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Review Article

The potential role of sclerostin in the development of osteoarthritis

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Abstract: Osteoarthritis (OA), a debilitating degenerative joint disease which is greatly influenced by alterations in the local mechanical loading environment in the joint. The exact aetiology of OA remains unknown, but loss of articular cartilage, subchondral sclerosis, and bone remodeling has been known to play important roles in OA development. Wnt/β-catenin signaling has a substantial role in bone and cartilage homeostasis in the adult skeleton, and has been implicated in the process of cartilage degradation and subchondral remodeling in OA. Sclerostin (SOST), secreted mainly by osteocytes and downregulated by mechanical loading, is a potent inhibitor of Wnt signaling and a regulator of bone metabolism. Thus, by studying the expression of sclerostin and the Wnt pathway, it is possible to investigate the role of the osteocyte in bone remodeling in human musculoskeletal disease, such as OA. However few of literatures have reported about the relation between Sclerostin and OA. In this review we have tried to summarize the current knowledge on the effect of Sclerostin and to explore the potential role of Sclerostin during the process of OA. A better understanding of the relationship between Sclerostin and cartilage/subchondral in both physiological and pathological conditions may lead to development of more effective strategies for treating OA patients.

Keywords: Sclerostin, Wnt/β-catenin signalling, osteoarthritis

Introduction

Osteoarthritis (OA) is a common degenerative joint disease and a major healthcare burden in today's aging population [1], which is characterized by progressive degeneration of articular cartilage, osteophyte formation, and subsequent joint space narrowing [2]. All structures within the joint may be affected during progression of the disease, but the underlying causes are not well understood. There are a number of known associated risk factors including age [3], gender [4], obesity [5], malalignment [6], genetic heritability [7], and previous joint trauma [8]. Nevertheless, loss of articular cartilage, subchondral sclerosis, and bone remodeling has been known to play important roles in OA development.

Recent studies have suggested the relevance of Wnt signaling in human OA [9, 10]. The Wnt signaling pathway comprises a family of regulating molecules that provides communication signals between cartilage and bone [11]. Thus Wnt signaling pathway has a substantial role in bone and cartilage homeostasis in the adult skeleton, and has been implicated in the process of cartilage degradation in osteoarthritis [12]. Microarray analysis of the expression of genes associated with the Wnt pathway also suggests the possible involvement of this pathway in altered bone remodeling in OA [13]. Sclerostin, a protein product of the SOST gene, secreted mainly by osteocytes decreases bone formation by inhibiting the terminal differentiation of osteoblasts and blocks Wnt/β-catenin signaling pathway via its interaction with the Low Density Lipoprotein Receptor-related Proteins-5/6 (LRP5/6) receptor [14, 15]. Interestingly, its antagonist role on BMP signaling is also linked with its interaction with the LRP5/6 receptor [16, 17].

Mabey et al [18] found that the plasma Sclerostin level in OA patients was significantly lower than healthy controls and Plasma and synovial fluid sclerostin levels were inversely associated with the radiographic severity of

knee OA. In addition, Sclerostin has also been found to be potentially beneficial in protecting against cartilage degradation [19] and decreased sclerostin expression of osteocytes is associated with increased cortical bone density in hip OA [12], indicating a potential role for sclerostin in OA pathogenesis. Taken together, these data suggest that sclerostin and Wnt signaling have potential importance in the etiology of OA.

The role of sclerostin in the etiology of OA

OA appears to be the result of a complex interplay between mechanical, cellular and biochemical factors. The etiology of OA is multifactorial and can be broadly divided into genetic and non-genetic factors. Genetic factors may be hereditary and altered gene expression pattern of cartilage and subchondral bone tissues [20]. The etiology of non-genetic factors remains largely unknown but the interaction of systemic and local factors together is most likely contribute to it [21, 22], such as age, gender, obesity, inactive lifestyle, joint injury and occupation (obesity, inactive lifestyle, joint injury and occupation may related to mechanical loading).

Age

Increased age is the most prominent risk factor for the initiation and progression of primary OA in typically affected joints [23]. The cases of OA found in young people are most likely due to mutations in matrix genes [24, 25]. However the exact mechanism between the increased prevalence and incidence of OA with age is poorly understood. The classic “wear and tear” theory is that the cumulative effect of mechanical load over the years may cause “wear and tear” clinically and cartilage breakdown pathologically [25]. It is widely known that osteocytes are the major cell types that response to mechanical loading and sclerostin is mainly secreted by osteocytes. Thus sclerostin may play a role in the age-related OA. A previous cross-sectional study reported that circulating levels of sclerostin were increased in both women and men between the ages of 21 and 97 years [26]. Other investigators have also reported similar, serum sclerostin levels are affected by age [27-32], raising the possibility that decreased production of sclerostin by osteocytes in bone contributes to the age-related osteophyte in OA and increased production contributes to osteoporosis in humans.

Gender

Females are associated with a higher prevalence and severity of OA and are more likely to suffer more severe radiographic knee OA than men, particularly following menopause. There was consistent evidence that females were at higher risk of knee OA [33]. The increase in incidence of OA in female, particularly at the time of menopause, has raised the role of estrogen in OA. Since Estrogen receptor pathways are obligatory to mechanotransduction signaling of osteocyte and sclerostin is regulated in osteocytes by mechanical loading of bone. It may indicate that Sclerostin level was correlated with menstrual period, this is consistent with previous studies [34, 35]. All of these suggested a complex interplay of Sclerostin, mechanical loading, and bone turnover related to sex steroids.

Mechanical loading

Mechanical factors play important roles in promoting both the health of a joint and its degeneration. The articular surface plays an indispensable role in load transfer across the joint and there is enough evidence that conditions leading to increased load transfer or altered patterns of load distribution can accelerate the instigation and progression of OA [36]. Such abnormal mechanical loading would compromise the overlying articular cartilage and underlying subchondral bone in joints leading to cartilage degeneration and subchondral bone remodeling.

Mechanical loading of cartilage is an essential component in maintaining healthy and functional articular cartilage. However excessive or abnormal mechanical loading accelerates cartilage degeneration and increases chondrocyte death [37, 38]. A recent study by Saito et al [39] highlights mechanical stress-induced changes in chondrocytes and proposes treatment through histone deacetylase (HDAC) inhibitors. Since mechanical loading is known to influence sclerostin expression [40], and loading is known to affect signal transduction in articular cartilage, with the addition of that sclerostin can be expressed in Articular Cartilage [41], it is possible that unique loading signals associ-

ated with different zonal regions in the articular cartilage may contribute to the regulation of sclerostin expression.

Acting as mechanosensors, osteocytes are able to integrate the mechanical and biochemical signals that regulate osteoblastogenesis and osteoclastogenesis, thus governing bone modeling and remodeling. Sclerostin, secreted mainly by osteocytes, is an important negative regulator of bone formation that has been proposed to have a key role in regulating the response to mechanical loading [14]. Wnt signaling and BMP are involved in osteoblastogenesis and bone formation [42]. Sclerostin has actions as both a BMP antagonist [43] and Wnt signaling antagonist by binding LRP5/6 receptor [44]. Collectively, these data suggest an important role of Sclerostin involve in the etiology of OA due to the abnormal mechanical loading.

The role of sclerostin in the pathophysiology of OA

Initially, OA has been considered to be limited to the articular cartilage; however growing evidence has indicated that the condition involves the entire joint [45-47]. Although the loss of articular cartilage has been thought to be the primary change, it remains unclear whether underlying subchondral bone changes occur before or after cartilage changes related with clinical symptoms [48]. Nevertheless, it is obvious that changes in all tissues, such as destruction of the articular cartilage, changing underlying subchondral bone structure, and chronic inflammation of the synovium, can be considered as a cause of the abnormal state leading to OA.

Articular cartilage

Under normal conditions, articular chondrocytes maintain a dynamic homeostasis between synthesis and degradation of extracellular matrix (ECM) components [49]. In osteoarthritic states, however, a disruption of homeostasis results in loss of cartilage tissue, clonal expansion of chondrocytes in the depleted regions, induction of oxidative states in a stressful cellular environment, and eventually, apoptosis of cells [50]. A series of catabolic and anabolic mediators have been found to play key roles in articular cartilage homeostasis and the development of OA. Some specific signaling pathways which induced by catabolic and anabolic growth factors and cytokines, such as the Wnt/β-catenin signaling pathway, have been well-recognized as critical regulator of bone and cartilage homeostasis [51-54]. In adult cartilage, increased Wnt/β-catenin stimulates tissue breakdown rather than formation [55]. Since Wnt-induced signaling protein-1 (WISP-1) is increased in OA and over-expressed of WISP-1 will induce cartilage degradation by upregulating matrix metalloproteinases (MMPs) and aggrecanases [10]. Thus Wnt/β-catenin signaling may stimulate articular cartilage degradation via up-regulation of MMPs. Sclerostin (SOST), a soluble inhibitors of WNT signaling [56], can also be expressed by articular chondrocytes [41]. In cell-based studies, it was proposed to play a chondroprotective role in response to catabolic signals [19]. All of these data suggest a protective role of sclerostin in articular cartilage during the development of OA.

Subchondral bone

The subchondral bone is also considered to play a key role in the pathophysiology of OA [57]. Although It is not yet clear whether changes within subchondral bone precede or after changes in the articular Cartilage, the two processes are closely related. Chiba et al [58] considers Subchondral bone changes as a result/cause of cartilage loss in OA. Recent data suggests that structural changes in subchondral trabecular bone are associated with cartilage degeneration in animal models of OA [59-61] and in human [10, 62]. During the development of OA, there is a progressive increase in the subchondral bone plate thickness, a modification in the architecture of subchondral trabecular bone, formation of new bone at the joint margins-osteophytes [63]. These changes may be due to the abnormal function of subchrondral osteoblasts in OA patients [64, 65]. The abnormal expression of phenotypic markers and reduced mineralization of OA osteoblast is linked with the stimulation of the Wnt antagonist DKK2 [66] and SOST [67], as well as the inhibition of the Wnt agonist, R-spondin 2 [68]. SIRT1 and TGF-β1 may be responsible for the increased SOST expression of OA osteoblast which contributes to reduce Wnt/β-catenin signaling and mineralization in these cells [67].

Moreover, Sclerostin may also act as a paracrine regulator of osteoclastic activity [69]. Since Osteoprotegerin (OPG), a potent inhibitor of the pro-osteoclastogenic RANKL-RANK signaling pathway, is also expressed in response to Wnt signaling [70, 71], together with the activity of sclerostin as a Wnt inhibitor, it indicate that sclerostin may support osteoclast activity by a RANKL-RANK signaling pathway. This is consistent with study of Wijenayaka and Atkins et al [70]. They suggested that sclerostin stimulated osteocyte support of osteoclastogenesis and did so in a RANKL-dependent manner.

Although bone sclerosis and subchondral bone plate thickening are consistent discovery in clinical OA, we now have found that this change is not a increase of bone formation itself, but because of bone type 1 collagen extracellular matrix increased with an imbalance in α1 to α2 chains leading to a reduced mineralization [64, 69]. Therefore, sclerostin could participate in the abnormal mineralization of this matrix and may act through regulation of the PHEX/MEPE (phosphate regulating gene with homologies to endopeptidases on the Xchromosome/matrix extracellular phosphoglycoprotein) axis at the preosteocyte stage and serves as a master regulator of physiologic bone mineralization, consistent with its localization in vivo and its established role in the inhibition of bone formation [70]. In addition, Wnt signaling and BMP are involved in bone formation [42] and Wnt signaling is required for BMP to stimulate ALP activity in several osteoblastic cell lines [71]. Microarray analysis of Wnt pathway also suggests the possible involvement of this pathway in altered bone remodeling in OA [13]. Inhibition of Wnt signaling and BMP by sclerostin therefore may effect on bone formation and bone remodeling [72] in OA. Taken together, all these data demonstrate that the anti-anabolic action and catabolic action of sclerostin may be a potential mechanism of subchondral bone changes in OA.

Synovial membrane

There is increasing evidence that synovial inflammation plays an important role in the symptoms and structural progression of OA. Importantly, synovitis has been shown to be correlated with symptom severity, rate of cartilage degeneration and osteophytosis in OA [73]. Furthermore, synovitis is an indicator of pathology and a predictor of disease progression [74]. Although it is still unknown that if sclerostin can expression in synovial membrane, we can find sclerostin in synovial fluid and it is inversely associated with the radiographic severity of knee OA [18]. Wnt and the Wnt inhibitor, secreted frizzled-related protein (FRP), can also be expressed in OA synovium [75]. In addition that sclerostin can prevent Wnt protein binding to secreted frizzled-related protein and its coreceptors via binding to Wnt coreceptors, (LRP-5/6) [76]. Thus sclerostin, expressed by articular chondrocytes and osteocytes, may secreted into synovial fluid and effected on synovial membrane.

The potential role of sclerostin in the treatment of OA

As we know, osteoporosis therapies are associated with the changes of serum sclerostin levels and monoclonal antibodies to sclerostin have advanced to phase II clinical trials or beyond. However it still unclear the role of sclerostin in the pathogenesis of OA and the potential utility of treating osteoarthritis by altering sclerostin distribution is not known. It has been recognized that Wnt signaling was involved in cartilage degeneration [19, 55] and bone remodeling [13] in development of OA, raising the possibility that modulation of Wnt signaling might be beneficial in OA therapy. Sclerostin is found to be an inhibitor of Wnt signaling, together with the fact that sclerostin can be expressed by osteocytes and articular chondrocytes, suggesting that sclerostin may be a new molecular target for the treatment of OA in humans.

Traditionally, bisphosphonates are widely used in the treatment of osteoporosis via inhibiting bone resorption and bone turnover. In recent years, several studies have showed the chondroprotective role of bisphosphonates in the treatment of OA [77-79]. It has also reported that bisphosphonate therapy is associated with increasing serum levels of sclerostin [80, 81]. Furthermore, increasing sclerostin expression found in cartilage in OA may protect against cartilage degradation by inhibiting Wnt-b-catenin signaling and catabolic MMP expression [19]. There is evidence that MMP inhibition and downregulation by bisphosphonates [82]. These results implicated that bisphospho-

nates may protect articular chondrocytes by increasing sclerostin and then decreasing the expression of MMPs. On the other hand, decreasing expression was found in subchondral bone [19] and upregulation of sclerostin by bisphosphonates may prevent disease-associated subchondral bone sclerosis. Recent pre-clinical studies have shown that bisphosphonates could prevent subchondral bone lesions due to their ability to inhibit altered bone remodeling [83, 84]. As we mention above, Wnt pathway may involve in altered bone remodeling in OA and the inhibitory effect of sclerostin to this pathway, suggest the possible involvement of sclerostin in bisphosphonates therapy.

Conclusions

Since the discovery of Wnt signaling pathway and understanding the role of osteocyte and sclerostin in skeletal homeostasis, there has been a remarkable progress. OA is one of the highest prevalence joint disease in the worldwide and its development takes place in consecutive steps of breakdown and attempted regeneration. Improved understanding of the relationship between Sclerostin, Wnt signaling and cartilage/subchondral in both physiological and pathological conditions led to the development of novel OA therapies.

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Disclosure of conflict of interest

None.

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