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REVIEW

Pathological progression of osteoarthritis: a perspective on subchondral bone

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Abstract **Osteoarthritis (OA) is a degenerative bone disease associated with aging. The rising global aging population has led to a surge in OA cases, thereby imposing a significant socioeconomic burden. Researchers have been keenly investigating the mechanisms underlying OA. Previous studies have suggested that the disease starts with synovial inflammation and hyperplasia, advancing toward cartilage degradation. Ultimately, subchondral-bone collapse, sclerosis, and osteophyte formation occur. This progression is deemed as "top to bottom." However, recent research is challenging this perspective by indicating that initial changes occur in subchondral bone, precipitating cartilage breakdown. In this review, we elucidate the epidemiology of OA and present an in-depth overview of the subchondral bone's physiological state, functions, and the varied pathological shifts during OA progression. We also introduce the role of multifunctional signal pathways (including osteoprotegerin (OPG)/receptor activator of nuclear factor-kappa B ligand (RANKL)/receptor activator of nuclear factor-kappa B (RANK), and chemokine (CXC motif) ligand 12 (CXCL12)/CXC motif chemokine receptor 4 (CXCR4)) in the pathology of subchondral bone and their role in the "bottom-up" progression of OA. Using vivid pattern maps and clinical images, this review highlights the crucial role of subchondral bone in driving OA progression, illuminating its interplay with the condition.**

Keywords osteoarthritis; subchondral bone; OPG/RANKL/RANK; CXCL12/CXCR4

Introduction

Osteoarthritis (OA) is a common chronic and degenerative bone disease [1]. According to statistics, more than 500 million people suffer from OA worldwide [2]. The pathological changes in OA are complex. They include synovial inflammation, hyperplasia, cartilage injury, biomechanical imbalance, and pathological changes of subchondral bone (including sclerosis, osteophyte, and collapse) [3]. Although cartilage loss is traditionally regarded as a key feature in diagnosing OA, recent understanding points to the involvement of all joint structures [4]. Controversy remains regarding whether the initial pathological change in OA originates in subchondral bone, calcified cartilage, or cartilage. Advanced microimaging technology have revealed the dynamic sequence from early-stage subchondral-bone loss to late-stage trabecular sclerosis, accompanied by subchondral-bone cysts, microfractures, abnormal angiogenesis, and eventual cartilage destruction [5,6]. Accordingly, the contribution of subchondral-bone changes to early OA is eliciting increased research attention [7,8]. Pathological changes in subchondral bone are believed to be caused by pathological processes involving coupling interactions among osteoblasts, osteoclasts, and endothelial cells [9]. These biological processes include bone resorption, bone-remodeling imbalance, abnormal angiogenesis, pain-factor release, and cartilage-matrix degradation [10]. Understanding the relevant mechanisms of pathological changes in subchondral bone may provide prevention and treatment measures into the early lesions for OA. This article introduces the epidemiology of OA and the normal state of subchondral bone, including function and structure. The pathological changes in subchondral-bone tissue at different pathological stages of OA are summarized.

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Moreover, we introduce the important role of two multifunctional signaling pathways, OPG/RANKL/RANK and CXCL12/CXCR4, in the pathological changes of subchondral bone in OA. This review aims to identify novel targets and innovative approaches to treating OA based on subchondral-bone-related pathological changes.

Epidemiology of OA

OA is an important public-health issue. Its exact cause is unknown, but it is believed to be related to aging [11] and to modifiable (obesity, history of traumatic surgery, high-intensity exercise, and hypertension) [12–15] and immutable risk factors (gender and genetics) [16,17]. OA affects multiple joints, including the temporomandibular joint, shoulder joint, wrist joint, hip joint, knee joint, and ankle joint. The knee and hip joints are most susceptible to developing OA [18]. With the arrival of global aging, the incidence of OA is rapidly increasing [19]. The Global Burden of Disease study has shown that the global number of OA patients is approximately 300 million in 2017 and has rapidly increased to 530 million in 2019. The incidence of OA has increased by 9.3% from 1990 to 2017 and by 13.25% from 1990 to 2019 [20,21]. For knee OA (KOA), the global prevalence rate of symptomatic knee OA is about 3.6% in 2010 [22], whereas a recent meta-analysis has found that from 2012 to 2016, the prevalence rate of symptomatic KOA is 14.6%, with the female prevalence rate of 19.1% higher than the male prevalence rate of 10.9% in China [23]. In South Korea, the prevalence of radiological KOA is 35.1% [24], indicating that radiological KOA is more common than symptomatic KOA [25]. For hip OA (HOA), Kim *et al.* (2014) conducted a community cohort study on 978 urban residents in the United States and found that the prevalence of symptomatic HOA is 4.2% [26]. A recent meta-analysis has found that the global prevalence of radiographic HOA is 4.01% [27]. Unlike KOA, the prevalence of radiographic HOA is consistent with that of symptomatic HOA. Moreover, the prevalence of OA varies in different regions. In 2019, the top three global rankings for prevalence rates of OA are East Asia, South Asia, and Western Europe [28,29]. In China, the difference between the south region and north region is not significant, but the prevalence rate in the western region is much higher than that in the eastern region. The prevalence of OA in rural areas is also much higher than that in urban areas [30]. OA has led to significant healthcare and socioeconomic burdens. The medical expenses of OA account for approximately 8% of the total global burden of diseases [31]. In 2019, OA contributed $460 billion to all-cause healthcare expenses in the United States [32]. Furthermore, the total medical expenses of OA patients are four times higher than those of non-OA patients [33].

Structure and function of subchondral bone

The human knee joint possesses a complex structure encompassing the femur, tibia, cartilage, synovium, menisci, tendons, and ligaments [34]. Anatomically, the knee joint can be divided into superficial and deep layers, comprising cartilage and subchondral bone, respectively [35].

Cartilage is divided into noncalcified and calcified cartilages. Noncalcified cartilage has aneural, avascular, and alymphatic tissues comprising > 70% water, 20%–30% extracellular matrix, and 1% chondrocytes [36]. Chondrocytes, the only cell type in cartilage, secrete proteoglycans, matrix metalloproteinases (MMPs), and other components to maintain a dynamic balance between the degradation and synthesis of the extracellular matrix [37]. In the physiological state, the noncalcified cartilage buffers the mechanical loading of compression, shearing, and other complex mechanical stimulations [38,39]. The hyaluronic acid and lubricin produced by chondrocytes and synovial cells also endow noncalcified cartilage with a unique low-friction articulating surface [40]. Positioned between the underlying subchondral bone and noncalcified cartilage, calcified cartilage comprises hydroxyapatite, collagen fibers, and proteoglycans [41], measuring ~20–250 μm thick and accounting for 3%–8% of the total cartilage thickness [42]. As a barrier between the subchondral bone and cartilage, cartilage blocks the passage of O_2 and maintains the cartilage tissue in a hypoxic microenvironment [43]. Importantly, the semipermeable membrane nature of calcified cartilage facilitates the passage of small molecules, maintaining material exchange and balance between cartilage and subchondral bone [44]. The calcified cartilage can also distribute and transmit mechanical pressure under physiological conditions [45].

Subchondral bone is categorized into subchondral-bone plate and subchondral trabecular bone based on anatomical features [46]. The subchondral-bone plate is a thin cortical layer closely positioned to the overlying calcified cartilage [47]. The subchondral-bone plate is not impenetrable; instead, it has many channels connecting the cartilage to subchondral trabecular bone. Numerous arteries, veins, and nerves penetrate these channels and extend small branches into the adjacent calcified cartilage [48]. The distribution and strength of the channel are not constant but are closely related to the magnitude of the joint compression force. In heavily stressed areas with thick subchondral-bone plates, channels are relatively concentrated and form tree-like meshes [49,50]. The

subchondral-bone plate is widely known to contribute mechanical strength to support the covered cartilage; however, its hardness is lower than that of the diaphyseal cortical bone [6,51]. In general, the subchondral-bone plate provides support for the cartilage and channels for the exchange of material between subchondral trabecular bone and cartilage.

Subchondral trabecular bone is located below the subchondral-bone plate. This structure is highly porous, has vigorous metabolism, and contains abundant blood vessels, nerves, and bone marrow [52]. Subchondral trabecular bone exhibits significant structural anisotropy, aligning with gravity-bearing orientation and proximity to the articular surface. Load direction and magnitude dictate internal bone architecture [53]. In the physiological state, subchondral trabecular bone plays an important role in absorbing pressure load, thereby providing nutrition to the overlying cartilage and structural support.

Under physiological conditions, osteochondral units comprising noncalcified cartilage, calcified cartilage, subchondral cortical bone, and subchondral trabecular bone adeptly transfer loads and provide structural support. Pathological changes in any tissue structure in the functional unit destroy the integrity of the joint mechanism and result in the loss of its physiological function. However, cartilage and subchondral bone exhibit different mechanical adaptabilities [54]. Subchondral bone can adjust its functional and structural properties by regulating the balance between osteoblast-dominated bone formation and osteoclast-dominated bone resorption [55], thus reestablishing normal physiological conditions [45]. This biological process enables bone to dynamically adapt to biomechanical factors, systemic hormones, and local osteolytic media. It provides a biological mechanism for the timely removal of damaged bone tissue caused by mechanical trauma. Mature chondrocytes maintain steady equilibrium between anabolism and catabolism. Cartilage can dynamically regulate the damage, but its ability to modify and repair the matrix is not as good as that of subchondral bone. Stress distribution in the cartilage changes with the expansion of subchondral bone. Even a slight 1%–2% increase in subchondral-bone size substantially amplifies stress on the cartilage [56]. The different adaptabilities of this cartilage and subchondral bone to mechanical injury drive early OA-related subchondral-bone changes.

Histopathological changes of subchondral bone in OA

In OA, histomorphology and pathological changes in cartilage and subchondral bone are closely related [57], even though the sequence of these changes remains debated [58]. In 1984, Radin intervened with continuous pulse loading on the hind limbs of a rabbit model. Bone scanning and biomarker technology reveals that mechanical forces and bone changes alone precede horizontal division and deep cartilage fibrillation and occur before changes in endochondral biochemical and cellular processes [59]. For more than four decades, an increasing number of studies have focused on the relationship between pathological changes in subchondral bone and the pathogenesis of OA. Subchondral-bone microstructural changes occur at different stages of OA, including subchondral-bone microinjury, subchondral-bone-marrow edema, subchondral-bone cysts, and subchondral sclerosis [45,60].

Subchondral-bone microdamage

Beneath the articular cartilage, precise remodeling by osteoblasts, osteoclasts, and osteocytes maintains the microstructure of subchondral bone. In healthy bone joints, subchondral bone exhibits a uniform distribution of plate- and rod-shaped trabeculae [61]. The knee joint has more trabecular rods than plates, resulting in a more flexible microstructure. This microstructure is an important determinant of trabecular bone mechanics [62]. OA is a degenerative joint disease with multiple risk factors, such as obesity, aging, previous joint injuries, and abnormal joint shape [63]. According to Wolff's law, the applied load dynamically determines the material properties and distribution of bone [64]. In the early stages of OA, elevated bone loads due to risk factors prompt subchondral-bone modifications, such as reduced density, trabecular structure degradation, and subchondral bone-plate thinning [65]. At this point, imaging findings of subchondral-bone microfractures are displayed in magnetic resonance imaging (MRI) (Fig. 1). In an early OA rabbit model, macrophage infiltration and overactive osteoclasts lead to substantial shifts in the number and structure of subchondral trabecular bone. These trabeculae exhibit lower density, higher porosity, and increased spacing, showing irregular damaged network structures and microfractures [66]. Furthermore, using a novel microanalytical approach, Chen *et al.* (2018) examined human OA via individual trabecular segmentation on microscopic computed tomography images [67]. Their findings reveal significant loss of rod-shaped trabecular bone and plate-shaped trabecular bone thickening beneath intact cartilage in early OA. These structural changes persist throughout OA progression and precede cartilage degradation.

Subchondral trabecular bone swiftly adapts to changing mechanical demands to maintain its physiological state, whereas the subchondral-bone plate demonstrates a comparatively slower adaptive response. Therefore, the subchondral-bone plate undergoes faster changes than

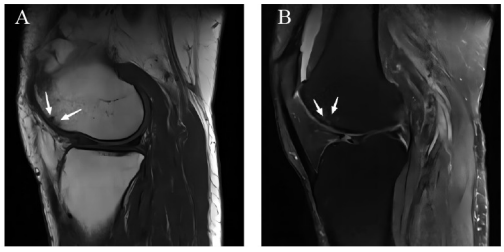

Fig. 1 Magnetic resonance imaging (MRI) of knee OA in a 65-year-old female. (A) Sagittal T1-weighted images shows minor subchondral-bone collapse in the distal femur, with subchondral-bone microfractures presenting as low signal (white arrow). (B) Sagittal T2-weighted fat suppression image shows the same lesion in the distal femur (white arrow).

subchondral trabecular bone in patients with OA [68]. Before pathological changes in subchondral trabecular bone occur, the cortical-bone plate becomes thinner, with a significant increase in porosity and a gradual increase in the mineral/matrix ratio. Scanning electron microscopy reveals rough collagen fiber surfaces, sparse arrangements, and notably enlarged gaps in the cortical-bone plate [69]. These plate pores may augment interactions among cartilage, bone marrow cells, and subchondral trabeculae in OA [70].

In the early stages of OA, subchondral bone undergoes decoupling of the remodeling process, which involves osteocytes, osteoclasts, and osteoblasts. Osteocytes are mechanosensing cells [71]. Excessive mechanical load increases the ratio of RANKL/OPG expression in osteocytes, causing excessive osteoclast formation and enhancing bone-resorption activity [72]. Mechanical stimulation causes osteocytes to secrete MMPs for the digestion and reconstruction of the surrounding bone matrix [73]. Osteoclasts are the primary cells responsible for bone resorption [74]. During osteoclast activity, CXCL12 recruits preosteoclast to relevant sites in the bone marrow. The receptor RANK, in conjunction with RANKL from osteoblasts, transforms these precursors into mature osteoclasts. Mature osteoclasts release hydrogen ions and catalyze enzymes involved in osteolysis [75]. Increased subchondral-bone angiogenesis and vascular invasion of avascular cartilage are diagnostic features of early OA in humans [76]. In the early stages of OA, preosteoclasts secrete excessive amounts of platelet-derived growth factor-BB (PDGF-BB), which activates platelet-derived growth-factor receptor signaling in endothelial cells to promote the abnormal angiogenesis of subchondral bone [77]. Mature osteoclasts resorb bone, causing a notable increase in transforming growth factor-β (TGF-β) within subchondral bone of patients with OA. TGF-β, as a proangiogenic factor, is known to significantly increase the number of H-type blood vessels in subchondral bone in the early stages of OA [66].

Pain is a typical clinical symptom of OA. It is associated with abnormal blood vessels and neuronal growth. Zhu *et al.* (2019) determined that netrin-1 secreted by osteoclasts during abnormal subchondral-bone remodeling plays a role in inducing sensory innervation and OA-related pain [78]. Osteoclast-secreted netrin-1 promotes the axonal growth of sensory neurons. However, the absorption of osteoclasts may also create an acidic microenvironment in subchondral bone, which sensitizes peripheral nociceptive neurons. Jiang *et al*. also demonstrated that prostaglandin E2 (PGE2)/E-type prostanoid receptor 4 (EP4) mediates innervation and angiogenesis in subchondral bone, thereby promoting the pathological progression and pain symptoms of OA [79]. Thus, osteoclasts contribute to diminished subchondral-bone mass and trabecular structure loss through absorption, as well as stimulate nerve and blood vessel growth within subchondral bone in OA. These phenomena drive disease progression and pain. Conversely, osteoblasts contribute to bone formation under physiological conditions. In early OA, subchondral-bone osteoblasts release elevated levels of RANKL, TGF, and vascular endothelial growth factor (VEGF). Thus, downstream effects including osteoclast maturation, abnormal angiogenesis, and osteosclerosis in late-stage OA are triggered [62].

In summary, the dysfunction of osteocyte osteoblasts and osteoclasts, especially the uncoupling between osteoblasts and osteoclasts caused by mechanical stress, leads to a series of pathological changes in subchondral bone. These changes include thinning and increased porosity of the subchondral-bone plate, structural and functional destruction of subchondral trabecular bone, and formation of abnormal blood vessels and nerve axons. Interestingly, the morphological and structural changes in the cartilage are not significant during this phase. However, biochemical analysis reveals significant proteoglycan reduction and notable increases in IL-1β and MMP-13 in the cartilage of patients with early-stage OA [80,81].

Bone-marrow edema-like lesions

Bone-marrow edema-like lesions fundamentally participate in the progression of OA and are considered a basic risk factor for pathological structural changes, as well as the most common imaging manifestations [82] (Fig. 2). Wilson *et al.* (1988) first localized and detected areas with increased signal strength in the tibia and femur of patients with OA by using an enhanced magnetic resonance [83]. Nevertheless, the specific pathological changes in bone edema remain unclear. Histological analysis, until 2010, disclosed that bone-marrow edema encompasses marrow fibrosis, vascular shifts, and local fat necrosis caused by trabecular microfractures [84]. Therefore, these pathological changes are referred to as

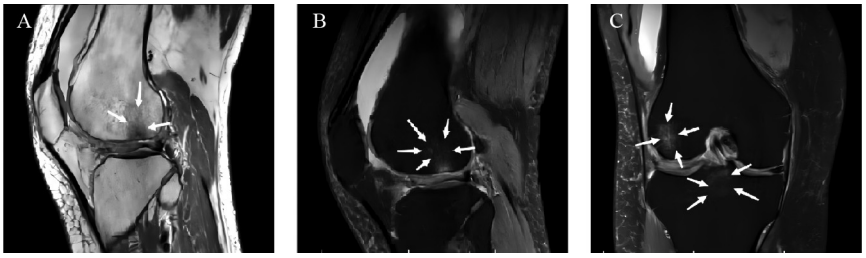

Fig. 2 Magnetic resonance imaging (MRI) of knee OA in a 62-year-old female. (A) Sagittal T1-weighted image shows diffuse bone-marrow edema at the distal end of the femur, presenting as low signal (white arrows). (B) Sagittal T2 intermediate-weighted fat-suppressed image shows the same lesion in the distal femur (white arrows). (C) Coronal fat-suppressed proton density (PD) MRI shows bone-marrow edema at the load-bearing site of the medial condyle of the femur and below the insertion point of the proximal cruciate ligament of the tibia (white arrows).

subchondral-bone-marrow lesions (SBMLs). SBMLs are conducive to the screening and diagnosis of early OA. Clinical studies have found a strong correlation between bone microstructural changes in bone-marrow legions (BMLs) and the pathological characteristics of cartilage structure and volume loss in the human tibial plateau, which has important diagnostic value in predicting the occurrence and development of OA [85]. Distinctive subchondral-bone pathology marks the anteromedial OA-BML region, featuring subchondral-bone plate thickening, heightened porosity, increased bone-volume percentage, thicker trabeculae, reduced separation, focal sclerosis, fewer rod-shaped trabeculae, and more plate-shaped trabeculae [86]. OA-related pain is closely associated with BMLs. Koushesh *et al*. found that excessive blood vessels and innervation in BMLs contribute to understanding the relationship between BMLs and OA-related pain [87]. Microarray analysis has demonstrated that the BML is a highly metabolically active region with increased cellular renewal, neuronal, bone remodeling, and inflammatory gene characteristics [88]. For example, the upregulation of stathmin 2 (*STMN2*) gene expression within the BML triggers abnormal neuronal structure formation and BML expansion, resulting in pain. Neurodevelopment and pain pathway signal transduction is represented by the expression of the Wnt, VEGF, and angiogenesis pathways, which promote the formation of abnormal blood vessels in the BML. Interestingly, the detection of serum biomarkers (tartrate-resistant acid phosphatase 5b (TRAcP5b) and cathepsin K (cath-K)) for bone turnover in patients with OA has revealed that the expression of TRAcP is more abundant in symptomatic pain patients with OA, thereby underscoring the role of BML subchondral osteoclast activity in OA pain development [89].

At this stage, the porosity of the subchondral-bone plate widens, creating a communication “channel” for cells and factors between the cartilage and subchondral regions. Abnormal blood vessels and nerves, generated by BMLs, traverse this channel, penetrating the calcified and noncalcified cartilage [90]. The bone-marrow-derived preosteoclasts enter the cartilage layer through the circulation of blood driven by CXCL12 and differentiate into the final mature osteoclasts, leading to cartilage deterioration [91]. Similarly, during periosteal vascular growth, preosteoclasts invade hypertrophic cartilage zones. The cartilage matrix is then co-reshaped by mature osteoclasts and hypertrophic chondrocytes, forming primary ossification [92]. Furthermore, various cytokines are secreted from the bone matrix in BMLs, such as calcium phosphate complexes and TGF-β1, which enters the cartilage along the channels [93]. The expression level of TGF is dramatically upregulated in a time- and dose-dependent manner in osteoclasts, leading to chondrocyte apoptosis through diffusion or blood transport to the cartilage layer [94]. Calcium-phosphate complexes increase the expression of MMP-3 in cartilage by activating nuclear factor-kappa B (NF-κB), leading to cartilage matrix degradation [95]. Chondrocytes regulate osteoclasts to promote subchondral-bone loss. Abnormal mechanical stimulation leads to the upregulation of TNF-α, IL-6, and IL-1β in chondrocytes [96]. TNF-α and IL-1β upregulate RANKL expression in osteoblasts, directly induce the differentiation of preosteoclast into multi-nucleated osteoclasts, and indirectly induce osteoclast formation [97]. The release of CXCL12 from apoptotic chondrocytes also has the strongest osteoclast-promoting effect via the activation of the extracellular regulated protein kinase 1/2 (ERK1/2) and p38 signaling pathways [98]. In summary, according to the osteoclast-chondrocyte crosstalk theory, the cartilage undergoes pathological changes in OA pathological progression, reducing its capacity to absorb abnormal mechanical stress, leading to inordinate subchondral-bone loading. Simultaneously, the high turnover rate of subchondral bone alters its biomechanical properties of early OA, transmitting shear forces to the cartilage region and thus leading to sustained cartilage destruction [99,100].

Pathological changes in the BML stage include further development of pathological changes in subchondral-bone microinjury. At this stage, mature osteoclasts

continue to reduce subchondral-bone density and destroy the trabecular bone structure. The subchondral-bone plate thickens and porosity increases, providing a channel for material exchange between the cartilage region and subchondral-bone region. Abnormally abundant blood vessels and nerves enter the cartilage through channels of the subchondral-bone plate. Abnormal nerve invasion results in pain. Conversely, abnormally invading blood vessels act as carriers of cytokines, contributing to cartilage destruction and disrupting the interplay between cartilage and subchondral bone, exacerbating their pathological changes.

Subchondral-bone cysts

Subchondral-bone cysts (SBCs) manifest in regions with pre-existing subchondral-bone-marrowbone-marrow edema-like signals, commonly appearing on MRI in advanced OA [101] (Fig. 3). Elevated peripheral cyst tendency and increased bone stress further deteriorate OA in a 3D simulation of a subchondral-bone cyst knee-joint model [102]. Additionally, the presence of SBCs is correlated with increased knee-joint pain in patients with KOA in a multicenter cohort study [103]. Although a close relationship between SBCs and OA has been established in clinical research, the mechanism of formation and composition of SBCs remains unclear. SBCs appear as clear fluid-signal areas on MRI, corresponding with clear glossy areas having sclerotic edges on radiographs [101]. Ranging from fibrous to fatty, SBCs typically contain vasculature, nerve fibers, bony spicules, cartilage islands, and vascular tissue. Additionally, bone-mineral density around SBCs increases while mineralization and elastic modulus of bone tissue decrease. Overlying cartilage thins, exacerbating the damage [104]. Interestingly, the concentrations of MMPs, PGE2, and NO are significantly higher in SBCs than in severe OA and normal joints, indicating higher biochemical activity in moderate joint OA [105]. Two popular theories are used to explain the mechanism of subchondral-bone cyst formation. The synovial breach theory posits that repeated microtrauma forms channels at the cartilage and osteocartilaginous junction. Synovial fluid infiltrates the subchondral-bone area through a "channel," gradually inducing subchondral-bone necrosis and cyst formation [106,107]. The bone contusion theory posits that abnormal mechanical stimulation leads to subchondral-bone microfractures and bone-marrow edema, thereby activating the bone-reconstruction process. Mature osteoclast and macrophages enhance bone absorption and phagocytosis. Mature osteoblasts promote new bone deposition, ultimately forming cavities with fiber content [108].

The formation of SBCs may result from the combined effects of these two mechanisms. Abnormal mechanical stimulation causes minor trauma to the cartilage, osteochondral junction, and subchondral bone, and the joint synovial fluid enters subchondral bone through the channel, causing bone resorption. Simultaneously, vascular rupture, local bone necrosis, and subsequent cyst formation are caused by the minimally invasive injury. Subchondral-bone cyst formation involves two stages. (1) The destructive phase begins with subchondral trabecular bone osteonecrosis and progresses with increased bone resorption followed by the formation of a cavity with fibrous content. (2) The productive phase involves hardened tissue creation at fibrous cavity edges, thereby increasing cyst volume and density. However, the corresponding decrease in bone mineralization and elastic modulus leads to an overall decrease in the ability of bones to withstand mechanical loads [109,110].

Additionally, SBCs exist in the non-load-bearing region of the joint, thereby challenging the two aforementioned biomechanical theories. Our group has previously emphasized that subchondral bone is an abundantly vascularized tissue, and any damage to blood vessels can lead to harmful consequences, such as increased bone resorption. Chan *et al.* (2017) found that hypertension is an independent risk factor for SBCs. They speculated that the pathogenesis of subchondral cysts may be related to

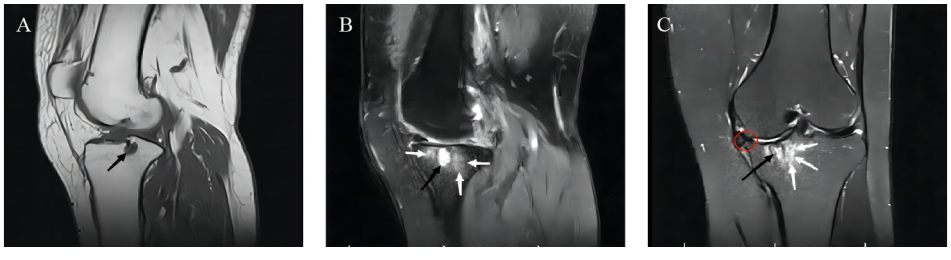

Fig. 3 MRI of knee OA in a 67-year-old female. (A) Sagittal T1-weighted image revealing a low signal subchondral-bone cyst at the proximal tibia (black arrows). (B) Sagittal fat-suppressed proton density (PD) MRI showing a subchondral-bone cyst at the proximal tibia (black arrow), surrounded by diffuse bone-marrow edema (white arrow). (C) Coronal T2 intermediate-weighted fat-suppressed image showing a subchondral-bone cyst at the proximal end of the tibia with varying internal signal strengths (black arrow) and surrounding diffuse bone-marrow edema. The red circle on the inner side of the joint indicates osteophyte formation.

blood vessels [111]. They further formulated the theory that endothelial dysfunction and vascular aging lead to chronic tissue ischemia, impaired neovascularization, and the exhaustion of perivascular cells in injured vessels, ultimately leading to subchondral-bone ischemia. The relationship between bone homeostasis and vascular pathology has long been studied, and vascular dysfunction has been proven as a potential risk factor for osteoporosis (OP) [112]. OP and SBCs reveal an imbalance between osteoclast-mediated bone resorption and osteoblast-mediated bone formation (with more osteoclasts than osteoblasts).

Briefly, SBCs further develop pathological changes in the bone-marrow edema. The formation of SBCs involves the secretion of inflammatory factors, enhanced bone turnover, and angiogenesis as a biological response to abnormal mechanical loads. The outcome is repeated injury to the cartilage and subchondral tissue during the development of arthritis. In the pathological progression of OA, subchondral-bone microfractures, subchondral-bone-marrowbone-marrow edema, subchondral-bone cysts, and osteophytes appear one after another, which become the main pathological changes of subchondral bone in OA (Fig. 4).

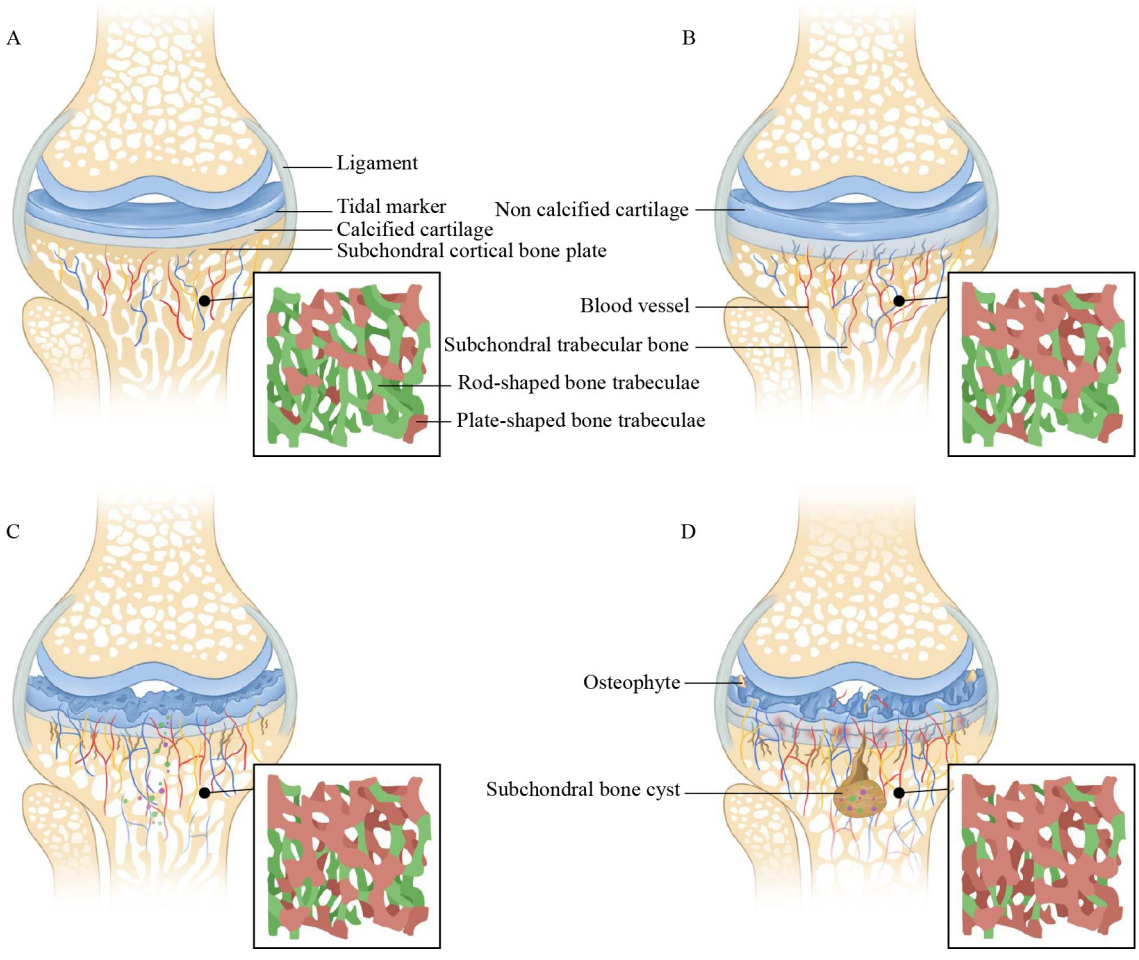

Fig. 4 Various stages of subchondral-bone pathology in OA progression. (A) Subchondral-bone structure of normal bone joints. The joint and calcified cartilages are separated with tidal markers, with subchondral cortical-bone plates and trabeculae below calcified cartilage. Under normal conditions, rod-shaped bone trabeculae (green) outnumber plate-shaped bone trabeculae (red). (B) Subchondral-bone microfracture. The overall structure of the cartilage remains intact, but cartilage edema becomes apparent. Microfractures develop in calcified cartilage. Subchondral cortical-bone plate thins, porosity increases, and blood vessels and nerves infiltrate calcified cartilage through enhanced pores. Subchondral trabeculae shift: rod-shaped (green) decrease, plate-shaped (red) increase. (C) Subchondral-bone-bone-marrow edema. Noncalcified cartilage surface displays concave-convex damage, tidal markers become tortuous, calcified cartilage thins, and damage increases. Subchondral cortical-bone plate thickens, porosity rises, and subchondral-bone cytokines enter cartilage through channels. Rod-shaped trabeculae (green) decrease, plate-shaped (red) increase. Abnormally abundant blood vessels and nerves enter the noncalcified cartilage area, gradually causing pain. (D) Subchondral-bone cyst stage. Severe destruction of noncalcified cartilage. Osteophytes are present around the joints. At this point, tidal markers curve and blur, calcified cartilage thickens and penetrates into noncalcified cartilage. Subchondral-bone plate thickens, channels increase. Subchondral trabecular bone hardens, rod-shaped rare, mostly plate-shaped. Bone cysts are rich in blood vessels, nerves, inflammation, and fluid emerge.

Multifunctional signaling pathways in OA

Following the successful establishment of a mouse OA model through surgical techniques [113], research on the pathological mechanisms of OA has become comprehensive, encompassing inflammatory response, oxidative stress, immunity, autophagy, biomechanical imbalance, aging, epigenetics, and other mechanisms [114–120]. The following major molecules and pathways are involved: Notch, NF-κB, TGF-β signaling, Wnt/β-catenin, and mitogen-activated protein kinase (MAPK) pathways [121–125]. In this review, we focus on the OPG/RANKL/RANK and CXCL12/CXCR4 pathways, as well as their multiple functions in subchondral bone and cartilage, to gain a comprehensive understanding of their roles in OA pathology.

OPG/RANKL/RANK pathway

OPG/RANKL/RANK is discovered in parallel investigations within the bone and immune systems as a signaling triad in the late 1990s. This signaling triad regulates various cellular and metabolic processes closely related to immunity, inflammation, bone homeostasis, and cancer [126–129]. As a cytokine belonging to the TNF receptor superfamily, osteoprotegerin (OPG) is encoded by the *TNFRSF11B* gene. OPG was first identified in mouse bone-marrow stromal cells, and B cells are the main source of OPG in the mouse bone marrow [130]. Initially termed OPG due to its bone-protective effects, the soluble protein OPG comprises 401 amino acids (aa) and weighs 60 kDa as a monomer. A 21 aa signal peptide is cleaved from the N terminus before monomer and dimer OPG forms are secreted, yielding a mature OPG protein of 380 aa. Subsequently, cyclic OPG exists as a homodimer with 60 kDa free monomers or in forms bound to its ligands RANKL and TNF-related apoptosis-inducing ligand with 120 kDa disulfide bonds [131]. OPG is also expressed in various cell types, such as blood cells, stem cells, vascular endothelial cells, and bone cells [132–138]. Furthermore, inflammatory cytokines (TNF-α, IL-1β, and IL-17) and hormones (estrogen) have been found to increase OPG levels [139–142].

RANKL is a type II membrane protein encoded by TNFSF1 and is produced by osteoblastic lineage cells [143,144]. It has been initially identified as an activator of dendritic cells expressed by T cells [145]. As a decoy receptor, OPG binds to RANKL via its N-terminal cysteine-rich domain and blocks the binding and activation of RANK, thereby blocking the main signaling pathway of preosteoclast differentiation and maturation [146]. Similar to OPG, RANKL is also a member of the TNF superfamily [147]. This protein is highly expressed in osteocytes, osteoblasts, activated T cells, and lymphocytes and is expressed at low levels in the bone marrow. Recent findings have revealed RANKL expression and synthesis in articular chondrocytes, although its primary expression occurs in osteocytes and osteoblasts [148,149]. In the skeletal system, RANKL binds to RANK on the surface of preosteoclasts in the form of a membrane. The RANKL–RANK complex activates the downstream signaling pathways related to osteoclast growth and maturation [150,151].

Human RANK is encoded by *TNFRSF11A* located on chromosome 18 and is a type I transmembrane protein containing 616 aa [143]. RANK is highly expressed in the osteoclast precursors, dendritic cells, mature osteoclasts, immune cells, and breast membranes [152]. As a transmembrane protein, RANK contains four cysteine-rich pseudorepeat sequences at the N terminus outside the cell membrane, and three TNF receptor-related factor (TRAF) binding domains at the carboxyl terminus inside the cell membrane [153]. Within the skeletal system, RANKL binds to RANK and activates TRAFs, especially TRAF6, acting as a messenger to initiate downstream signaling pathways. These pathways are NF-κB, protein kinase B (PKB), RAC-alpha serine/threonine-proteine kinase (AKT), MAPK cascade, and the c-Jun N-terminal kinase (JNK). These cascades lead to pathological changes such as OP and vascular calcification [154].

TRAFs are important downstream factors of the OPG/RANKL/RANK signaling pathway and are closely related to OA caused by pathological changes in subchondral bone [155]. TRAF is recruited in osteoclasts after RANKL activates RANK [156,157]. Mechanical pressure stimulates the abundant secretion of RANKL by osteoblasts, osteocytes, and chondrocytes. This RANKL binds to RANK on osteoclast precursor membranes, causing TRAF6 in the cytoplasm to accumulate on the cytoplasmic side of RANK and thus activating the NF-κB and MAPK (p38, ERK, and JNK) signaling pathways. Simultaneously, OPG secreted by osteoblasts, an inducible ligand of RANKL, prevents the differentiation and maturation of osteoclast precursors by combining with RANKL. After the NF-κB and MAPK signaling pathway are activated, the relevant molecules of each pathway enter the nucleus through phosphoric acid, initiating specific gene connections, transcription, and translation. Accordingly, osteoclast precursor transformation into mature osteoclasts is facilitated [158,159]. These mature osteoclasts adhere onto the surface of the subchondral-bone plate and trabecular bone, dissolving the bone matrix via enzyme release and acid products, leading to bone resorption. Hidden TGF-β in the bone matrix is simultaneously released [160–163]. During OA progression, heightened RANKL and RANK coupling due to abnormal mechanical pressure drives osteoclast precursor differentiation into mature osteoclasts. Osteoclast-mediated bone absorption surpasses osteoblast-mediated processes, perpetuating subchondral-bone

matrix destruction. Excessive matrix degradation releases substantial latent TGF-β, inducing MSC migration and osteoblast precursor differentiation, resulting in abnormal bone islands within the subchondral medullary cavity. This phenomenon disrupts the subchondral-bone microstructure, alters joint stress distribution, and eventually leads to cartilage degeneration [164]. Interestingly, TGF-β induces the abnormal angiogenesis of subchondral bone in early OA, particularly in type H blood vessels. Additionally, these type H blood vessels disrupt subchondral-bone reconstruction, alter microstructure, and ultimately lead to pathological changes in bone cysts and osteophytes [165,166]. Furthermore, cytokines secreted by many activated osteoclast precursors and mature osteoclasts including VEGF-A and PDGF-BB regulate the production of type H blood vessels, form a pathological coupling mechanism between abnormal angiogenesis and ectopic osteogenesis, and eventually lead to subchondral osteosclerosis and cystic changes [167–169]. The signaling triad can also be secreted by chondrocytes in human cartilage [170]. While RANKL and RANK are unlikely to participate directly in cartilage degradation or chondrocyte activation, RANKL protein in deep cartilage regions can diffuse to the thin layer of calcified cartilage. Here, it can combine with RANK on osteoclast precursors in subchondral bone, promoting the formation of osteoclasts and increasing subchondral-bone turnover related to OA development [170]. Although OPG is considered to have a protective effect on bones and has positive implications in OA progression, recent studies have found that OPG has a negative impact on cartilage. Steeve *et al*. found that OPG significantly increases the levels of two metabolic factors involved in cartilage degradation in chondrocytes: MMP-13 and protease-activated receptor 2 (PAR-2) [171]. MMP-13 causes excessive destruction of the cartilage matrix by degrading natural collagen and noncollagen macromolecules [172,173]. PAR-2 is related to cartilage matrix catabolism and inflammatory cascade reactions occurring in bone joints by upregulating MMP-13 and cyclooxygenase-2 (COX-2) levels [174,175]. Interestingly, PAR-2 is found to upregulate RANKL expression in osteoblasts beneath cartilage [176,177]. If the same phenomenon occurs in chondrocytes, with PAR-2 inducing increased OPG expression, it suggests a cascade reaction in cartilage matrix catabolism due to PAR-2.

The OPG/RANKL/RANK signaling triplet plays a crucial role in the pathological mechanism of OA (Fig. 5). RANKL binds to RANK on the surface of osteoclast precursors, leading to TRAF6 aggregation on the cytoplasmic side of RANK and activating the NF-κB and MAPK (p38, ERK, and JNK) signaling pathways. This activation promotes osteoclast maturation, subchondral-bone mass loss, and bone trabecular microstructure damage. The resulting bone-matrix degradation releases substantial TGF-β, contributing to abnormal blood vessel formation in subchondral bone and thus worsening its pathological changes. Simultaneously, the proliferation of H-shaped blood vessels causes crosstalk between inflammatory factors in subchondral bone and cartilage by providing a channel between the calcified cartilage and cartilage. Conversely, OPG promotes degradation of the cartilage matrix by increasing the MMP-13 and PAR-2 levels.

CXCL12/CXCR4 pathway

CXCL12/CXCR4, a chemokine isolated from mouse stromal cells in the 1990s, is initially recognized for its ability to induce the migration and activation of white blood cells [178,179]. CXCL12/CXCR4 has been proven to be a crucial signaling pathway in developmental processes, such as the generation and maintenance of hematopoietic stem cells, homing of germ cells, cardiogenesis, angiogenesis, and proper assembly of various neurons [180–182]. Human *CXCL12* is located on chromosome 10 and has a molecular weight of approximately 8 kDa and a total coding region of 267 bp [183]. CXCL12 is a small-molecule protein comprising 89 aa, with two cysteine residues and one central aa [184]. It has been originally discovered as a naturally purified chemokine from bone marrow stromal cells and is also known as stromal cell-derived factor-1 (SDF-1) [185]. SDF-1 is a member of the α-chemokine family and has two main splice variants: SDF-1α and SDF-1β. In human cells, six CXCL12 splice variants have been identified, namely, CXCL12 α to φ. The mouse *CXCL12* gene is located on chromosome 6, and only three splice variants (CXCL12 α to γ) have been identified [186,187]. In humans, CXCL12 is primarily expressed in stromal fibroblasts, lymphocytes, vascular endothelial cells, bone-marrow stromal cells, and tumor cells. It binds to the corresponding receptors and mediates various cellular processes, including the recruitment of stem cells to inflammatory and injury sites. It also plays an important role in immune regulation, invasion, migration, angiogenesis, immune escape, and the inflammatory microenvironment [188]. A variety of biological enzymes such as MMPs and cathepsins regulate these processes by establishing a chemokine gradient through CXCL12 degradation [189–192]. Interestingly, due to excellent homology between human and mouse genomes and proteins, mice have become a suitable model for studying the role of CXCL12 in various pathologies [193].

CXCL12 is the only known ligand of CXCR4. The combination of CXCL12 to CXCR4 leads to a series of biological effects [194]. The coding gene of human CXCR4 is located on chromosome 2q21. It is a receptor coupled with G protein with the circuitous sevenfold transmembrane structure, including $–NH_2$ and –COOH,

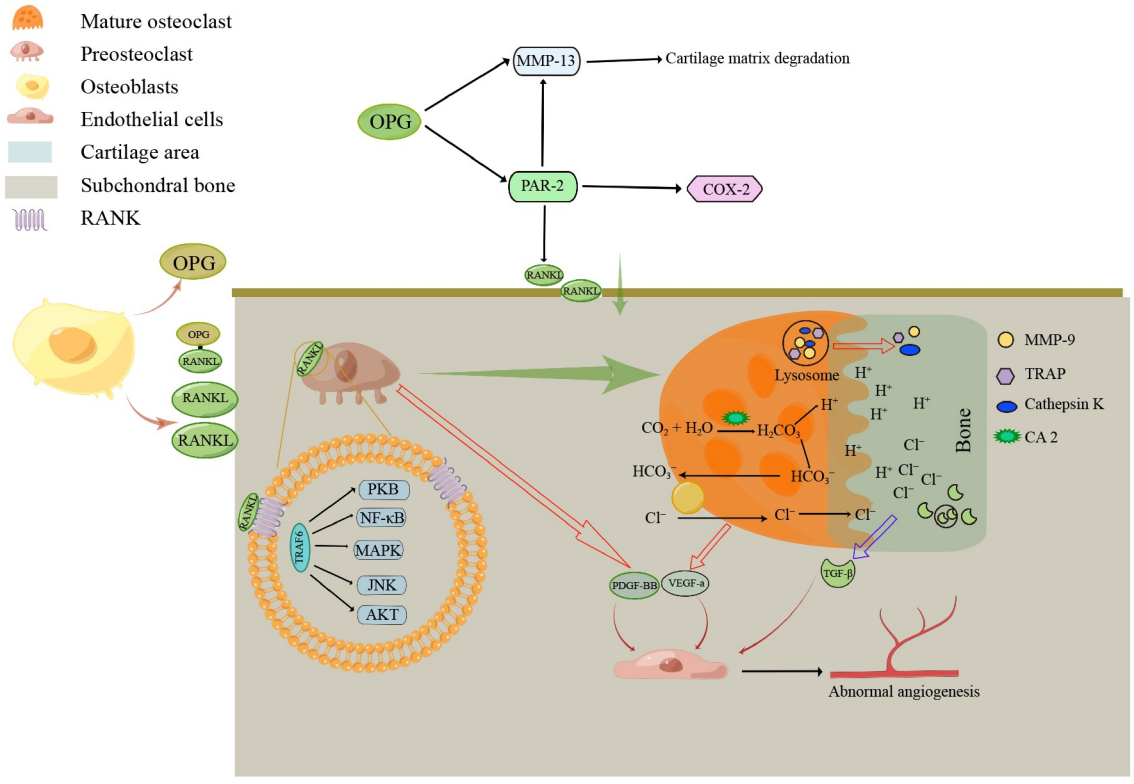

Fig. 5 Role of the OPG/RANKL/RANK signaling pathway in OA progression. RANKL secreted by osteoblasts binds to RANK on the surface of osteoclasts, promoting the development of preosteoclasts into mature osteoclasts and leading to the degradation of the subchondral-bone matrix. Preosteoclasts and mature osteoclasts produce PDGF-BB, VEGF-a, and TGF-β, fostering abnormal blood vessel generation in subchondral bone. Surprisingly, OPG in cartilage increases the levels of two metabolic factors, namely, MMP-13 and PAR-2, which are involved in chondrocyte cartilage degradation. PAR-2 can also induce the migration of RANKL from the cartilage toward subchondral bone. The picture was drawn using Figdraw.

which are composed of 352 aa [195,196]. CXCR4 is an evolutionarily conserved protein that shares 89% of its aa sequence with humans (352 aa) and mice (359 aa) [197]. CXCR4 is expressed in most tissues and organs in the body, such as the bone marrow and umbilical cord blood, as well as on various non-hematopoietic stem-cell surfaces, such as chondrocytes, epithelial cells, stromal cells, and endothelial cells [193]. CXCR4 combines with the specific ligand CXCL12, activating ERK 1/2, AKT, stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK), mammalian target of rapamycin, and NF-κB. It plays important roles in embryonic development, angiogenesis, cell migration, stem cell homing, immune response, inflammatory response, tumor growth, and metastasis [198–206].

The CXCL12/CXCR4 pathway is intimately related to the physiological and pathological states of skeletal muscles. Accordingly, its mechanism of action in subchondral bone and cartilage of the knee joint is receiving increased attention. A dramatic elevation of CXCL12 levels in the synovial fluid and serum is observed in patients with knee OA, and CXCL12 levels are closely correlated with the severity of OA [207–209]. We have previously emphasized that subchondral-bone loss is the initial pathological change associated with OA and is closely related to osteoclasts. Bone resorption involves continuous stages of migration, invasion, and homing of osteoclast precursors from peripheral circulation to the bone, which then differentiate into mature OCs, leading to bone resorption. The CXCL12/CXCR4 pathway plays a role in the recruitment of anterior osteoclasts from peripheral circulation to the bone [210,211]. CXCR4 is highly expressed in pre-OC cell lines. After interacting with CXCL12, it recruits osteoclast precursors to specific bone-marrow niches for OC development by inducing chemotaxis, increasing the expression levels of MMP-9 and collagen migration [212]. We clarified the important role of the OPG/RANKL/RANK signaling pathway in the development and maturation of preosteoclasts. The CXCL12/CXCR4 pathway also plays a significant role in preosteoclast development. TRAP, MMP9, and cathepsin K are involved in osteoclast differentiation and maturation. The CXCL12/CXCR4 pathway activates the p-ERK1/2 and p-p38 pathways, which are effective inducers of activator protein-1 (AP-1) activity. AP-1 increases the secretion of

TRAP, MMP9, and cathepsin K proteins and promotes the differentiation and maturation of preosteoclasts [213].

Previously, we have explored subchondral-bone loss, bone trabeculae fractures causing joint biomechanical imbalance, and abnormal mechanical stimulation leading to overlying cartilage damage. Cartilage injury is a typical pathological change and imaging manifestation of OA. The CXCL12/CXCR4 pathway plays a significant role in the pathological progression of OA. Specifically, CXCL12/CXCR4 leads to cartilage matrix degradation. Patients with OA have joint fluid CXCL12 levels 3.57 times higher than those of normal individuals, decreasing 5.1 times after synovectomy. Notably, CXCL12 can penetrate cartilage, indicating that CXCL12 synthesized by synovial cells can freely diffuse into the adjacent cartilage [214–216]. The CXCL12/CXCR4 pathway activates the ERK and P38 MAPK signaling pathways, promotes the release of MMPs from the cartilage matrix, and degrades type II collagen and aggrecan, which are important components of the cartilage matrix. Thus, cartilage degeneration is accelerated and OA is induced [213]. In human cartilage-explant cultures, CXCL12 induces matrix degradation, boosts MMP-13 expression, and releases glycosaminoglycans [217]. These catabolic processes in cultured chondrocytes are supported by the cell death and secretion of MMP-1, MMP-9, and MMP-13 through CXCL12 [215,218,219].

A recent study has found that the CXCL12/CXCR4 pathway promotes chondrocyte autophagy by upregulating the number of autophagosomes in chondrocytes, increasing the expression of autophagic proteins such as ULK-1LC3B and inhibiting the phosphorylation of mTOR signals upstream of autophagy [220]. The interaction between the cartilage and subchondral bone is considered a central feature in the occurrence and progression of OA [221–224]. The CXCL12/CXCR4 pathway is used as a messenger to harmonize the crosstalk between cartilage and subchondral bone during OA progression. Qin *et al.* (2019) found that the levels of CXCL12 increases in subchondral bone during OA progression, and that the CXCL12/CXCR4 pathway induces bone deterioration through the incorrect recruitment of mesenchymal stem cells and abnormal bone resorption. CXCL12 in subchondral bone may pass through pathological cracks in the subchondral-bone plate to reach the cartilage, linking subchondral-bone deterioration to cartilage degeneration. Subsequently, CXCL12 binds to CXCR4 on the surface of chondrocytes to cause cartilage destruction by inducing the transfer of TGF-β receptor type I from activin receptor-like kinase (ALK) 5 to ALK1 in chondrocytes [225]. Moreover, abnormal angiogenesis leading to vascular system invasion from subchondral bone into the cartilage is a typical pathological hallmark of OA in humans [226]. In subchondral bone, the CXCL12/CXCR4 pathway promotes the proliferation and migration of endothelial cells by activating the MAPK/ERK and PI3K/AKT signaling pathways, thereby accelerating the tubular formation ability of endothelial cells and ultimately leading to abnormal angiogenesis in subchondral bone [227]. Subchondral-bone neovascularization invades avascular cartilage, leading to cartilage degeneration and pain symptoms [228]. Interestingly, VEGF induces lymphangiogenesis and angiogenesis in the cartilage region [229,230]. Wang *et al*. (2017) found that CXCL12 binds to CXCR4 and activates downstream p38 MAPK, leading to increased VEGF expression in chondrocytes and chondrogenic progenitor cells. This biochemical process accelerates the invasion of vascular tides and formation of osteophytes, which are typical features of OA [231].

In summary, the CXCL12/CXCR4 pathway may accelerate OA pathological progression by coupling cartilage degeneration with subchondral-bone destruction (Fig. 6). In subchondral bone, the CXCL12/CXCR4 pathway collects preosteoclasts into specific bone-marrow niches through chemotaxis for osteoclast development. Interestingly, this pathway also promotes the maturation of preosteoclasts. In the cartilage, the CXCL12/CXCR4 pathway activates the ERK and P38MAPK pathways to promote cartilage-matrix degradation. Simultaneously, as a multifunctional "messenger," the CXCL12/CXCR4 pathway crosstalk between cartilage and subchondral bone accelerates the pathological progression of OA. Within subchondral bone and cartilage, the CXCL12/CXCR4 pathway induces the secretion of angiogenic factors such as VEGF. The outcome is abnormal angiogenesis. The exchange of inflammatory factors between cartilage and subchondral bone is promoted as well, further exacerbating OA.

The migration and maturation of osteoclasts play important roles in the pathological changes of subchondral bone. During this process, the CXCL12/CXCR4 pathway recruits preosteoclasts from the peripheral circulation to specific bone-marrow regions. The OPG/RANKL/RANK pathway promotes the development and maturation of osteoclasts in specific regions. Accordingly, these two pathways cooperate with each other during the migration and maturation of osteoclasts. Meanwhile, two multifunctional pathways OPG/RANKL/RANK and CXCL12/CXCR4 promote autophagy and apoptosis of chondrocytes, accelerating the degradation of cartilage matrix. These two multifunctional pathways also promote the abnormal angiogenesis of subchondral bone, i.e., new blood vessels invading avascular cartilage, leading to cartilage degeneration, cytokine crosstalk, and joint pain. Therefore, these two multifunctional pathways play important roles in the pathological changes of

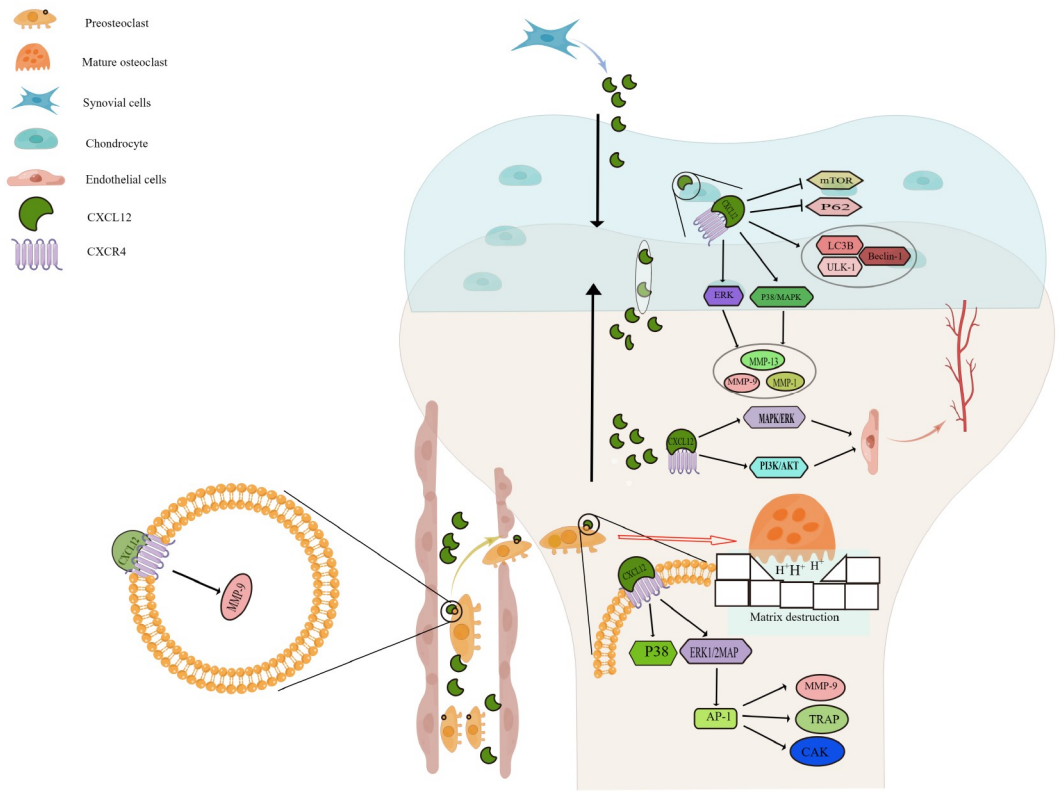

Fig. 6 Role of the CXCL12/CXCR4 signaling pathway in OA progression. CXCL12 binds to the CXCR4 receptor on the surface of preosteoclasts in the peripheral circulation, increasing MMP-9 expression, boosting preosteoclast chemotaxis, and recruiting them into specific bone marrow. In the bone marrow, CXCL12/CXCR4 activates downstream pathways, ultimately promoting the differentiation and maturation of osteoclasts, leading to bone matrix degradation. CXCL12/CXCR4 also regulates the downstream MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase signaling pathway) and P13K/AKT (lipid kinase phoshoinositide-3-kinase signaling pathway) pathways to induce abnormal angiogenesis in subchondral bone. Additionally, the CXCL12 protein in subchondral bone enters the cartilage through "cracks" and works together with the CXCL12 protein produced by synovial cells on chondrocyte CXCR4 receptors. This phenomenon stimulates stromal-cell-derived factor production, elevating autophagosome numbers and autophagy protein expression in chondrocytes and thus leading to degraded cartilage matrix. The picture was drawn using Figdraw.

different structures of the joint. Studying these two pathways can help us better understand the pathological mechanisms of OA and provide ideas for the targeted treatment of OA.

Conclusions

Under normal physiological conditions, subchondral bone effectively absorbs mechanical loads, maintaining joint function and overlying cartilage stability. The impact of pathological changes in subchondral bone in OA is gaining significant research attention. In subchondral bone, abnormal mechanical stimulation disrupts the balance between osteoclast-mediated bone absorption and osteoblast-mediated bone formation, and subchondral bone successively presents pathological changes, such as bone loss, microfracture, subchondral-bone edema, and SBCs. Multiple signaling pathways play important roles in pathological progression. In this review, we detail the important roles of two multifunctional pathways, the OPG/RANKL/RANK and CXCL12/CXCR4 signaling pathways, in the pathological progression of OA in subchondral bone. Both pathways vividly regulate the recruitment and differentiation of anterior osteoclasts in subchondral bone and the maturation of osteoclasts, leading to an imbalance in bone reconstruction. Simultaneously, they regulate abnormal H-type angiogenesis, guiding vascular tissue into avascular overlying cartilage through the subchondral-bone plate. This feature enhances crosstalk between subchondral bone and cartilage. The influx of harmful factors into cartilage cause the pathological degradation of the cartilage matrix, resulting in typical OA pathological changes.

Future studies focusing on osteoblasts, osteoclasts, osteocytes, and corresponding multifunctional signaling pathways and cytokines in subchondral bone can help better elucidate the role of subchondral-bone pathological changes in OA. This knowledge can guide the development of novel drugs targeting these changes for OA prevention and treatment.

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Compliance with ethics guidelines

Conflicts of interest Xuefei Li, Wenhua Chen, Dan Liu, Pinghua Chen, Shiyun Wang, Fangfang Li, Qian Chen, Shunyi Lv, Fangyu Li, Chen Chen, Suxia Guo, Weina Yuan, Pan Li, and Zhijun Hu declare that they have no conflict of interest.

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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