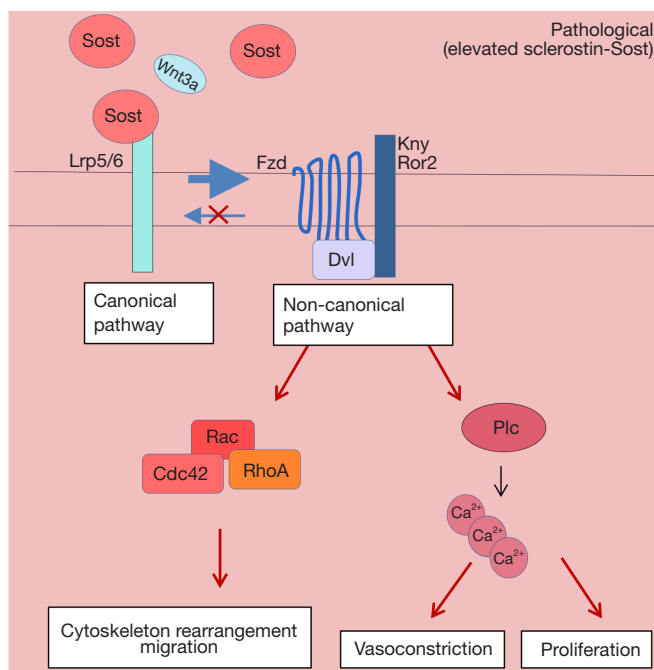


Figure 2 Potential involvement of sclerostin on SMC in PH. Sclerostin blocks the canonical Wnt pathway by binding to LRP5/6. FZD (frizzled) receptor is then free to interact with another co-receptor (Kny or Ror2) and activate non-canonical pathway. Rac, Cdc42 and RhoA are small GTPases protein involved in cell polarity and cytoskeleton rearrangement. Plc (phospholipase C) is responsible for activating the downstream signalling which leads to increase intracellular calcium. SMC, smooth muscle cells; PH, pulmonary hypertension.

the hypoxic lung regions and divert the blood flow towards better oxygenated regions, thereby increasing the efficiency of gas exchange (42). Due to the vasoconstrictive status and substantial remodelling of their pulmonary arteries, PH patients are often hypoxic, and this decrease in oxygen concentration could lead to sclerostin upregulation. Similarly, IL-6 is a cytokine shown to be elevated in PH (43,44) and over-expression of IL-6 in mice results in spontaneous PH development (45). The increased level of IL-6 could contribute to increased sclerostin production. These abovementioned factors are only few known stimuli inducing sclerostin levels, however, we do not know whether other molecules with an established role in PH development (such as PDGF-BB) could also affect sclerostin expression. Nitric oxide, hypoxia and IL-6 could enhance sclerostin production triggering then sclerostin-action on BMP and Wnt pathways leading to perpetuation of the disease.

Sclerostin: potential involvement in PH

Several studies have delineated disturbances of BMP and Wnt pathways in PH, however, the underlying molecular

mechanisms responsible for these alterations are not yet known. One could speculate that excess sclerostin levels due to upregulation by NO, hypoxia, IL-6 or other factors, could disturb the BMP and Wnt pathways helping the perpetuation of the disease in a vicious circle. To date, the role of sclerostin on vascular cells has not yet been investigated. Sclerostin could affect the physiological homeostasis of EC and SMC driving endothelial dysfunction and vascular remodelling and thereby contributing to the pathophysiology of PH.

Here, we suggest a possible mechanism of action of sclerostin on SMC and EC which might take part to the pathomechanism underlying PH.

In SMC sclerostin elevation could lead to inhibition of the canonical Wnt pathway by binding to LRP5/6. This would activate the non-canonical pathway leading to migration and intracellular calcium increase. Increase of intracellular calcium is a very important signalling event which induces contraction of SMC (46). It has been shown that SMC isolated from the pulmonary artery of PH patients present higher intracellular calcium than SMC isolated from healthy lungs. This leads to increased susceptibility

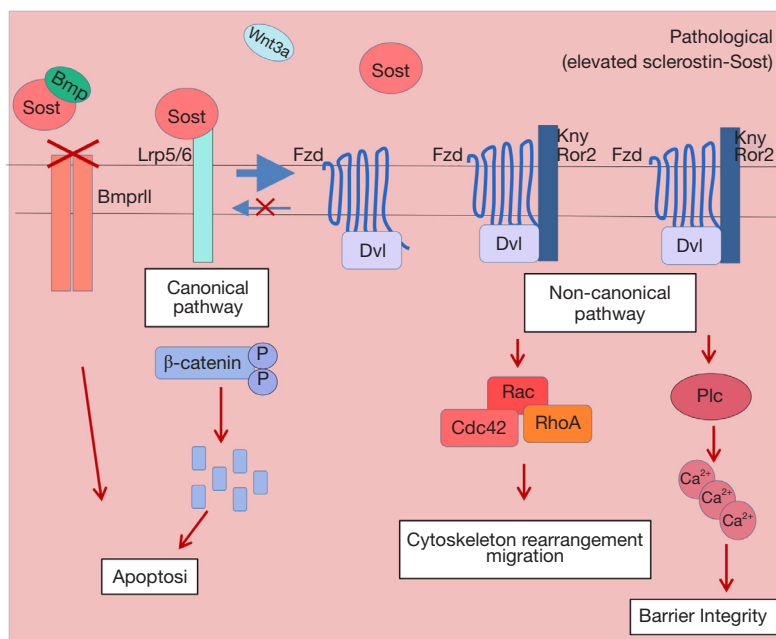


Figure 3 Potential involvement of sclerostin on EC in PH. Sclerostin blocks the canonical Wnt pathway by binding to LRP5/6. FZD (frizzled) receptor and simultaneously could block BMPRII activation by sequestering BMP ligand. These events might result in apoptosis of EC. Additionally similarly to the SMC the activated non-canonical pathway would lead to cytoskeleton rearrangement and decreased barrier integrity. PH, pulmonary hypertension; EC, endothelial cell; BMP, bone morphogenetic protein; SMC, smooth muscle cells.

for SMC contraction which consequently translates for higher pulmonary vascular tone (46). Additionally, elevated intracellular calcium in SMC, is often associated to increased proliferative potential (*Figure 2*).

Sclerostin could also act on the EC of the pulmonary vessels. In this vascular cell type it could induce apoptosis by binding to LRP5/6 and inhibiting the canonical Wnt pathway. At the same time, as BMP has been shown to induce β-catenin activation, sclerostin would also block BMP-induced survival of EC. Additionally, similarly to SMCs, the blockage of the canonical pathway would lead to activation of the non-canonical pathway, affecting the cytoskeleton and intracellular calcium of EC leading to alterations of cell to cell contact and impairment of the barrier integrity of the endothelial layer (*Figure 3*).

Concluding remarks

The current research is mostly focused on the role of sclerostin in bone remodelling and hence it is commonly known as an osteocyte-specific protein. However, a growing body of evidence shows that sclerostin is expressed and

plays an important role in other tissues and organs as well. Although sclerostin has been reported to be present in the lung and in the cardiovascular system, its role in their physiological and pathological conditions has not been studied yet. In light of the simultaneous effect of sclerostin on both BMP and Wnt pathways and the involvement of these two pathways in the pathogenesis of PH, one can speculate that sclerostin could be a very interesting candidate for the pathogenesis of PH. In vitro functional studies should elucidate the influence of sclerostin on vasoreactivity and barrier integrity—the main physiological function of smooth muscle and ECs. Additionally, *ex vivo* vascular force measurements by wire myography and lung dynamic assessments by isolated-perfused lung system would facilitate to understand the role of sclerostin in vascular tone, resistance, as well as vascular permeability and oedema formation in a more physiological context. Eventually, *in vivo* studies (e.g., Sugen/Hypoxia rat model) would be essential to prove the relevance of sclerostin in PH. These studies would open up new avenues, where sclerostin could be investigated on a much broader horizon beyond bone remodelling.

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