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SYSTEMATIC REVIEW

The role of cells and signal pathways in subchondral bone in osteoarthritis

P. Luo,
Q. Yuan,
M. Yang,
X. Wan,
P. Xu

From HongHui Hospital, Xi'an Jiaotong University, Xi'an, China

Osteoarthritis (OA) is mainly caused by ageing, strain, trauma, and congenital joint abnormalities, resulting in articular cartilage degeneration. During the pathogenesis of OA, the changes in subchondral bone (SB) are not only secondary manifestations of OA, but also an active part of the disease, and are closely associated with the severity of OA. In different stages of OA, there were microstructural changes in SB. Osteocytes, osteoblasts, and osteoclasts in SB are important in the pathogenesis of OA. The signal transduction mechanism in SB is necessary to maintain the balance of a stable phenotype, extracellular matrix (ECM) synthesis, and bone remodelling between articular cartilage and SB. An imbalance in signal transduction can lead to reduced cartilage quality and SB thickening, which leads to the progression of OA. By understanding changes in SB in OA, researchers are exploring drugs that can regulate these changes, which will help to provide new ideas for the treatment of OA.

Cite this article: *Bone Joint Res* 2023;12(9):536–545.

Keywords: Subchondral bone, Osteoarthritis, Bone remodelling

Article focus

- This article reviews the role of cells and signal pathways in subchondral bone (SB) in osteoarthritis (OA).

Key messages

- The signal transduction mechanism in SB is critical to the balance between cartilage and SB.
- The imbalance of signal transduction in SB will promote the occurrence and development of OA.
- Understanding the signal transduction in SB is helpful in OA treatment.

Strengths and limitations

- Understanding the cells and signal transduction in SB is necessary for the stability of articular cartilage and the balance of bone remodelling, which is helpful when it comes to the exploration of the new pathogenesis of OA.
- The treatment of SB damage in OA greatly broadens the visual field of clinical treatment of OA.
- As all the studies included in this review are in English, the literature here may not be comprehensive enough.

Introduction

The development of osteoarthritis (OA) is mainly due to ageing, obesity, trauma, and congenital joint abnormalities that cause articular cartilage degeneration.[1] OA mainly occurs in middle-aged and elderly individuals, especially in weight-bearing joints and joints associated with more activity (such as the knee joint, hip joint, cervical vertebra, and lumbar vertebra).[2] Its clinical features mainly include chronic progressive joint pain, tenderness, stiffness, and limited movement.[3] Genetic factors may include the inheritance of cartilage and subchondral bone (SB) and changes in gene expression patterns.[4] Epidemiological studies have indicated that OA is mainly a mechanically induced disease, and many factors further affect its severity.[5]

Several tissues of the joint, including cartilage, the synovium, and subchondral bone, play key roles in the occurrence/progression of OA lesions.[6] During the initiation/progression of OA, SB is the site of many dynamic morphological variations due to various cellular metabolic changes, which are part of the pathological process.[7] SB and cartilage form the bone-cartilage unit, which participates in the pathophysiological

Correspondence should be sent to Peng Xu; email: xupeng369@mail.xjtu.edu.cn

doi: 10.1302/2046-3758.129.BJR-2023-0081.R1

Bone Joint Res 2023;12(9):536–545.

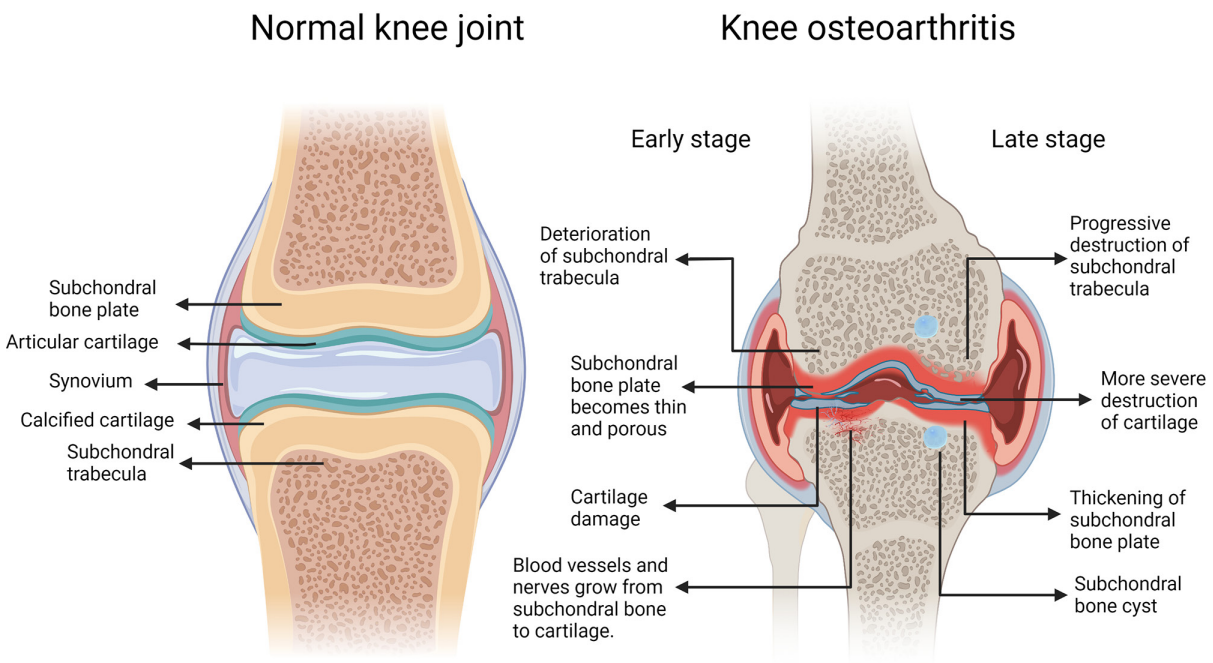

Fig. 1

Subchondral bone (SB) in normal joints and osteoarthritis (OA). Normal knee joints include cartilage, synovium, and SB. SB also includes subchondral bone plate (SBP) and subchondral trabecula. In early OA, the SBP becomes thinner and porous. Cartilage and SB trabeculae deteriorated. At the same time, blood vessels and nerves grow from subchondral bone to cartilage. In late OA, calcified cartilage appears in the articular cartilage area and the SBP thickens. At the same time, subchondral trabecular sclerosis and progressive cartilage destruction lead to bone cyst-like lesions.

process of OA at the mechanical level.[8] Since the observable structural difference between articular cartilage and SB is important to the progression of OA, an increasing number of studies have focused on its participation and role in the pathological process of OA.[9-11]

During the pathogenesis of OA, cartilage and SB undergo catabolic and anabolic remodelling.[12] This change in SB is not only a secondary manifestation of OA, but also an active part of OA, which is closely associated with the disease severity. Therefore, in this review, we discuss the communication between SB cells and various signal transduction mechanisms, and how their regulation promotes the progression of OA.

Changes in subchondral bone in OA

SB generally refers to the bone composition of the distal end of calcified cartilage, which can be divided into two parts: the subchondral bone plate (SBP) and the subchondral bone trabecula.[13] The SBP is located below the calcified cartilage and is composed of a layer of cortical plate containing pores. The SBP is a layer of highly vascularized cortical bone located above the trabecular bone.[14] The osteochondral plate is the exchange site for bone and cartilage, by which bone provides nutrients for cartilage. Some blood vessels and nerves enter the calcified cartilage through the pores in the SBP.[15,16] The distribution and strength of these channels depend not only on age but also on the pressure transmitted by cartilage and subchondral bone in the joint, and shape and diameter vary with the thickness of the cortex.[17] The subchondral trabecula, which is located in the lower part of the SBP, is a porous structure rich with blood vessels, which plays a key role in load absorption and cartilage nutrient supply.[18-20] Subchondral cancellous bone has a non-homogeneous structure, which varies with the distance from the joint surface and has structural and mechanical anisotropy.[21] SB dynamically adapts to mechanical force through coordinated bone remodelling.[22] Bone resorption and the formation of osteoblasts are key factors in the bone remodelling process.[23] SB responds quickly to mechanical load through bone remodelling and forms normal physiological conditions to adapt to joint movement.

In the different stages of OA, there are microstructural changes in SB (Figure 1). For example, Klose-Jensen et al[24] observed enhanced SB turnover in early OA. In early OA, the SBP became thinner and porous, which was accompanied by subchondral trabecular deterioration and degeneration.[25] Furthermore, blood vessels and nerves grow from SB to cartilage. In late OA, Botter et al[26] found that calcified cartilage and SBP thickening occurred in severely eroded articular cartilage areas, while sclerosing subchondral trabeculae destruction resulted in bone cyst-like lesions. However, SBP thickening and modulation of bone from rod-like to plate-like structures does not depend on the severity of articular cartilage erosion.

Cells in subchondral bone remodelling

Osteoclasts. Osteoclasts are formed by the differentiation of bone marrow myeloid progenitor cells and play

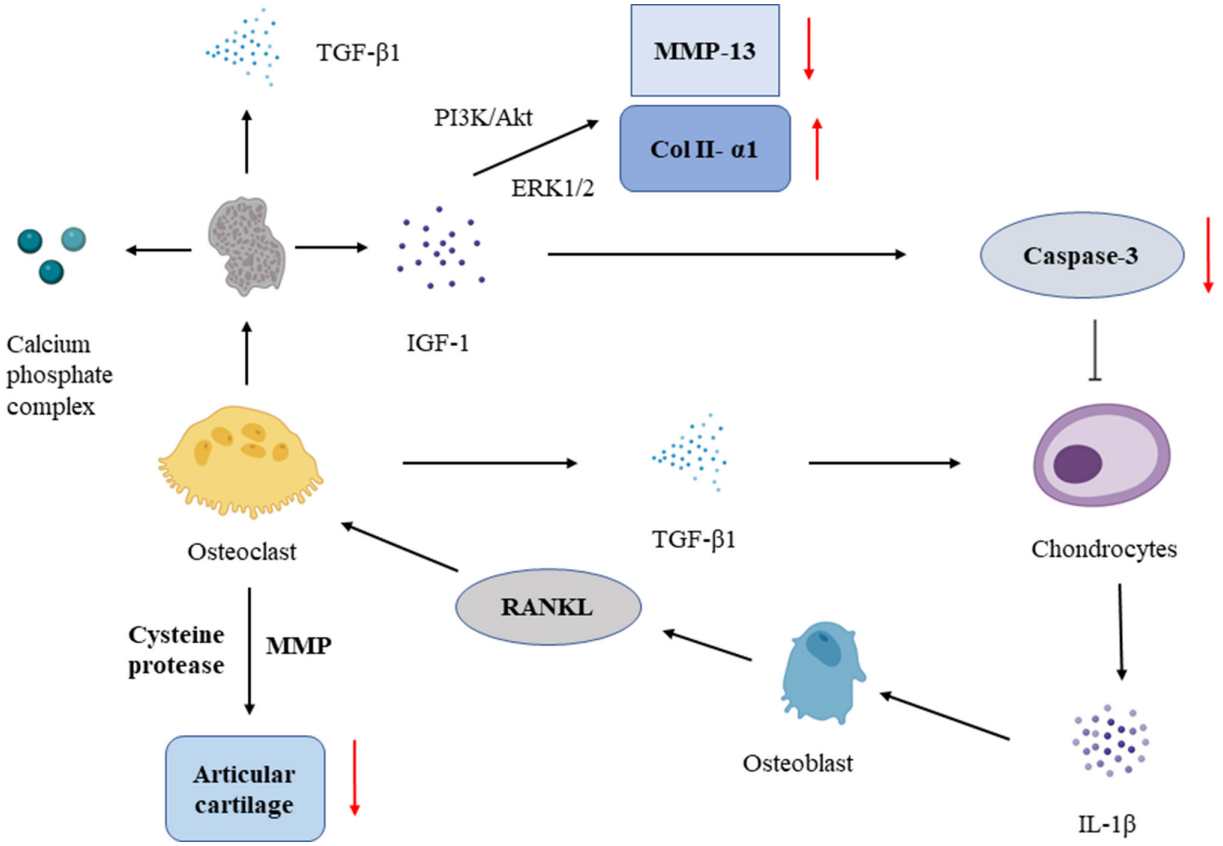

Fig. 2

The role of osteoclasts in subchondral bone in osteoarthritis (OA). Mature osteoclasts attach to the bone surface and dissolve bone during bone remodelling. After osteolysis, various factors including transforming growth factor beta-1 (TGF-β1), insulin-like growth factor (IGF)-1, and calcium phosphate complex are released from the bone matrix. Osteoclasts degrade articular cartilage in a matrix metalloproteinase (MMP)-dependent and cysteine protease-dependent manner. IGF-1 promotes the expression of colagen type II alpha 1 (Col II α1) and inhibits the expression and enzyme activity of MMP-13 by activating phosphatidylinositol 3 kinase (PI3K)/Akt and ERK1/2 pathways in rat endplate chondrocytes. In addition, IGF-1 signal protects chondrocytes from apoptosis by reducing caspase-3 activity. Interleukin 1 beta (IL-1β), released by chondrocytes, upregulates the expression of receptor activator of nuclear factor kappa-B ligand (RANKL) in osteoblasts and indirectly induces osteoclast formation.

an important role in bone resorption. In addition, these cells are closely related to bone metabolism.[27] Relevant experimental results show that the activity level of osteoclast precursors is increased during periosteal vascular growth, and these cells invade the hypertrophic area of cartilage and then interact with the cells in it, resulting in significant changes in the morphology of the cartilage matrix and the formation of primary ossification centres.[28,29] Relevant experimental results show that osteoclasts can degrade the osteochondral connection, which is mainly achieved in a matrix metalloproteinase (MMP)- and cysteine proteinase-dependent manner, leading to a certain reduction in bone density.[30] Most mature osteoclasts appear on the bone surface and play a key role in bone remodelling. There are many factors that are closely related to bone metabolism in the bone matrix, including transforming growth factor beta-1 (TGF-β1). Insulin-like growth factor-1 (IGF-1) and the calcium phosphate complex can regulate bone metabolism, thus affecting the state of joints.[31] Zhang et al's research[32] shows that under certain mechanical stimulation, TGF-β1 is expressed in osteoclasts. The expression level of TGF-β1 was significantly increased, and the expression level was increased when the intensity of stimulation increased. Comparative analysis showed that when chondrocytes are cultured with osteoclasts, the level of chondrocyte apoptosis was significantly increased. In addition, treatment with a TGF-β1 receptor (TGF-β1R) inhibitor could reverse chondrocyte apoptosis and reduce cartilage degeneration in rat OA.[32] These studies have shown that TGF-β1 in SB can be transferred to the cartilage layer, which has an adverse effect on chondrocytes. IGF-1 is a protective factor in the synthesis and metabolism of chondrocytes. IGF-1 promotes collagen type II alpha 1 (Col II-α1) expression and inhibits MMP-13 expression by activating the PI3K/Akt and extracellular signal-regulated kinase (ERK1)/2 pathways (Figure 2).[33] Moreover, insulin-like growth factor-1 (IGF-1) signalling can inhibit chondrocyte apoptosis by decreasing caspase-3 activity.[34] In addition, various cytokines released by chondrocytes have certain effects on osteoclasts. Changes in the biomechanical properties of joints reduce the expression of interleukin 1 beta (IL-1β) in primary chondrocytes.[35] IL-1β upregulates the expression of receptor activator of nuclear factor kappa-B ligand

(RANKL) in osteoblasts, causes osteoclast formation, and induces the formation of multinucleated osteoclasts (Figure 2).[36] High expression of tumour necrosis factor-α (TNF-α) and IL-6 in OA chondrocytes was detected in an OA model.[37] TNF-α leads to osteoclast differentiation by activating nuclear factor kappa B (NF-κB) in a RANKL-independent manner.[38] In addition, TNF-α can indirectly induce osteoclast formation by stimulating osteoblast expression of RANKL.[39] IL-6 indirectly induces osteoclast formation by activating the signalling factor gp130.[40] Furthermore, hypertrophic chondrocytes are associated with senescent chondrocytes and can produce catabolic enzymes and chemokines (collectively referred to as ageing-related secretory phenotypes) to adjust the behaviour of subchondral osteoclasts.[41,42]

Osteoblasts. Osteoblasts differentiate from mesenchymal cells and promote bone formation.[43,44] In OA, the activity of osteoblasts in SB is changed. Compared with normal osteoblasts, OA subchondral osteoblasts have increased levels of alkaline phosphatase activity, RANKL, osteocalcin (OCN), TGF-β1, IGF-1, and vascular endothelial growth factor (VEGF) release.[45-47] VEGF release was also shown to be driven by hypoxia in primary human OA osteoblasts, which indicates that the release of VEGF may not be just a characteristic manifestation of OA subchondral osteoblasts.[48] This increase in biological factors may lead to sclerosis, osteoclast formation, and angiogenesis.[49,50] There is growing evidence that the formation of unmineralized immature new bone may cause osteoids in SB (cortical plate level and trabecular bone level), which has an adverse effect on tissue properties.[51] For example, in OA-hardened subchondral cortical plates and bone trabeculae, osteoblasts have decreased mineralization abilities, which may be related to increased osteoblast production of type I collagen (Col I).[52] Chan et al[53] found that one of the molecular mechanisms for the decrease in SB mineralization ability was the increased expression of TGF-β in human OA subchondral osteoblasts, which may induce the expression of the mineralization inhibitor dickkopf-2 (DKK2). In addition, a significant decrease in some mineralized proteins in osteoblasts in sclerosing SB may lead to increased bone remodelling or abnormal bone matrix mineralization.[54] In addition, ECM is secreted by osteoblasts and has some effects on bone mineralization. For example, calcium, phosphate, magnesium ions, and TGF-β1 stored in ECM can regulate bone homeostasis during bone remodelling.[55,56]

Osteocytes. Osteocytes are cells in the mineralized bone matrix, accounting for 90% to 95% of all cells in adult bones; they play an important multifunctional role in regulating bone homeostasis.[57] In a recent genome-wide association study on osteocytes, new candidate loci related to OA were identified, suggesting that the expression of these genes in osteocytes may contribute to SB remodelling, which is important in the pathogenesis of OA.[58] Subchondral osteosclerosis is the main pathophysiological manifestation of advanced OA and can disrupt cartilage homeostasis in patients with OA.[59] Increases in bone mass, mineral density, and subchondral osteosclerosis have been reported in patients with OA, which may be due to a combination of repetitive microinjuries/fractures caused by mechanical load imbalance.[60] The hardened SB has several structural features, including increased bone volume and density, a thickened SB plate, increased trabecular thickness, and reduced trabecular separation.[7] Jaiprakash et al[61] found that these SB variations in OA were associated with the level of osteocyte markers. There was a decrease in sclerostin (SOST) and an increase in DMP1 expression in OA samples. Up until now, many scholars have studied the physiological effects of SOST.[62,63] For example, many scholars have shown that the loss of SOST expression can enhance osteogenesis (Figure 3).[62,64] Conversely, mice overexpressing SOST exhibit overall suppressed bone formation, resulting in notable reductions of bone mass and volume.[65-67] Mice overexpressing a transgene in which SOST is driven by the entire human SOST promoter (bacterial artificial chromosome (BAC)-SOST mice) also displayed reduced cancellous bone of the axial and appendicular skeleton due to reductions in bone formation.[67,68] In addition, some studies have shown that SOST reaches the bone surface through the lacunocanalicular network, where it inhibits classic Wnt/β-catenin (cWnt) signal transduction in osteoblasts, which is related to the regulation of bone mass.[69-71] Therefore, a decrease in the expression of SOST in OA osteocytes may be the reason for the increase in SB mass in OA. Contrary to the SOST level, an increased level of dentin matrix acidic phosphoprotein (DMP1) can lead to mineralization disorders and significantly delay osteoblast differentiation.[72] Therefore, the abnormal mineral metabolism in SB in OA may be related to high expression of DMP1 in these osteocytes.[73] In vivo results indicate that DMP1 is actively involved in bone dynamic balance, and mechanical loading can stimulate osteocytes to express DMP1.[74-76] The increased level of DMP1 in subchondral osteocytes in OA is harmful to the normal mineralization process of SB in OA, resulting in an increase in osteoid volume and irregular bone mineralization. Jaiprakash et al[61] observed that osteocytes (OA osteocyte phenotype) in OA SB were more round, rougher, and not arranged in any specific direction, but normal osteocytes showed uniformly arranged osteocytes. These results suggest that the irregular shape of osteocytes can promote OA, which may change the ability of bone to perceive mechanical stimuli, resulting in variations in mineral density.[77,78]

Osteocytes secrete not only SOST and DMP1, but also TGF-β1, RANKL, and TNF-α to regulate bone homeostasis in subchondral bone, thus affecting OA. For example, Dai et al[79] found that the TGF-β signal was activated in SB underneath the partial and full defect cartilage. Moreover, it has been found that loading can cause an increase in the anabolism of cortical bone, and that its mechanism is associated with the inhibition of the TGF-β-smad2/3 pathway in osteocytes.[80] Osteocytes are the main producers of RANKL.[81,82] Osteocyte apoptosis may indirectly stimulate osteoclastogenesis by inducing stromal/

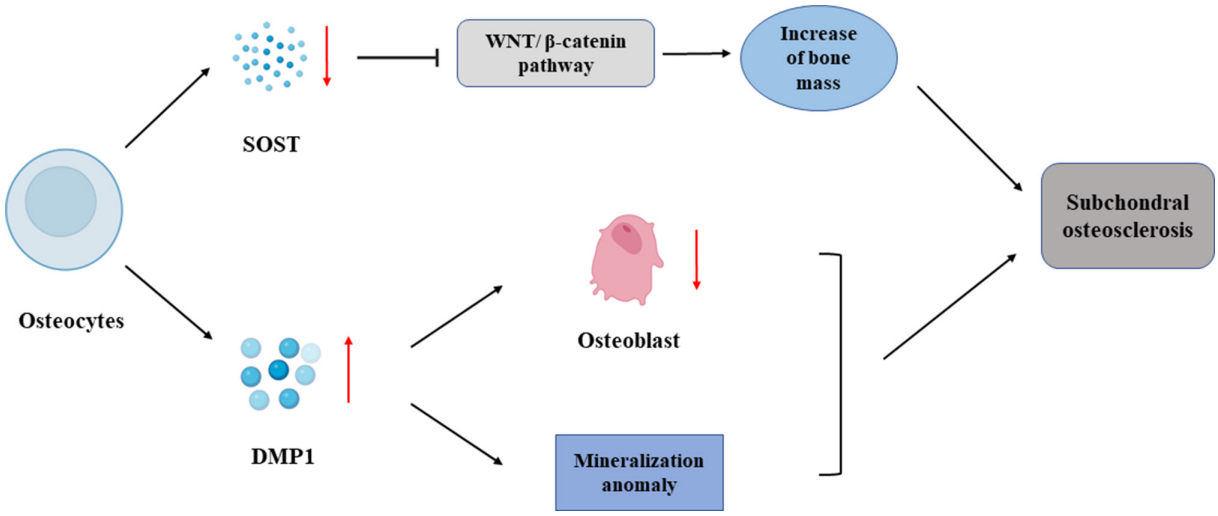

Fig. 3

The role of osteocytes in subchondral bone in osteoarthritis (OA). In OA, the expression of sclerostin (SOST) in subchondral bone decreased, while the expression of dentin matrix protein-1 (DMP1) increased. SOST reached the bone surface through the lacunocanalicular network, where it inhibits the classical Wnt/β-catenin signal transduction of osteoblasts and regulates bone mass. The increased expression of DMP1 can lead to mineralization disorder and significantly delay osteoblast differentiation.

osteoblastic cells to secrete RANKL.[82] In addition, RANKL secreted by osteocytes can induce osteoclast recruitment and differentiation to regulate chondrocytes indirectly.[83] A previous study showed that osteocytes express tumour necrosis factor receptor 1 (TNFR1) and TNFR2, and TNF-α enhances RANKL expression in osteocytes directly and induces osteoclast formation both in vitro and in vivo.[84]

Signalling pathways in subchondral bone remodelling

Signal transduction mechanisms in subchondral bone are necessary to maintain the balance between a stable phenotype, ECM synthesis, and bone remodelling in articular cartilage and SB.[85] An imbalance in signal transduction can lead to reduced cartilage quality and SB thickening, which leads to the progression of OA.[86]

WNT signalling pathway. WNT is an extracellular glycoprotein whose signal transduction involves different Wnt receptors that regulate β-catenin-dependent and non-canonical β-catenin-dependent pathways.[87] It has been reported that WNT signal transduction is a key factor in cartilage, bone, and joint development.[88] Moreover, the WNT pathway is important in bone pattern shaping.[89] Typical WNT signal transduction is necessary to maintain mature articular cartilage, which is characterized by prolonged cell survival and no hypertrophic differentiation.[90] In addition to cartilage formation, WNT signal transduction is important for bone development. High levels of WNT signal transduction can induce osteosclerosis.[91] Wnt signalling is activated by reducing the Wnt antagonist β-catenin, resulting in bone formation and in thicker and harder bone.[90,92,93] Wu et al[94] evaluated the effect of Wnt inhibitors on OA in subchondral osteoblasts. Quantitative real-time polymerase chain reaction (qRT–PCR) analysis of β-catenin and transcription factor 4 (TCF-4) showed that their levels increased in the late stages of OA, while the level of sclerosin was lower than that in early OA samples. In osteoblasts, lower expression of the Wnt agonist R-spondin-2 gene was related to the increase in sclerosin levels.[64,95] In addition, osteocytes communicate through Wnt signals and play a role in synthesis and metabolism through osteoblast-mediated osteogenesis.[96-99] DKK-1-mediated Wnt signal inactivation downregulates VEGF expression, resulting in reduced SB growth, osteoblast inactivation, and osteophyte formation.[100] As a non-classical activator of the Wnt pathway, Wnt5a expression is increased fivefold in OA osteoblasts.[101] Additionally, in bone remodelling in SB, osteoblasts and osteoclasts, which are the main cells associated with bone remodelling, are regulated by Wnt5a.[102] For example, poor bone quality and formation were observed in Wnt5a-knockout mice.[103] Compared with normal osteoblasts, osteoblasts harvested from OA joints showed irregular Wnt5a ligand expression, increased alkaline phosphatase (ALP) activity, and OCN release. Inhibiting Wnt5a expression could correct the abnormal ALP activity of OA osteoblasts to some extent.[101] This evidence suggests that Wnt5a signal transduction may cause an imbalance in osteoblasts and osteoclasts, which increases SB remodelling and participates in excessive mineralization and formation.

TGF-β/BMP signalling pathway. The TGF-β superfamily includes approximately 40 members, such as TGF-β, nodal proteins, activin, and bone morphogenetic protein (BMP).[104] TGF-β/BMP is important in bone formation and has a variety of functions in vivo.[105] Zhen et al[56] found higher levels of TGF-β in the SB of OA mice and human knee OA models than in healthy controls. The increased expression of TGF-β in SB caused OA-like symptoms in rats: a reduced level of proteoglycan, increased fractions and numbers of blood vessels in SBP, and increased bone

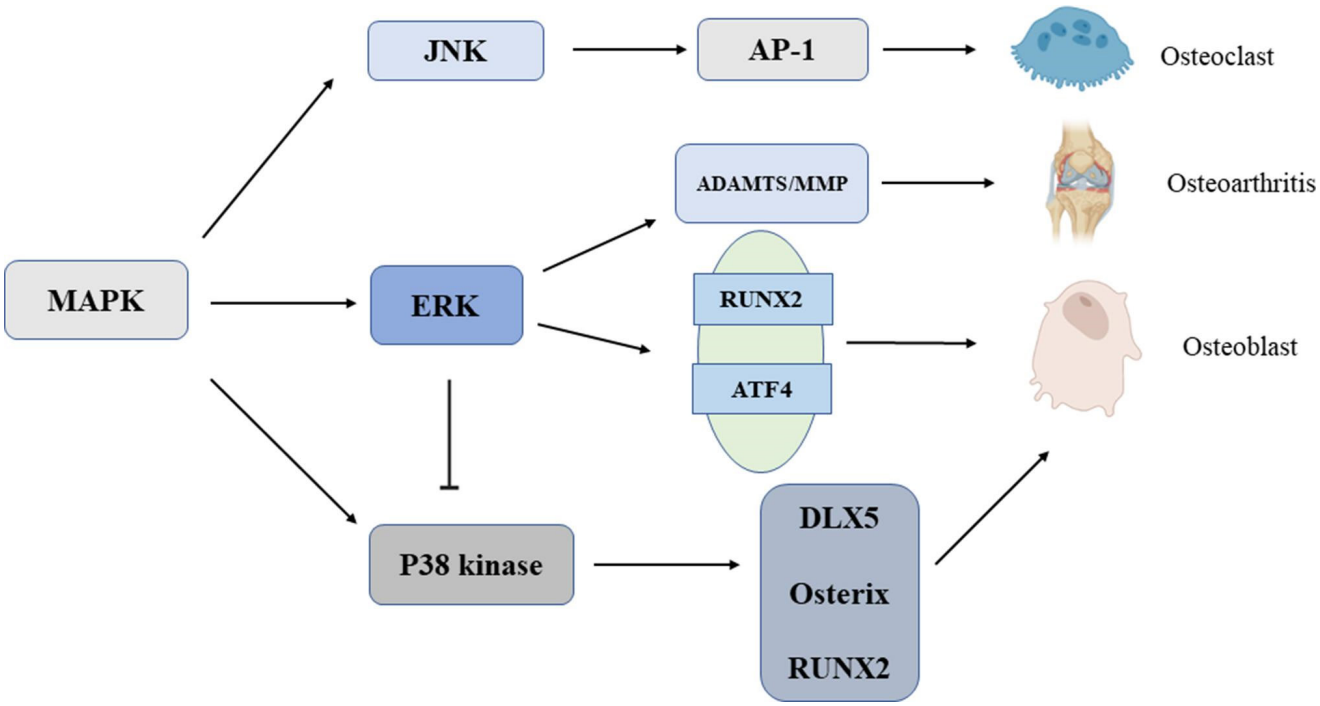

Fig. 4

Mitogen-activated protein kinase (MAPK) signal pathway in subchondral bone. The MAPK family consists of three kinases: extracellular signal-regulated kinase (ERK), stress-activated protein kinase/c-Jun N-terminal kinase (JNK), and p38 kinase. ERK signal transduction mediates the early and late differentiation of osteoblasts by phosphorylating key transcription factors (such as runt-related transcription factor 2 (RUNX2)) and activating transcription factor 4 (ATF4). Moreover, p38 signal transduction can also promote osteoblast differentiation through phosphorylation of distal-less homeo box 5 (DLX5), Osterix, and RUNX2. ERK, p38, and JNK all promote osteoclast differentiation by regulating activating protein 1 (AP-1) as a key medium for osteoclast formation. In addition, the upregulation of a disintegrin-like and metalloproteinase with thrombospondin (ADAMTS) and matrix metalloproteinases (MMPs) mediated by the activation of ERK signalling pathway plays an important role in the early development of osteoarthritis.

mesenchymal stem cells in SB marrow, which promoted new bone formation in SB.[56] Inhibiting TGF-β1 restored the microstructure of SB by preventing angiogenesis, reducing the number of MSCs undergoing osteogenesis, reducing proteoglycan loss, and increasing bone calcification.[56] In OA, the SBP was significantly thicker than that in healthy subjects. The coordinated regulation of sclerosin and SBP is important in joint homeostasis.[106,107] Because the expression of sclerosin is induced by TGF-β,[80,108] and suppressed in the presence of load,[109] TGF-β is important in regulating the thickness of the SBP. A previous study showed that canonical activation of WNT signals can induce WNT1-inducible-signalling pathway protein 1 (WISP-1) secretion in human OA cartilage.[110] WISP-1 has been shown to have osteogenic effects by promoting osteoblast differentiation.[111] As observed in OA, the secretion of WISP-1 may exert osteogenic effects on SB. In addition, WISP-1 can regulate TGF-β signal transduction by inhibiting Smad2.[111] Therefore, the interaction between TGF-β and the WISP-1 signalling pathway may directly determine the response of cartilage and SB in OA.

MAPK signalling pathway. Mitogen-activated protein kinases (MAPKs) are a group of serine/threonine kinases that are present in all eukaryotes and respond to multiple stimuli. The MAPK family includes three major kinases: ERK, JNK, and p38 kinase (Figure 4).[112] In bone biology, MAPKs have been shown to play important roles in adjusting bone mass by controlling the differentiation of osteoblasts and osteoclasts.[113,114] ERK, p38, and JNK can accelerate osteoclast differentiation by altering activating protein 1 (AP-1), a key mediator of osteoclast formation. ERK signal transduction mediates the different stages of osteoblast differentiation by phosphorylating key transcription factors (such as runt-related transcription factor 2 (RUNX2)) and activating transcription factor 4 (ATF4).[115] Similarly, p38 signal transduction promotes osteoblast differentiation based on the phosphorylation of distal-less homeobox 5 (DLX5) and RUNX2.[116] Recently, the MAPK family was thought to be related to the pathophysiology of OA. Mechanical strain induction can produce MMP-13 via the activation of ERK in osteoblasts.[117] In response to mechanical strain, osteoblasts in subchondral bone begin to produce MMP-13, which can stimulate cartilage degeneration. Moreover, OA articular chondrocytes have a significant effect on subchondral osteoblasts, and this effect is mainly mediated by ERK activation.[118] An experimental study showed that OA subchondral osteoblasts have a certain regulatory effect on p38 signal activity in articular cartilage, and can regulate the expression levels of proliferative genes. This regulatory effect is mainly mediated by ERK signalling.[119] The abnormal secretion of ADAMTS and MMPs in joints plays a key role in the early

progression of OA. The upregulation of ADAMTS and MMPs is mediated by the activated ERK pathway in corresponding cells. In affected articular chondrocytes, the overexpression of MMPs in the coculture system could be reversed by inhibiting the ERK signal pathway with PD98059.[119] Moreover, soluble factors released from SB mediate the release of MMPs in normal SB by activating the ERK signalling pathway.[120] Activation of protease-activated receptor (PAR-2) in OA chondrocytes and cartilage can affect SB resorption by enhancing the levels of MMP-1, MMP-9, and IL-6.[121] Its effect is mediated by ERK and p38 signalling activity, and adjusting the level of PAR-2 can alleviate the symptoms of OA, which suggests a promising target for OA therapy.

Treatments for the changes in subchondral bone in OA

In addition to well-known conventional drugs for OA therapy,[122,123] some drugs that regulate changes in SB have recently become the focus of researchers.[124] For example, the efficacy of anti-reabsorption agents in OA therapy has been assessed by restoring abnormal SB remodelling. Some scholars have found that bisphosphonates may play a key role in OA mainly through their role in SB.[125] Patients with significant cartilage loss retained vertical trabecular structure after treatment with risedronate (RIS).[126] However, at present, clinical researchers have not recommended bisphosphate as a drug for the treatment of OA.[127] In addition, there is no unified standard for the dose and administration mode of bisphosphate in the treatment of OA. Therefore, whether bisphosphate should be used as a drug for the treatment of OA needs further evaluation. In animal models, there are other inhibitors of bone absorption (cathepsin K inhibitor and strontium ranelate) that may protect SB and cartilage, and can be used as clinical drugs for OA therapy.[128-130]

Increased osteoclast activity leads to excessive activation of TGF-β1 signalling in SB, and so subchondral TGF-β1 may be a therapeutic target for OA.[56] In addition, blocking H-type angiogenesis in an animal model of OA could inhibit cartilage destruction and SB loss.[131] For instance, bevacizumab (a vascular endothelial growth factor blocking antibody) can reduce subchondral H-vessel formation levels in OA models and delay the progression of OA.[132] In addition to drug-mediated inhibition of VEGF, factors secreted by osteoclasts or osteoblasts in the SB microenvironment of OA, such as TGF-β1, platelet-derived growth factor-BB, and sLIT3, can exert positive effects on subchondral angiogenesis. Therefore, antagonists of these molecules may be potential drugs for the treatment of OA.[133] For instance, Cui et al[133] found that halofuginone alleviates OA by inhibiting the activity of TGF-β and H-type angiogenesis in SB. In addition, baicalein alleviates OA by protecting SB and inhibiting angiogenesis and synovial proliferation.[134] Dihydroartemisinin reduces the inhibitory effect of scleroprotein by reducing leukaemia inhibitory factor secretion by osteoclasts, thus reducing abnormal bone remodelling, inhibiting SB angiogenesis, and further slowing the progression of OA.[135] Production of nerve growth factor (NGF) by osteoclast precursors is a key driver of subchondral innervation during the development of OA.[136] There is evidence that the small molecular coupling of the TGF-β receptor inhibitor TLY-2109761 can significantly reduce the excessive production of prostaglandin E2 (PGE2) by osteoblasts and relieve pain in OA mice by restoring abnormal bone remodelling.[137] Moreover, diacetate and emodin may regulate the abnormal metabolism of subchondral osteoblasts in OA by increasing the level of β-catenin in subchondral osteoblasts by reducing DKK-1 and DKK-2 levels, which has a positive effect on the abnormal Wnt system in OA.[138] Some scholars have reported the positive effects of resveratrol on osteoblasts in OA SB by inhibiting the cWnt pathway. Abed et al[46] noted that resveratrol could promote the expression of β-catenin in SB and may activate cWnt signal transduction, which may play a beneficial role in SB changes in OA.

In conclusion, SB changes are an important part of the occurrence and development of OA. Cells and signal transduction in SB are necessary for the stability of articular cartilage and SB, and for the balance of bone remodelling. There is clear evidence that OA induces changes in bone homeostasis of the SB, tipping it to an increase in bone remodelling that results in osteosclerosis and some bone lesions. This change in bone homeostasis can in turn lead to a worsening of the disease by further inducing cartilage damage, inflammation, pain, etc. Thus, controlling SB homeostasis could be a possible target in OA.

References

1. **Glyn-Jones S**, **Palmer AJR**, **Agricola R**, **et al**. Osteoarthritis. *Lancet*. 2015;386(9991):376–387.
2. **Martel-Pelletier J**, **Barr AJ**, **Cicuttini FM**, **et al**. Osteoarthritis. *Nat Rev Dis Primers*. 2016;2:16072.
3. **Mandl LA**. Osteoarthritis year in review 2018: clinical. *Osteoarthritis Cartilage*. 2019;27(3):359–364.
4. **Boer CG**, **Hatzikotoulas K**, **Southam L**, **et al**. Deciphering osteoarthritis genetics across 826,690 individuals from 9 populations. *Cell*. 2021;184(24):6003–6005.
5. **Felson DT**, **Anderson JJ**, **Meenan RF**. The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. Results of two metaanalyses. *Arthritis Rheum*. 1990;33(10):1449–1461.
6. **Prieto-Alhambra D**, **Judge A**, **Javaid MK**, **Cooper C**, **Diez-Perez A**, **Arden NK**. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. *Ann Rheum Dis*. 2014;73(9):1659–1664.
7. **Li G**, **Yin J**, **Gao J**, **et al**. Subchondral bone in osteoarthritis: insight into risk factors and microstructural changes. *Arthritis Res Ther*. 2013;15(6):223.
8. **Suri S**, **Walsh DA**. Osteochondral alterations in osteoarthritis. *Bone*. 2012;51(2):204–211.
9. **Kwan Tat S**, **Lajeunesse D**, **Pelletier JP**, **Martel-Pelletier J**. Targeting subchondral bone for treating osteoarthritis: what is the evidence? *Best Pract Res Clin Rheumatol*. 2010;24(1):51–70.
10. **Karsdal MA**, **Leeming DJ**, **Dam EB**, **et al**. Should subchondral bone turnover be targeted when treating osteoarthritis? *Osteoarthritis Cartilage*. 2008;16(6):638–646.
11. **Ansboro S**, **Greiser U**, **Barry F**, **Murphy M**. Strategies for improved targeting of therapeutic cells: implications for tissue repair. *Eur Cell Mater*. 2012;23:310–318.
12. **Goldring SR**, **Goldring MB**. Changes in the osteochondral unit during osteoarthritis: structure, function and cartilage-bone crosstalk. *Nat Rev Rheumatol*. 2016;12(11):632–644.

13. **Goldring MB**, **Goldring SR**. Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis. *Ann N Y Acad Sci*. 2010;1192:230–237.
14. **Imhof H**, **Sulzbacher I**, **Grampp S**, **Czerny C**, **Youssefzadeh S**, **Kainberger F**. Subchondral bone and cartilage disease: a rediscovered functional unit. *Invest Radiol*. 2000;35(10):581–588.
15. **Kon E**, **Ronga M**, **Filardo G**, **et al**. Bone marrow lesions and subchondral bone pathology of the knee. *Knee Surg Sports Traumatol Arthrosc*. 2016;24(6):1797–1814.
16. **Sun Q**, **Li G**, **Liu D**, **et al**. Peripheral nerves in the tibial subchondral bone: the role of pain and homeostasis in osteoarthritis. *Bone Joint Res*. 2022;11(7):439–452.
17. **Gomoll AH**, **Madry H**, **Knutsen G**, **et al**. The subchondral bone in articular cartilage repair: current problems in the surgical management. *Knee Surg Sports Traumatol Arthrosc*. 2010;18(4):434–447.
18. **Castañeda S**, **Roman-Blas JA**, **Largo R**, **Herrero-Beaumont G**. Subchondral bone as a key target for osteoarthritis treatment. *Biochem Pharmacol*. 2012;83(3):315–323.
19. **Beverly MC**, **Murray DW**. Subchondral physiology and vasculo-mechanical factors in load transmission and osteoarthritis. *Bone Joint Res*. 2021;10(9):571–573.
20. **Zhou J**, **He Z**, **Cui J**, **et al**. Identification of mechanics-responsive osteocyte signature in osteoarthritis subchondral bone. *Bone Joint Res*. 2022;11(6):362–370.
21. **Holopainen JT**, **Brama PAJ**, **Halmesmäki E**, **et al**. Changes in subchondral bone mineral density and collagen matrix organization in growing horses. *Bone*. 2008;43(6):1108–1114.
22. **Goldring SR**. Alterations in periarticular bone and cross talk between subchondral bone and articular cartilage in osteoarthritis. *Ther Adv Musculoskelet Dis*. 2012;4(4):249–258.
23. **Feng X**, **McDonald JM**. Disorders of bone remodeling. *Annu Rev Pathol*. 2011;6:121–145.
24. **Klose-Jensen R**, **Hartlev LB**, **Boel LWT**, **et al**. Subchondral bone turnover, but not bone volume, is increased in early stage osteoarthritic lesions in the human hip joint. *Osteoarthritis Cartilage*. 2015;23(12):2167–2173.
25. **Bobinac D**, **Marinovic M**, **Bazdulj E**, **et al**. Microstructural alterations of femoral head articular cartilage and subchondral bone in osteoarthritis and osteoporosis. *Osteoarthritis Cartilage*. 2013;21(11):1724–1730.
26. **Botter SM**, **van Osch GJVM**, **Clockaerts S**, **Waarsing JH**, **Weinans H**, **van Leeuwen JPTM**. Osteoarthritis induction leads to early and temporal subchondral plate porosity in the tibial plateau of mice: an in vivo microfocal computed tomography study. *Arthritis Rheum*. 2011;63(9):2690–2699.
27. **Teitelbaum SL**. Bone resorption by osteoclasts. *Science*. 2000;289(5484):1504–1508.
28. **Tonna S**, **Poulton IJ**, **Taykar F**, **et al**. Correction: Chondrocytic ephrin B2 promotes cartilage destruction by osteoclasts in endochondral ossification. *Development*. 2017;144(3):530.
29. **Wang B**, **Jin H**, **Shu B**, **Mira RR**, **Chen D**. Chondrocytes-specific expression of osteoprotegerin modulates osteoclast formation in metaphyseal bone. *Sci Rep*. 2015;5:13667.
30. **Löfvall H**, **Newbould H**, **Karsdal MA**, **et al**. Osteoclasts degrade bone and cartilage knee joint compartments through different resorption processes. *Arthritis Res Ther*. 2018;20(1):67.
31. **Croucher PI**, **McDonald MM**, **Martin TJ**. Bone metastasis: the importance of the neighbourhood. *Nat Rev Cancer*. 2016;16(6):373–386.
32. **Zhang R-K**, **Li G-W**, **Zeng C**, **et al**. Mechanical stress contributes to osteoarthritis development through the activation of transforming growth factor beta 1 (TGF-β1). *Bone Joint Res*. 2018;7(11):587–594.
33. **Zhang M**, **Zhou Q**, **Liang Q-Q**, **et al**. IGF-1 regulation of type II collagen and MMP-13 expression in rat endplate chondrocytes via distinct signaling pathways. *Osteoarthritis Cartilage*. 2009;17(1):100–106.
34. **Párrizas M**, **Saltiel AR**, **LeRoith D**. Insulin-like growth factor 1 inhibits apoptosis using the phosphatidylinositol 3′-kinase and mitogen-activated protein kinase pathways. *J Biol Chem*. 1997;272(1):154–161.
35. **Fujisawa T**, **Hattori T**, **Takahashi K**, **Kuboki T**, **Yamashita A**, **Takigawa M**. Cyclic mechanical stress induces extracellular matrix degradation in cultured chondrocytes via gene expression of matrix metalloproteinases and interleukin-1. *J Biochem*. 1999;125(5):966–975.
36. **Cao Y**, **Jansen IDC**, **Sprangers S**, **et al**. IL-1β differently stimulates proliferation and multinucleation of distinct mouse bone marrow osteoclast precursor subsets. *J Leukoc Biol*. 2016;100(3):513–523.
37. **Pearson MJ**, **Herndler-Brandstetter D**, **Tariq MA**, **et al**. IL-6 secretion in osteoarthritis patients is mediated by chondrocyte-synovial fibroblast cross-talk and is enhanced by obesity. *Sci Rep*. 2017;7(1):3451.
38. **Kobayashi K**, **Takahashi N**, **Jimi E**, **et al**. Tumor necrosis factor alpha stimulates osteoclast differentiation by a mechanism independent of the ODF/RANKL-RANK interaction. *J Exp Med*. 2000;191(2):275–286.
39. **Lam J**, **Takeshita S**, **Barker JE**, **Kanagawa O**, **Ross FP**, **Teitelbaum SL**. TNF-alpha induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. *J Clin Invest*. 2000;106(12):1481–1488.
40. **Kudo O**, **Sabokbar A**, **Pocock A**, **Itonaga I**, **Fujikawa Y**, **Athanasou NA**. Interleukin-6 and interleukin-11 support human osteoclast formation by a RANKL-independent mechanism. *Bone*. 2003;32(1):1–7.
41. **Engsig MT**, **Chen QJ**, **Vu TH**, **et al**. Matrix metalloproteinase 9 and vascular endothelial growth factor are essential for osteoclast recruitment into developing long bones. *J Cell Biol*. 2000;151(4):879–889.
42. **Rim YA**, **Nam Y**, **Ju JH**. The role of chondrocyte hypertrophy and senescence in osteoarthritis initiation and progression. *Int J Mol Sci*. 2020;21(7):2358.
43. **Ali E**, **Birch M**, **Hopper N**, **Rushton N**, **McCaskie AW**, **Brooks RA**. Human osteoblasts obtained from distinct periarticular sites demonstrate differences in biological function in vitro. *Bone Joint Res*. 2021;10(9):611–618.
44. **Clarke B**. Normal bone anatomy and physiology. *Clin J Am Soc Nephrol*. 2008;3 Suppl 3(Suppl 3):S131–9.
45. **Kwan Tat S**, **Pelletier JP**, **Lajeunesse D**, **Fahmi H**, **Lavigne M**, **Martel-Pelletier J**. The differential expression of osteoprotegerin (OPG) and receptor activator of nuclear factor kappaB ligand (RANKL) in human osteoarthritic subchondral bone osteoblasts is an indicator of the metabolic state of these disease cells. *Clin Exp Rheumatol*. 2008;26(2):295–304.
46. **Abed É**, **Delalandre A**, **Lajeunesse D**. Beneficial effect of resveratrol on phenotypic features and activity of osteoarthritic osteoblasts. *Arthritis Res Ther*. 2017;19(1):151.
47. **Corrado A**, **Neve A**, **Cantatore FP**. Expression of vascular endothelial growth factor in normal, osteoarthritic and osteoporotic osteoblasts. *Clin Exp Med*. 2013;13(1):81–84.
48. **Bouvard B**, **Abed E**, **Yéléhé-Okouma M**, **et al**. Hypoxia and vitamin D differently contribute to leptin and dickkopf-related protein 2 production in human osteoarthritic subchondral bone osteoblasts. *Arthritis Res Ther*. 2014;16(5):459.
49. **Wang T**, **Wen CY**, **Yan CH**, **Lu WW**, **Chiu KY**. Spatial and temporal changes of subchondral bone proceed to microscopic articular cartilage degeneration in guinea pigs with spontaneous osteoarthritis. *Osteoarthritis Cartilage*. 2013;21(4):574–581.
50. **Truong L-H**, **Kuliwaba JS**, **Tsangari H**, **Fazzalari NL**. Differential gene expression of bone anabolic factors and trabecular bone architectural changes in the proximal femoral shaft of primary hip osteoarthritis patients. *Arthritis Res Ther*. 2006;8(6):R188.
51. **Day JS**, **Ding M**, **van der Linden JC**, **Hvid I**, **Sumner DR**, **Weinans H**. A decreased subchondral trabecular bone tissue elastic modulus is associated with pre-arthritic cartilage damage. *J Orthop Res*. 2001;19(5):914–918.
52. **Couchourel D**, **Aubry I**, **Delalandre A**, **et al**. Altered mineralization of human osteoarthritic osteoblasts is attributable to abnormal type I collagen production. *Arthritis Rheum*. 2009;60(5):1438–1450.
53. **Chan TF**, **Couchourel D**, **Abed E**, **Delalandre A**, **Duval N**, **Lajeunesse D**. Elevated Dickkopf-2 levels contribute to the abnormal phenotype of human osteoarthritic osteoblasts. *J Bone Miner Res*. 2011;26(7):1399–1410.
54. **Sanchez C**, **Mazzucchelli G**, **Lambert C**, **Comblain F**, **DePauw E**, **Henrotin Y**. Comparison of secretome from osteoblasts derived from sclerotic versus non-sclerotic subchondral bone in OA: A pilot study. *PLoS One*. 2018;13(3):e0194591.
55. **Allori AC**, **Sailon AM**, **Warren SM**. Biological basis of bone formation, remodeling, and repair-part II: extracellular matrix. *Tissue Eng Part B Rev*. 2008;14(3):275–283.
56. **Zhen G**, **Wen C**, **Jia X**, **et al**. Inhibition of TGF-β signaling in mesenchymal stem cells of subchondral bone attenuates osteoarthritis. *Nat Med*. 2013;19(6):704–712.
57. **Bonewald LF**. The amazing osteocyte. *J Bone Miner Res*. 2011;26(2):229–238.
58. **Youlten SE**, **Kemp JP**, **Logan JG**, **et al**. Osteocyte transcriptome mapping identifies a molecular landscape controlling skeletal homeostasis and susceptibility to skeletal disease. *Nat Commun*. 2021;12(1):2444.
59. **Hilal G**, **Martel-Pelletier J**, **Pelletier JP**, **Ranger P**, **Lajeunesse D**. Osteoblast-like cells from human subchondral osteoarthritic bone demonstrate an altered phenotype in vitro: possible role in subchondral bone sclerosis. *Arthritis Rheum*. 1998;41(5):891–899.
60. **Burr DB**, **Radin EL**. Microfractures and microcracks in subchondral bone: are they relevant to osteoarthrosis? *Rheum Dis Clin North Am*. 2003;29(4):675–685.
61. **Jaiprakash A**, **Prasadam I**, **Feng JQ**, **Liu Y**, **Crawford R**, **Xiao Y**. Phenotypic characterization of osteoarthritic osteocytes from the sclerotic zones: a possible pathological role in subchondral bone sclerosis. *Int J Biol Sci*. 2012;8(3):406–417.

62. **Poole KES**, **van Bezooijen RL**, **Loveridge N**, **et al**. Sclerostin is a delayed secreted product of osteocytes that inhibits bone formation. *FASEB J*. 2005;19(13):1842–1844.
63. **Delgado-Calle J**, **Sato AY**, **Bellido T**. Role and mechanism of action of sclerostin in bone. *Bone*. 2017;96:29–37.
64. **Abed É**, **Couchourel D**, **Delalandre A**, **et al**. Low sirtuin 1 levels in human osteoarthritis subchondral osteoblasts lead to abnormal sclerostin expression which decreases Wnt/β-catenin activity. *Bone*. 2014;59:28–36.
65. **Rhee Y**, **Allen MR**, **Condon K**, **et al**. PTH receptor signaling in osteocytes governs periosteal bone formation and intracortical remodeling. *J Bone Miner Res*. 2011;26(5):1035–1046.
66. **Loots GG**, **Kneissel M**, **Keller H**, **et al**. Genomic deletion of a long-range bone enhancer misregulates sclerostin in Van Buchem disease. *Genome Res*. 2005;15(7):928–935.
67. **Winkler DG**, **Sutherland MK**, **Geoghegan JC**, **et al**. Osteocyte control of bone formation via sclerostin, a novel BMP antagonist. *EMBO J*. 2003;22(23):6267–6276.
68. **Kramer I**, **Loots GG**, **Studer A**, **Keller H**, **Kneissel M**. Parathyroid hormone (PTH)-induced bone gain is blunted in SOST overexpressing and deficient mice. *J Bone Miner Res*. 2010;25(2):178–189.
69. **Li X**, **Zhang Y**, **Kang H**, **et al**. Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling. *J Biol Chem*. 2005;280(20):19883–19887.
70. **van Bezooijen RL**, **Roelen BAJ**, **Visser A**, **et al**. Sclerostin is an osteocyte-expressed negative regulator of bone formation, but not a classical BMP antagonist. *J Exp Med*. 2004;199(6):805–814.
71. **Sutherland MK**, **Geoghegan JC**, **Yu C**, **et al**. Sclerostin promotes the apoptosis of human osteoblastic cells: a novel regulation of bone formation. *Bone*. 2004;35(4):828–835.
72. **George A**, **Ramachandran A**, **Albazzaz M**, **Ravindran S**. DMP1--A key regulator in mineralized matrix formation. *J Musculoskelet Neuronal Interact*. 2007;7(4):308.
73. **Lu Y**, **Yuan B**, **Qin C**, **et al**. The biological function of DMP-1 in osteocyte maturation is mediated by its 57-kDa C-terminal fragment. *J Bone Miner Res*. 2011;26(2):331–340.
74. **Gluhak-Heinrich J**, **Ye L**, **Bonewald LF**, **et al**. Mechanical loading stimulates dentin matrix protein 1 (DMP1) expression in osteocytes in vivo. *J Bone Miner Res*. 2003;18(5):807–817.
75. **Feng JQ**, **Ward LM**, **Liu S**, **et al**. Loss of DMP1 causes rickets and osteomalacia and identifies a role for osteocytes in mineral metabolism. *Nat Genet*. 2006;38(11):1310–1315.
76. **Feng JQ**, **Huang H**, **Lu Y**, **et al**. The Dentin matrix protein 1 (Dmp1) is specifically expressed in mineralized, but not soft, tissues during development. *J Dent Res*. 2003;82(10):776–780.
77. **Burra S**, **Nicolella DP**, **Francis WL**, **et al**. Dendritic processes of osteocytes are mechanotransducers that induce the opening of hemichannels. *Proc Natl Acad Sci U S A*. 2010;107(31):13648–13653.
78. **Rubin C**, **Judex S**, **Hadjiargyrou M**. Skeletal adaptation to mechanical stimuli in the absence of formation or resorption of bone. *J Musculoskelet Neuronal Interact*. 2002;2(3):264–267.
79. **Dai G**, **Xiao H**, **Liao J**, **et al**. Osteocyte TGFβ1-Smad2/3 is positively associated with bone turnover parameters in subchondral bone of advanced osteoarthritis. *Int J Mol Med*. 2020;46(1):167–178.
80. **Nguyen J**, **Tang SY**, **Nguyen D**, **Alliston T**. Load regulates bone formation and Sclerostin expression through a TGFβ-dependent mechanism. *PLoS One*. 2013;8(1):e53813.
81. **Nakashima T**, **Hayashi M**, **Fukunaga T**, **et al**. Evidence for osteocyte regulation of bone homeostasis through RANKL expression. *Nat Med*. 2011;17(10):1231–1234.
82. **Bellido T**. Osteocyte-driven bone remodeling. *Calcif Tissue Int*. 2014;94(1):25–34.
83. **Cabahug-Zuckerman P**, **Frikha-Benayed D**, **Majeska RJ**, **et al**. Osteocyte apoptosis caused by hindlimb unloading is required to trigger osteocyte RANKL production and subsequent resorption of cortical and trabecular bone in mice femurs. *J Bone Miner Res*. 2016;31(7):1356–1365.
84. **Marahleh A**, **Kitaura H**, **Ohori F**, **et al**. TNF-α directly enhances osteocyte RANKL expression and promotes osteoclast formation. *Front Immunol*. 2019;10:2925.
85. **Lories RJ**, **Luyten FP**. The bone-cartilage unit in osteoarthritis. *Nat Rev Rheumatol*. 2011;7(1):43–49.
86. **Kovács B**, **Vajda E**, **Nagy EE**. Regulatory effects and interactions of the Wnt and OPG-RANKL-RANK signaling at the bone-cartilage interface in osteoarthritis. *Int J Mol Sci*. 2019;20(18):4653.
87. **Russell JO**, **Monga SP**. Wnt/β-catenin signaling in liver development, homeostasis, and pathobiology. *Annu Rev Pathol*. 2018;13:351–378.
88. **Lodewyckx L**, **Lories RJU**. WNT Signaling in osteoarthritis and osteoporosis: what is the biological significance for the clinician? *Curr Rheumatol Rep*. 2009;11(1):23–30.
89. **Hall CL**, **Kang S**, **MacDougald OA**, **Keller ET**. Role of Wnts in prostate cancer bone metastases. *J Cell Biochem*. 2006;97(4):661–672.
90. **Zhu M**, **Tang D**, **Wu Q**, **et al**. Activation of beta-catenin signaling in articular chondrocytes leads to osteoarthritis-like phenotype in adult beta-catenin conditional activation mice. *J Bone Miner Res*. 2009;24(1):12–21.
91. **Jenkins ZA**, **van Kogelenberg M**, **Morgan T**, **et al**. Germline mutations in WTX cause a sclerosing skeletal dysplasia but do not predispose to tumorigenesis. *Nat Genet*. 2009;41(1):95–100.
92. **Lodewyckx L**, **Luyten FP**, **Lories RJ**. Genetic deletion of low-density lipoprotein receptor-related protein 5 increases cartilage degradation in instability-induced osteoarthritis. *Rheumatology (Oxford)*. 2012;51(11):1973–1978.
93. **Lories RJU**, **Peeters J**, **Bakker A**, **et al**. Articular cartilage and biomechanical properties of the long bones in Frzb-knockout mice. *Arthritis Rheum*. 2007;56(12):4095–4103.
94. **Wu L**, **Guo H**, **Sun K**, **Zhao X**, **Ma T**, **Jin Q**. Sclerostin expression in the subchondral bone of patients with knee osteoarthritis. *Int J Mol Med*. 2016;38(5):1395–1402.
95. **Abed É**, **Chan TF**, **Delalandre A**, **Martel-Pelletier J**, **Pelletier JP**, **Lajeunesse D**. R-spondins are newly recognized players in osteoarthritis that regulate Wnt signaling in osteoblasts. *Arthritis Rheum*. 2011;63(12):3865–3875.
96. **Goldring SR**. The osteocyte: key player in regulating bone turnover. *RMD Open*. 2015;1(Suppl 1):e000049.
97. **Tu X**, **Delgado-Calle J**, **Condon KW**, **et al**. Osteocytes mediate the anabolic actions of canonical Wnt/β-catenin signaling in bone. *Proc Natl Acad Sci U S A*. 2015;112(5):E478–86.
98. **Duan P**, **Bonewald LF**. The role of the wnt/β-catenin signaling pathway in formation and maintenance of bone and teeth. *Int J Biochem Cell Biol*. 2016;77(Pt A):23–29.
99. **Joeng KS**, **Lee Y-C**, **Lim J**, **et al**. Osteocyte-specific WNT1 regulates osteoblast function during bone homeostasis. *J Clin Invest*. 2017;127(7):2678–2688.
100. **Funck-Brentano T**, **Bouaziz W**, **Marty C**, **Geoffroy V**, **Hay E**, **Cohen-Solal M**. Dkk-1-mediated inhibition of Wnt signaling in bone ameliorates osteoarthritis in mice. *Arthritis Rheumatol*. 2014;66(11):3028–3039.
101. **Martineau X**, **Abed É**, **Martel-Pelletier J**, **Pelletier J-P**, **Lajeunesse D**. Alteration of Wnt5a expression and of the non-canonical Wnt/PCP and Wnt/PKC-Ca2+ pathways in human osteoarthritis osteoblasts. *PLoS One*. 2017;12(8):e0180711.
102. **Kobayashi Y**, **Uehara S**, **Udagawa N**, **Takahashi N**. Regulation of bone metabolism by Wnt signals. *J Biochem*. 2016;159(4):387–392.
103. **Maeda K**, **Kobayashi Y**, **Udagawa N**, **et al**. Wnt5a-Ror2 signaling between osteoblast-lineage cells and osteoclast precursors enhances osteoclastogenesis. *Nat Med*. 2012;18(3):405–412.
104. **Guo X**, **Wang XF**. Signaling cross-talk between TGF-beta/BMP and other pathways. *Cell Res*. 2009;19(1):71–88.
105. **Katagiri T**, **Takahashi N**. Regulatory mechanisms of osteoblast and osteoclast differentiation. *Oral Dis*. 2002;8(3):147–159.
106. **Jia H**, **Ma X**, **Wei Y**, **et al**. Loading-induced reduction in sclerostin as a mechanism of subchondral bone plate sclerosis in mouse knee joints during late-stage osteoarthritis. *Arthritis Rheumatol*. 2018;70(2):230–241.
107. **Bailey KN**, **Nguyen J**, **Yee CS**, **Dole NS**, **Dang A**, **Alliston T**. Mechanosensitive control of articular cartilage and subchondral bone homeostasis in mice requires osteocytic transforming growth factor β signaling. *Arthritis Rheumatol*. 2021;73(3):414–425.
108. **Loots GG**, **Keller H**, **Leupin O**, **Murugesh D**, **Collette NM**, **Genetos DC**. TGF-β regulates sclerostin expression via the ECR5 enhancer. *Bone*. 2012;50(3):663–669.
109. **Robling AG**, **Niziolek PJ**, **Baldridge LA**, **et al**. Mechanical stimulation of bone in vivo reduces osteocyte expression of Sost/sclerostin. *J Biol Chem*. 2008;283(9):5866–5875.
110. **Blom AB**, **Brockbank SM**, **van Lent PL**, **et al**. Involvement of the Wnt signaling pathway in experimental and human osteoarthritis: prominent role of Wnt-induced signaling protein 1. *Arthritis Rheum*. 2009;60(2):501–512.
111. **Inkson CA**, **Ono M**, **Kuznetsov SA**, **Fisher LW**, **Robey PG**, **Young MF**. TGF-beta1 and WISP-1/CCN-4 can regulate each other's activity to cooperatively control osteoblast function. *J Cell Biochem*. 2008;104(5):1865–1878.
112. **Johnson GL**, **Lapadat R**. Mitogen-activated protein kinase pathways mediated by ERK, JNK, and p38 protein kinases. *Science*. 2002;298(5600):1911–1912.
113. **Stanton LA**, **Underhill TM**, **Beier F**. MAP kinases in chondrocyte differentiation. *Dev Biol*. 2003;263(2):165–175.
114. **Majidinia M**, **Sadeghpour A**, **Yousefi B**. The roles of signaling pathways in bone repair and regeneration. *J Cell Physiol*. 2018;233(4):2937–2948.

115. **Greenblatt MB**, **Shim JH**, **Glimcher LH**. Mitogen-activated protein kinase pathways in osteoblasts. *Annu Rev Cell Dev Biol*. 2013;29:63–79.
116. **Oh CD**, **Chang SH**, **Yoon YM**, **et al**. Opposing role of mitogen-activated protein kinase subtypes, erk-1/2 and p38, in the regulation of chondrogenesis of mesenchymes. *J Biol Chem*. 2000;275(8):5613–5619.
117. **Yang CM**, **Chien CS**, **Yao CC**, **Hsiao LD**, **Huang YC**, **Wu CB**. Mechanical strain induces collagenase-3 (MMP-13) expression in MC3T3-E1 osteoblastic cells. *J Biol Chem*. 2004;279(21):22158–22165.
118. **Prasadam I**, **Friis T**, **Shi W**, **van Gennip S**, **Crawford R**, **Xiao Y**. Osteoarthritic cartilage chondrocytes alter subchondral bone osteoblast differentiation via MAPK signalling pathway involving ERK1/2. *Bone*. 2010;46(1):226–235.
119. **Prasadam I**, **van Gennip S**, **Friis T**, **Shi W**, **Crawford R**, **Xiao Y**. ERK-1/2 and p38 in the regulation of hypertrophic changes of normal articular cartilage chondrocytes induced by osteoarthritic subchondral osteoblasts. *Arthritis Rheum*. 2010;62(5):1349–1360.
120. **Prasadam I**, **Crawford R**, **Xiao Y**. Aggravation of ADAMTS and matrix metalloproteinase production and role of ERK1/2 pathway in the interaction of osteoarthritic subchondral bone osteoblasts and articular cartilage chondrocytes -- possible pathogenic role in osteoarthritis. *J Rheumatol*. 2012;39(3):621–634.
121. **Boileau C**, **Amiable N**, **Martel-Pelletier J**, **Fahmi H**, **Duval N**, **Pelletier J-P**. Activation of proteinase-activated receptor 2 in human osteoarthritic cartilage upregulates catabolic and proinflammatory pathways capable of inducing cartilage degradation: a basic science study. *Arthritis Res Ther*. 2007;9(6):R121.
122. **McAlindon TE**, **Bannuru RR**, **Sullivan MC**, **et al**. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage*. 2014;22(3):363–388.
123. **Chen C-H**, **Kang L**, **Chang L-H**, **et al**. Intra-articular low-dose parathyroid hormone (1-34) improves mobility and articular cartilage quality in a preclinical age-related knee osteoarthritis model. *Bone Joint Res*. 2021;10(8):514–525.
124. **Zong Z**, **Zhang X**, **Yang Z**, **et al**. Rejuvenated ageing mesenchymal stem cells by stepwise preconditioning ameliorates surgery-induced osteoarthritis in rabbits. *Bone Joint Res*. 2021;10(1):10–21.
125. **Walsh DA**, **Chapman V**. Bisphosphonates for osteoarthritis. *Arthritis Res Ther*. 2011;13(5):128.
126. **Buckland-Wright JC**, **Messent EA**, **Bingham CO**, **Ward RJ**, **Tonkin C**. A 2 yr longitudinal radiographic study examining the effect of A bisphosphonate (risedronate) upon subchondral bone loss in osteoarthritic knee patients. *Rheumatology (Oxford)*. 2007;46(2):257–264.
127. **Kawai T**, **Nishitani K**, **Okuzu Y**, **et al**. Bisphosphonate use is associated with a decreased joint narrowing rate in the non-arthritic hip. *Bone Joint Res*. 2022;11(11):826–834.
128. **Kadri A**, **Ea HK**, **Bazille C**, **Hannouche D**, **Lioté F**, **Cohen-Solal ME**. Osteoprotegerin inhibits cartilage degradation through an effect on trabecular bone in murine experimental osteoarthritis. *Arthritis Rheum*. 2008;58(8):2379–2386.
129. **Connor JR**, **LePage C**, **Swift BA**, **et al**. Protective effects of a cathepsin K inhibitor, SB-553484, in the canine partial medial meniscectomy model of osteoarthritis. *Osteoarthritis Cartilage*. 2009;17(9):1236–1243.
130. **Rodrigues TA**, **de Oliveira Freire A**, **Carvalho HCO**, **et al**. Prophylactic and therapeutic use of strontium ranelate reduces the progression of experimental osteoarthritis. *Front Pharmacol*. 2018;9:975.
131. **Nagai T**, **Sato M**, **Kutsuna T**, **et al**. Intravenous administration of anti-vascular endothelial growth factor humanized monoclonal antibody bevacizumab improves articular cartilage repair. *Arthritis Res Ther*. 2010;12(5):R178.
132. **Lu J**, **Zhang H**, **Cai D**, **et al**. Positive-feedback regulation of subchondral H-type vessel formation by chondrocyte promotes osteoarthritis development in mice. *J Bone Miner Res*. 2018;33(5):909–920.
133. **Cui Z**, **Crane J**, **Xie H**, **et al**. Halofuginone attenuates osteoarthritis by inhibition of TGF-β activity and H-type vessel formation in subchondral bone. *Ann Rheum Dis*. 2016;75(9):1714–1721.
134. **Li B**, **Chen K**, **Qian N**, **et al**. Baicalein alleviates osteoarthritis by protecting subchondral bone, inhibiting angiogenesis and synovial proliferation. *J Cell Mol Med*. 2021;25(11):5283–5294.
135. **Ma L**, **Zhao X**, **Liu Y**, **Wu J**, **Yang X**, **Jin Q**. Dihydroartemisinin attenuates osteoarthritis by inhibiting abnormal bone remodeling and angiogenesis in subchondral bone. *Int J Mol Med*. 2021;47(3):04855.
136. **Xie H**, **Cui Z**, **Wang L**, **et al**. PDGF-BB secreted by preosteoclasts induces angiogenesis during coupling with osteogenesis. *Nat Med*. 2014;20(11):1270–1278.
137. **Zhu J**, **Zhen G**, **An S**, **et al**. Aberrant subchondral osteoblastic metabolism modifies $Na_v1.8$ for osteoarthritis. *Elife*. 2020;9:e57656.
138. **Martel-Pelletier J**, **Mineau F**, **Hum D**, **Pelletier J-P**. THU0473 Diacerein reduces antagonists of WNT enabling this system's activity in human osteoarthritic subchondral bone osteoblasts. *Ann Rheum Dis*. 2015;74(Suppl 2):371.

Author information:
- P. Luo, PhD, Orthopaedic Surgeon
- Q. Yuan, PhD, Orthopaedic Surgeon
- M. Yang, PhD, Orthopaedic Surgeon
- X. Wan, PhD, Orthopaedic Surgeon
- P. Xu, MD, Head of Department

Department of Joint Surgery, HongHui Hospital, Xi'an Jiaotong University, Xi'an, China.

Author contributions:
- P. Luo: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing.
- Q. Yuan: Project administration, Investigation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing.
- M. Yang: Project administration, Resources, Writing – review & editing.
- X. Wan: Resources, Writing – review & editing.
- P. Xu: Conceptualization, Methodology.

Funding statement:
- The authors disclose receipt of the following financial or material support for the research, authorship, and/or publication of this article: this work was supported by the National Natural Science Foundation of China (82072432).

ICMJE COI statement:
- None.

Data sharing:
- The data that support the findings for this study are available to other researchers from the corresponding author upon reasonable request.

Open access funding:
- The open access fee for this article was self-funded.