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Review

Pathological Roles of the STAT3 Pathway in the Pathogenesis of Osteoarthritis

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Abstract

Osteoarthritis (OA) is characterized by progressive cartilage degeneration, synovial inflammation, and subchondral bone remodeling. Mechanical stress and inflammation, mediated by activation of innate immunity and cellular senescence, may function as bidirectional, mutually reinforcing drivers of OA onset and progression. Signal transducer and activator of transcription 3 (STAT3), activated by various factors, regulates multiple intracellular pathophysiological processes. In the OA joint, sustained STAT3 activation is observed in synovial fibroblasts, chondrocytes, osteoblasts, and macrophages. This review summarizes accumulating evidence for STAT3 involvement in the onset and progression of OA and highlights the pathological roles of the STAT3 signaling pathway in OA pathogenesis. STAT3 activation stimulates the production of matrix-degrading enzymes in chondrocytes and enhances the release of proinflammatory cytokines in synovial fibroblasts. Additionally, STAT3 activation in macrophages accelerates the secretion of inflammatory mediators, thereby creating a vicious cycle that sustains chronic inflammation in the OA joint. Moreover, STAT3 activation causes abnormal bone sclerosis due to disturbances in subchondral bone remodeling. Altered subchondral bone structure may, in turn, activate the STAT3 signaling pathway in chondrocytes through changes in mechanical loading. Therefore, this exacerbating feedback loop between cartilage and subchondral bone further accelerates OA progression. Collectively, these STAT3-mediated multicellular interactions contribute to disease onset and progression throughout the joint and likely constitute a critical pathological pathway in OA development.

Keywords: osteoarthritis; STAT3; IL-6; chondrocyte; synovial fibroblast; macrophage; subchondral bone; mechanical stress; damage-associated molecular pattern; pyroptosis

1. Introduction

Osteoarthritis (OA) affects the entire joint structures, leading to articular cartilage degradation, synovial inflammation, and subchondral bone remodeling. Accumulating evidence indicates that this chronic joint disease involves the interactions between mechanical stress and inflammatory processes, which are mediated by interconnected molecular signaling pathways [1]. Among a variety of intracellular signaling pathways, the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway plays an essential role in OA pathogenesis [2]. This JAK/STAT pathway is activated by cytokines, growth factors, and other relevant stimuli [2]. Interaction of tyrosine kinase-associated receptors in the cell membrane with cytokines or growth factors activates JAK through tyrosine residue phosphorylation [3]. Subsequently, this signaling pathway facilitates signal transduction from extracellular factors to the nucleus [4]. A number of cytokines can activate the JAK/STAT pathway by binding as ligands to regulate the target gene expression, including interleukins (ILs). JAKs, a family of non-transmembrane tyrosine kinases, comprise JAK1, JAK2, JAK3, and tyrosine kinase (Tyk) 2. Following tyrosine phosphorylation of the receptor-associated JAKs, the receptors recruit STATs for further activation, tyrosine phosphorylation, and dimerization. The STAT family includes STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6, which show distinct biological effects. Upon activation, the STAT dimers translocate to the nucleus and regulate transcription [5]. Recently, the JAK/STAT3 pathway has been shown to participate in the inflammatory and immune responses, cartilage remodeling, and metabolic regulation in OA joints [2,6]. This narrative review focuses on the roles of the JAK/STAT3 signaling network in mediating multicellular interactions that drive the pathophysiology of OA onset and progression.

2. Pathogenesis of OA

OA affects all the joint tissues, including the articular cartilage, the synovium, and the subchondral bone. The pathological processes of disease onset and progression are described in this section.

2.1 Alterations in the Articular Cartilage at the Initial Stage of OA

Pathological changes in the articular extracellular matrix have been studied in animal models and OA cartilage specimens, revealing significant functional, compositional, and structural alterations in both the articular cartilage and periarticular bone from the earliest stages of OA [7]. One of

the first changes observed is an increase in cartilage water content, accompanied by glycosaminoglycan loss, which leads to matrix swelling [8,9]. Early cartilage degradation occurs in the superficial zone and progressively extends to deeper zones as OA advances [10]. Proteoglycan breakdown is primarily driven by the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family, which cleaves the aggrecan core protein [11]. Meanwhile, the collagen network in articular cartilage is vulnerable to degradation by matrix metalloproteinases (MMPs) as well as mechanical stress [12].

2.2 Mechanical Stress at the Initial Stage of OA

Joint tissues are subjected to various mechanical stresses, including shear forces, compressive forces, and tensile strain, which are essential for tissue maintenance and function. Although the precise mechanisms by which mechanical load contributes to OA are not fully understood, excessive or abnormal forces can overwhelm the joint's adaptive capacity, leading to cartilage degradation and OA [13,14]. Factors such as obesity, injury, or malalignment can cause abnormal mechanical loading, disrupting cartilage homeostasis [15]. Chondrocytes sense mechanical stress through mechanotransduction pathways, which normally regulate the synthesis and degradation of cartilage matrix to maintain tissue integrity under physiological loading. In contrast, excessive or abnormal stress can trigger increased MMP production and accelerate OA progression [16,17].

In the early stages of OA, excessive mechanical loading can alter chondrocyte function via cell-surface mechanosensors. For example, in a rabbit hindlimb model, mechanical load caused fibrillation and splitting of articular cartilage, accompanied by disrupted proteoglycan turnover due to altered chondrocyte metabolism [18]. Some chondrocytes may initially increase synthetic activity in an attempt to repair damaged cartilage, as reflected by enhanced proteoglycan staining around the cells [19]. However, aging chondrocytes can adopt a senescence-associated secretory phenotype (SASP), producing proinflammatory cytokines, chemokines, and MMPs that predispose cartilage to OA [20].

Enzymes released by chondrocytes degrade the cartilage matrix, generating matrix fragments that act as damage-associated molecular patterns (DAMPs). These DAMPs engage cell-surface receptors such as Toll-like receptors (TLRs) and also activate the synovium, which releases proinflammatory cytokines that further stimulate chondrocytes, reinforcing a catabolic state [7] (Fig. 1).

2.3 Programmed Cell Death During OA Development

Recent studies suggest that programmed cell death is a key contributor to OA development [21]. Increased chondrocyte apoptosis is observed in the middle and deep layers of OA cartilage, and the number of apoptotic chondrocytes positively correlates with the severity of cartilage destruction in humans [22]. Apoptosis in chondrocytes is primarily induced by IL-1β and tumor necrosis factor-α (TNF-α) [23,24].

Beyond apoptosis, cellular pyroptosis has gained attention in OA research, as its mechanisms in regulating disease progression have become clearer [25,26] (Fig. 1). DAMPs derived from the extracellular matrix signal through TLRs to induce proinflammatory gene expression [27]. Notably, TLR expression is elevated in OA cartilage compared with normal cartilage [28]. Fibronectin fragments can enhance MMP production via TLR signaling in chondrocytes [28], and hyaluronan fragments similarly act as DAMPs to stimulate proinflammatory cytokine production through the TLR pathway [29].

Recognition of danger signals by TLRs initiates innate pattern recognition and activates cytosolic receptors, including nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs). Activated NLRs assemble into a multiprotein intracellular complex called the inflammasome [30]. Among these, the NLR family pyrin domain-containing 3 (NLRP3) inflammasome plays a central role in innate immune and inflammatory responses, and its activation is regulated by DAMPs [31]. NLRP3 activation begins when DAMPs bind to TLRs, triggering the nuclear factor-κB (NF-κB) pathway [32]. Activated NF-κB stimulates transcription of NLRP3, caspase family proteins, and precursors of IL-1β and IL-18 [33]. DAMPs can also promote NLRP3 activation through TLR- and BRCA1/BRCA2-containing complex subunit 3 (BRCC3)-mediated deubiquitination, priming it for NLRP3 inflammasome assembly [34].

Assembly of the NLRP3 inflammasome recruits and activates caspase-1, which cleaves pro-IL-1β and pro-IL-18 into their active forms [33]. NLRP3 inflammasome activation also cleaves gasdermin D (GSDMD) at its N-terminus [35]; the resulting pore-forming GSDMD fragment (GSDMD-NT) oligomerizes by binding to acidic phospholipids on the inner leaflet of the plasma membrane, forming pores that disrupt membrane integrity and release IL-1β, IL-18, and intracellular DAMPs such as high mobility group box 1 (HMGB1) [36,37]. In addition, DAMPs stimulate MMP release via NLRP3 activation [38]. Released IL-1β promotes chondrocyte apoptosis and increases production of matrix-degrading enzymes, contributing to cartilage breakdown [39,40], while IL-18 inhibits proteoglycan synthesis and chondrocyte proliferation [41]. Extracellular HMGB1 further amplifies the inflammatory response in chondrocytes [42].

2.4 Cellular Senescence During OA Development

Cellular senescence plays a key role in aging and age-related diseases in response to various stressors, and many age-associated pathologies are linked to the presence of senescent cells *in vivo* [43]. In articular cartilage, chon-

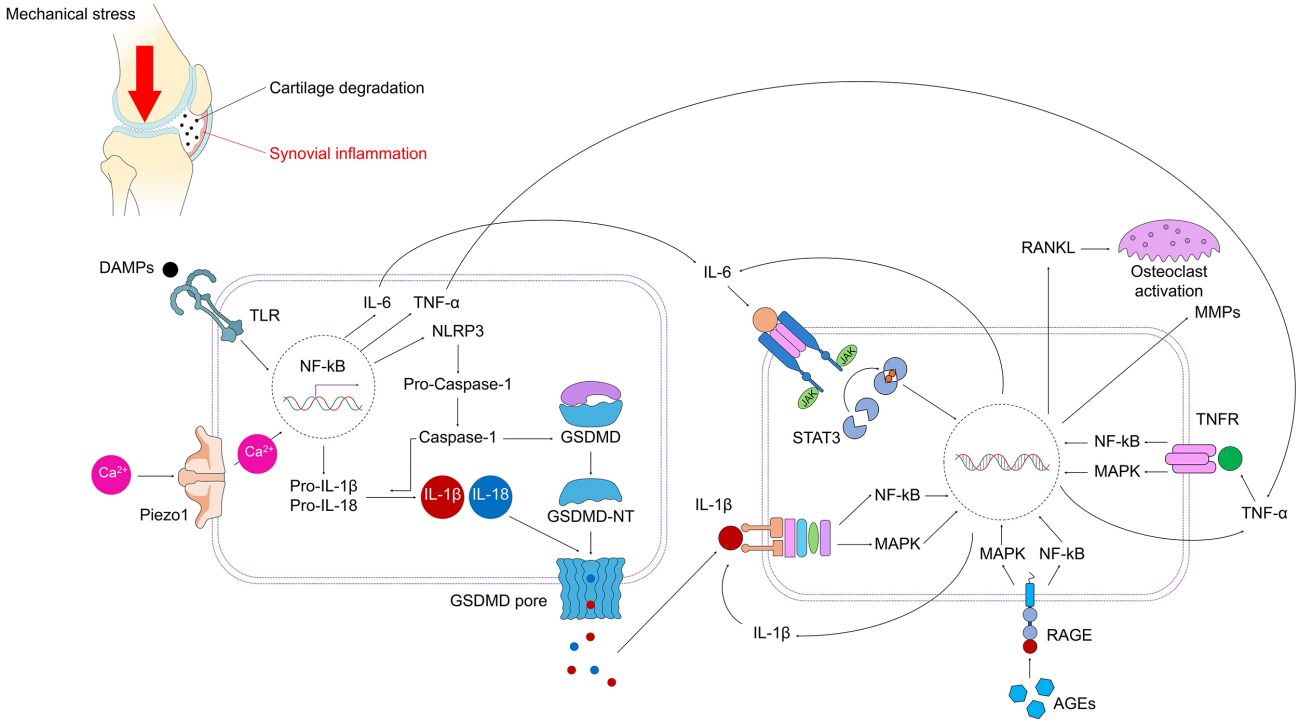

Fig. 1. Pathophysiology of osteoarthritis during disease onset and progression. Toll-like receptors (TLRs) recognize damage-associated molecular patterns (DAMPs), stimulating the expression of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) and activating nuclear factor-κB (NF-κB). Activated NF-κB promotes transcription of NLRP3 (nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3), caspase family proteins, and the precursors of IL-1β and IL-18. Assembly of the NLRP3 inflammasome recruits and activates caspase-1, which cleaves pro-IL-1β and pro-IL-18 into their mature forms. NLRP3 inflammasome activation also cleaves gasdermin D (GSDMD) at its N-terminus; the resulting pore-forming GSDMD fragment (GSDMD-NT) oligomerizes by binding to acidic phospholipids on the inner leaflet of the plasma membrane, forming pores that disrupt membrane integrity and release proinflammatory cytokines, including IL-1β and IL-18. Mechanical overloading activates Piezo1 in synovial fibroblasts, stimulating cytokine secretion via the NF-κB/NLRP3 pathway. IL-6–mediated activation of the Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) pathway promotes proinflammatory effects, including production of cartilage-degrading enzymes, matrix metalloproteinases (MMPs), and receptor activator of nuclear factor-κB ligand (RANKL), which drives osteoclastogenesis. Advanced glycation end-products (AGEs) also exert catabolic effects through the receptor for AGEs (RAGE). MAPK, mitogen-activated protein kinase.

drocyte senescence is closely associated with OA pathogenesis. It is primarily driven by mechanical and oxidative stress. Mechanical overloading can promote cellular senescence by reducing F-box and WD repeat domain-containing 7 (FBXW7) expression, a protein that normally mitigates intracellular stress responses. This reduction accelerates senescence and cartilage catabolism through activation of stress-related signaling pathways [44]. Senescent chondrocytes secrete SASP, which includes proinflammatory cytokines, chemokines, and proteases. These factors amplify local joint inflammation, further promoting cartilage degradation and synovial inflammation [44,45]. Accumulation of senescent cells in articular cartilage therefore sustains chronic inflammation and drives OA progression [46].

Aging also alters cartilage matrix properties through the accumulation of AGEs, which modify the composition and mechanical characteristics of the matrix [20]. Cartilage stiffening caused by excessive AGE accumulation can further exacerbate OA development [44].

2.5 Alterations in Synovium at the Initial Stage of OA

Significant changes occur in the synovial tissue during the early stages of OA, including hyperplasia, hypertrophy, low-grade inflammation, fibrosis, and angiogenesis. Increased macrophage infiltration amplifies synovial inflammation and plays a central role in cartilage degradation through the release of proinflammatory factors. Adipose tissue, including the infrapatellar fat pad, also contributes to OA by interacting with synovial tissues and releasing adipokines that exacerbate joint damage [47].

The mechanosensitive ion channel Piezo1 converts mechanical stress sensed at the cell membrane into electrical signals via Ca^{2+} influx [48]. In rat knee joints, mechanical stress activates Piezo1 in synovial fibroblasts, leading

to increased NF-κB p65 phosphorylation and elevated levels of NLRP3, caspase-1, GSDMD, IL-1β, IL-18, IL-6, and TNF-α. Mechanical stress also promotes synovial fibrosis. These findings suggest that Piezo1 upregulation in the synovium under mechanical overload drives proinflammatory cytokine production and synovial fibrosis through the NF-κB/NLRP3 pathway [49] (Fig. 1).

TLRs are expressed in synovial fibroblasts [50], and their activation by DAMPs generated under mechanical stress can induce inflammasome assembly and trigger pyroptosis [51] (Fig. 1). NLRP3 levels are elevated in OA synovium compared with normal tissue [52], and NLRP3 activation triggered by DAMPs leads to the release of proinflammatory factors, including IL-1β, into synovial fluid, which further stimulates synovial fibroblasts to secrete cytokines [53]. During pyroptosis, large amounts of HMGB1 are released [54], and HMGB1 is overexpressed in OA synovial tissues [55]. Similar to chondrocytes, fibronectin fragments can induce the production of matrix-degrading enzymes, such as MMP-13, via TLR signaling in synovial fibroblasts [56].

Senescent synovial cells produce SASP factors that promote inflammation and cartilage matrix degradation. IL-1 and IL-6 contribute to synovial fibroblast senescence and joint deterioration. Cartilage damage and fibrous synovitis driven by senescent synovial cells alter the joint microenvironment and accelerate OA progression [46].

Macrophages help maintain tissue homeostasis and protect against infection. M1-like macrophages are anti-microbial and pro-inflammatory, whereas M2-like macrophages are anti-inflammatory. An imbalance favoring M1-like macrophages leads to chronic inflammation and may contribute to OA development. Indeed, M1-like macrophages are increased in OA synovium [57]. These cells can be activated via TLRs in response to DAMPs (Fig. 2). One such DAMP is the type II collagen fragment COL2A1, generated by catabolic enzymes induced by inflammatory mediators [58]. Macrophages recognize COL2A1 through pattern recognition receptors [59], which drives M1 polarization and increases production of inflammatory mediators, including TNF-α and IL-1β [60]. This mechanism likely plays a key role in initiating synovial inflammation and contributes to OA onset.

2.6 Alterations in the Subchondral Bone During OA Development

Growing evidence indicates that subchondral bone remodeling is closely linked to articular cartilage degradation [61]. Microstructural analyses indicate that changes in the subchondral bone and overlying cartilage occur simultaneously [62]. In OA, the subchondral bone exhibits increased cortical plate thickness and altered trabecular bone mass and architecture as the disease progresses [63,64]. During the early stages of OA, subchondral bone shows increased porosity, accelerated remodeling, and reduced mineralization. As OA advances, the bone becomes sclerotic, with increased density but decreased remodeling activity [47]. Altered bone turnover affects mineralization and may compromise structural integrity, reducing the bone's ability to absorb mechanical stress [63,65,66]. Additionally, bone cysts and osteophytes often form at the articular margins, accompanied by bone attrition, flattening, and deformation of the subchondral surface [64,67]. Bone marrow lesions in OA subchondral bone are commonly observed in areas of increased mechanical loading [7] or denuded cartilage [68], highlighting the role of overlying cartilage in distributing mechanical forces and protecting subchondral bone from excessive stress. Histological studies suggest that these lesions are associated with trabecular microfractures and focal bone remodeling [69]. Remodeling at microdamage sites may be driven by local release of signaling mediators that recruit bone precursor cells to restore structural integrity [70].

In response to abnormal mechanical stress, subchondral bone undergoes modeling and remodeling with dysregulated activation of transforming growth factor (TGF)-β signaling. This results in bone resorption in the early stages of OA and excessive sclerosis in advanced disease [61,71]. TGF-β is therefore a key cytokine in subchondral bone. Elevated TGF-β1 levels are observed in human OA subchondral bone, and transgenic overexpression of TGF-β1 in osteoblasts induces OA. Conversely, inhibition of TGF-β in subchondral bone reduces cartilage degradation in a mouse OA model following anterior cruciate ligament transection [61].

3. STAT3 Signaling Pathway in the Progression of OA

Emerging evidence indicates that the JAK/STAT3 signaling pathway mediates cartilage degradation and synovial inflammation in OA through proinflammatory cytokines [72]. Activation of this pathway promotes cartilage breakdown by upregulating MMPs and ADAMTS, while also increasing production of proinflammatory mediators such as nitric oxide and prostaglandin E2 [73]. In synovial fibroblasts, JAK/STAT3 activation by IL-1β and IL-6 drives proliferation and further cytokine release, establishing a positive feedback loop that perpetuates joint destruction and inflammation [74]. Sustained STAT3 activation is observed in chondrocytes, synovial fibroblasts, macrophages, and osteoblasts in OA joints [75]. This section focuses on the roles of the JAK/STAT3 pathway in individual cell types during OA progression.

3.1 Chondrocytes

3.1.1 Chondroprotective Effects Mediated by STAT3

Evidence suggests that STAT3 contributes to early cartilage homeostasis. At the initial stage of OA, STAT3 may support repair by promoting chondrocyte differentiation into progenitor-like cells. It also regulates the expression

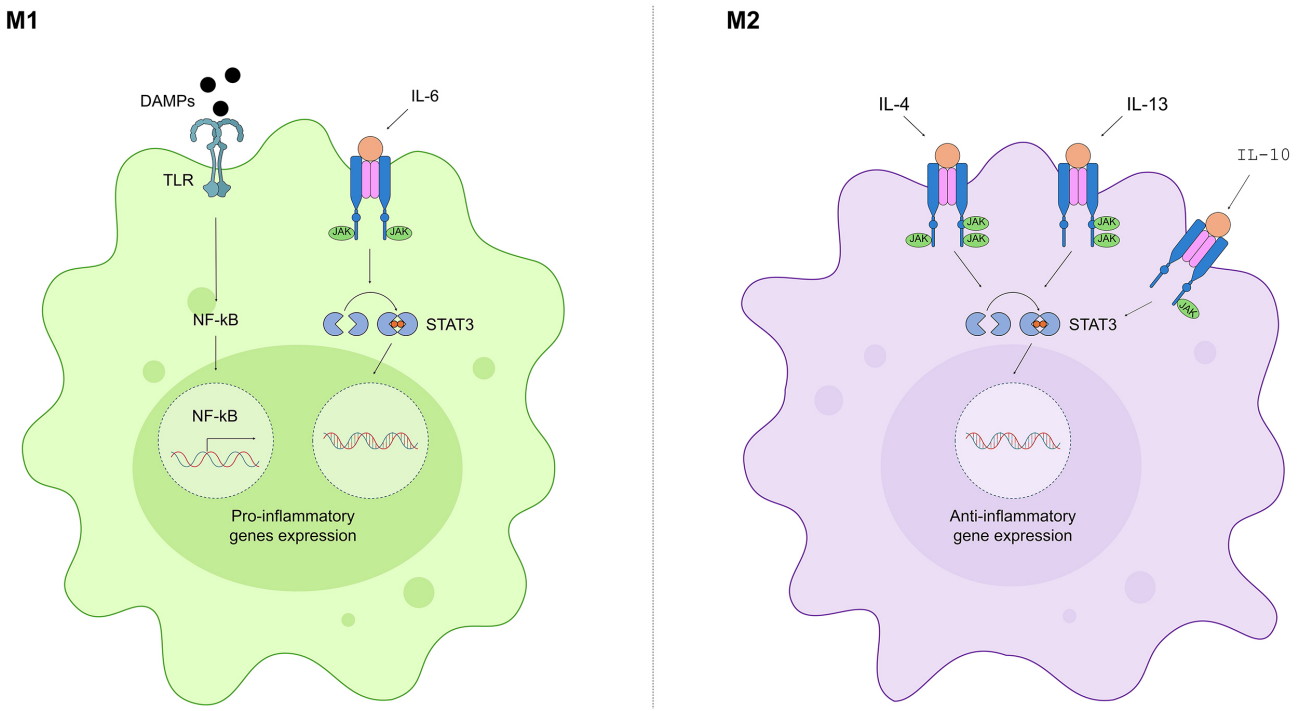

Fig. 2. Role of signal transducer and activator of transcription 3 (STAT3) in macrophage polarization. DAMPs are recognized by macrophages through TLRs, promoting M1 polarization and increased production of inflammatory mediators via the NF-κB pathway. Interleukin (IL)-6 further activates M1-like macrophages through the JAK2/STAT3 signaling pathway. Conversely, anti-inflammatory cytokines such as IL-4, IL-10, and IL-13, produced by synovial tissue and cartilage, drive M2-like macrophage activation via the JAK/STAT3 pathway to counteract inflammation.

of DNA methyltransferase 3 beta (DNMT3B), thereby epigenetically influencing cartilage development [76]. Levels of IL-4 are elevated in OA synovial fluid and synovial cells, and serum concentrations of soluble IL-4 receptor are higher in patients with OA compared to healthy individuals [77,78]. IL-4 exerts anti-inflammatory effects in chondrocytes [79], and these effects are mediated via the JAK/STAT pathway [80]. Through this pathway, IL-4 induces Cbp/p300-interacting protein 2 (CITED2) expression in human chondrocytes, which suppresses MMP-13 production and exerts a chondroprotective effect [81,82].

IL-10 also plays a key anti-inflammatory role. Chondrocytes can synthesize IL-10, which contributes to the regulation of cartilage matrix turnover [83]. Binding of IL-10 to its receptors, IL-10R1 and IL-10R2, activates the JAK/STAT and suppressor of cytokine signaling (SOCS) pathways [84]. Through this mechanism, IL-10 promotes chondroprotection by enhancing type II collagen and aggrecan synthesis, inhibiting MMP production, and exerting anti-apoptotic and anti-inflammatory effects [40]. Suppressor of cytokine signaling 3 (SOCS3) further modulates this system by inhibiting JAK and STAT3 phosphorylation, thus suppressing JAK/STAT3 pathway activation [85,86]. TGF-β1 can protect chondrocytes from IL-6–induced catabolism by reducing SOCS3 expression and limiting STAT3 phosphorylation [87].

3.1.2 Cartilage Degradation Mediated by STAT3 Pathway

At the initial stage of OA, chondrocytes produce SASP factors, including IL-1β and cartilage-degrading enzymes [20]. In addition, mechanical loading of the articular cartilage generates degradation products that act as DAMPs via TLRs, inducing pyroptosis and further IL-1β release (Fig. 1). IL-1β plays a central role in OA pathogenesis by stimulating proinflammatory cytokine production, including IL-6, promoting catabolic processes, and suppressing anabolic activity in cartilage [40].

The Rho family GTPase Cdc42 is highly expressed in the articular cartilage of OA mouse models following surgical destabilization of the medial meniscus. Cdc42 mediates IL-1β-induced IL-6 production, which in turn activates the JAK/STAT3 pathway to regulate inflammation in chondrocytes [88] (Fig. 3). TNF-α can also stimulate IL-6 production [42], reinforcing its contribution to OA progression through JAK/STAT3 signaling [89]. IL-1β can further drive chondrocytes toward a senescent phenotype, increasing SASP factor production, including IL-6 [90], which amplifies autocrine and paracrine senescence. IL-6 signaling via JAK/STAT3 stabilizes cellular senescence, as STAT3 disruption can block SASP-mediated paracrine senescence [91]. STAT3 and phosphorylated STAT3 levels are elevated in OA chondrocytes compared with normal cartilage [88].

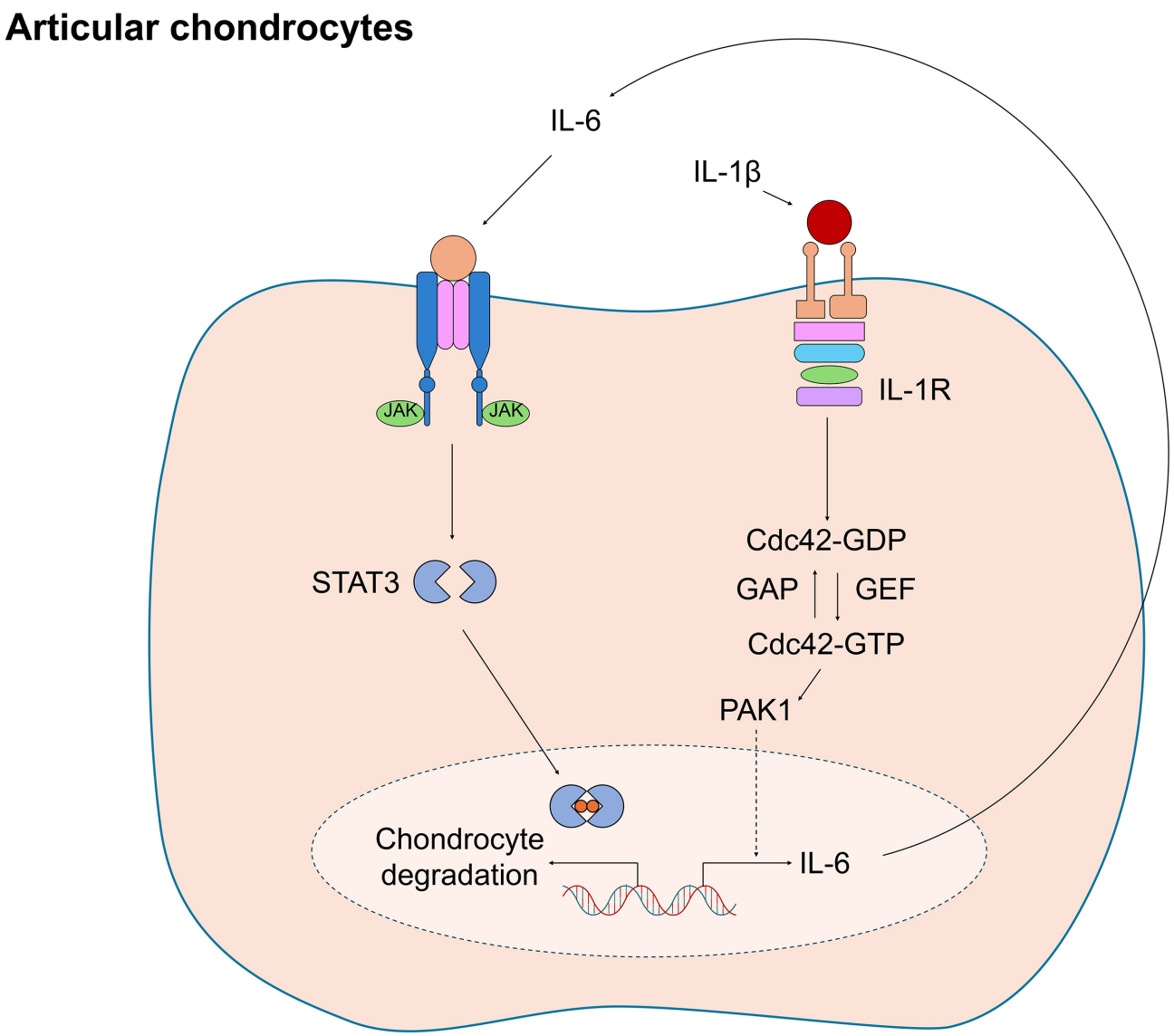

Fig. 3. Roles of Cdc42 and signal transducer and activator of transcription 3 (STAT3) in articular cartilage degradation. Cdc42 promotes IL-6 production, which subsequently activates the JAK/STAT3 pathway in response to IL-1β stimulation. IL-1R, interleukin-1 receptor; GDP, guanosine diphosphate; GAP, guanosine triphosphate-activating protein; GEF, guanine nucleotide exchange factor; GTP, guanosine triphosphate; PAK1, p21-activated kinase 1.

As OA progresses, sustained STAT3 activation in chondrocytes triggers proinflammatory intracellular signaling pathways, promoting disease progression through NF-κB signaling [92]. AGEs also reduce type II collagen synthesis while increasing MMP-13 expression via JAK/STAT3 activation [93] (Fig. 1). Receptor tyrosine kinase-like orphan receptor 1 (ROR1), which is upregulated in OA cartilage, promotes nuclear translocation of STAT3 and its binding to the ROR1 promoter. This positive feedback loop between ROR1 and STAT3 enhances cartilage degradation by upregulating MMP-13 and ADAMTS-5 through NF-κB activation [94].

At later stages of OA, chemokines C-X-C chemokine ligand 8 (CXCL 8) and CXCL11 are elevated in synovial fluid, promoting chondrocyte apoptosis, suppressing proliferation, and increasing expression of IL-1β, TNF-α, IL-6, and MMPs via upregulated STAT3, NF-κB, and c-Jun N-terminal kinase pathways [95]. Additionally, TANK-binding kinase 1 (TBK1) activates JAK/STAT3 signaling in chondrogenic ATDC5 cells, and TBK1 silencing reduces MMP-3, MMP-13, and ADAMTS-4 expression, attenuating cartilage degradation through this pathway [96].

3.2 Synovial Fibroblasts

Synovitis is a major feature of OA. Increasing evidence shows that STAT3 is activated in synovial fibroblasts, establishing a proinflammatory feedback loop that accelerates the production of inflammatory mediators, exacerbates tissue damage, and promotes OA progression [75].

Mechanical overloading activates Piezo1 in synovial fibroblasts, stimulating the release of IL-1β and IL-6 via the NF-κB/NLRP3 pathway [49] (Fig. 1). NLRP3 expression is markedly elevated in OA synovium [52]. At early stages of OA, DAMPs released from cartilage under mechanical stress may trigger NLRP3 activation in synovial fibroblasts, leading to IL-1β production [53] (Fig. 1). IL-1β, in turn, induces IL-6 synthesis in synovial fibroblasts, activating the JAK/STAT3 pathway and increasing production of matrix-degrading enzymes [75]. Gastric cancer–associated transcript 3, a long noncoding RNA, has also been shown to promote synovial fibroblast proliferation via the IL-6/STAT3 pathway [97].

Inflammation further contributes to synovial fibrosis [98]. The JAK2/STAT3 pathway is involved in this process [99], with TGF-β promoting fibrosis through IL-6/JAK2/STAT3 signaling [100]. Fibrotic synovium impairs the maintenance of low-friction properties and chondrocyte nourishment, exacerbating cartilage damage [101,102].

IL-1β can also induce IL-23 production in synovial fibroblasts. IL-23 subsequently promotes IL-8 and IL-6 production [103] and enhances receptor activator of NF-κB ligand (RANKL) expression in OA synovial fibroblasts mediated by the JAK2/STAT3 and NF-κB pathways, facilitating osteoclastogenesis from monocytes [104].

3.3 Macrophages

An imbalance between proinflammatory M1-like and anti-inflammatory M2-like macrophages is now recognized as a key driver of chronic low-grade inflammation, contributing to OA progression [57]. Indeed, OA severity is significantly associated with an increased M1/M2 macrophage ratio [105].

At early stages of OA, macrophages can recognize DAMPs in the joint cavity via TLRs [59]. This interaction promotes M1 polarization, leading to the production of proinflammatory mediators such as TNF-α and IL-1β [60] (Fig. 2). This mechanism may initiate the inflammatory response associated with OA onset. Consequently, OA synovium contains elevated numbers of M1-like macrophages that secrete IL-1β and TNF-α. These cytokines induce apoptosis and senescence in chondrocytes and synovial fibroblasts via inflammatory signaling pathways [106,107], and stimulate the production of SASP factors, including IL-6. As a result, IL-6 levels are markedly elevated in OA synovial fluid [108]. IL-6 further activates M1-like macrophages through the JAK2/STAT3 pathway [109,110] (Fig. 2), promoting production of MMPs and aggrecanases that drive cartilage degradation [111,112].

To counteract inflammation in OA joints, cartilage and synovium secrete anti-inflammatory cytokines such as IL-4, IL-10, and IL-13. These cytokines activate M2-like macrophages via the JAK/STAT3 pathway [2] (Fig. 2). IL-4 phosphorylates STAT3 and enhances its DNA-binding activity [113], while IL-10 mediates negative feedback regulation of inflammation through the JAK1/STAT3 pathway [114]. IL-13 induces M2 polarization via the JAK2/STAT3 and Tyk2/STAT1/STAT6 pathways [113].

3.4 Subchondral Bone

Mechanical overloading induces modeling and remodeling of subchondral bone, accompanied by abnormal activation of the TGF-β pathway. This TGF-β activation promotes bone resorption during the early stage of OA and excessive bone sclerosis at later stages, primarily mediated by mesenchymal stem cells (MSCs) [61,71]. In OA mouse models using anterior cruciate ligament transection, MSCs in subchondral bone secrete higher levels of IL-6 compared with normal MSCs, resulting in enhanced IL-6/STAT3 signaling in these cells. Activation of the IL-6/STAT3 pathway likely plays a key role in mediating the inflammatory and catabolic effects of mechanical stress on cartilage and subchondral bone [115]. Increased subchondral bone turnover is also associated with abnormal osteophyte formation. Synovial lining macrophages may contribute to osteophyte development, as induction of apoptosis in these macrophages can inhibit TGF-β–mediated osteophyte formation [116].

Elevated IL-6 in OA joints stimulates RANKL production in osteoblasts, promoting osteoclast formation and bone resorption [117,118,119] (Fig. 1). IL-1 similarly enhances osteoclastogenesis and bone resorption [120] (Fig. 1), while IL-23 induces RANKL expression in synovial fibroblasts via STAT3 and NF-κB pathways [104]. In osteoclasts, dysregulated STAT3 signaling disrupts subchondral bone homeostasis, contributing to aberrant bone sclerosis [121]. Together, proinflammatory cytokines and RANKL synergistically drive osteoclast-mediated bone resorption, leading to the structural abnormalities observed in OA subchondral bone [122].

Abnormal angiogenesis is also evident in OA subchondral bone [123,124]. STAT3 activation in H-type endothelial vessels promotes proliferation, migration, and angiogenesis, exacerbating angiogenesis-associated osteogenesis and cartilage degeneration. These processes collectively contribute to subchondral bone remodeling and sclerosis in OA joints [125].

4. Potential Therapeutic Interventions by Targeting the STAT3 Pathway

4.1 Therapeutic Candidates Targeting the STAT3 Pathway

As mentioned previously, overactivation and/or overexpression of STAT3 drives inflammatory responses and cartilage degradation in OA joints. Consequently, various strategies have been explored to develop STAT3 inhibitors for clinical use.

Tofacitinib and baricitinib, which act as dual JAK1/STAT3 inhibitors, are already approved for the treatment of rheumatoid arthritis. These JAK inhibitors considerably reduce phosphorylated STAT3 levels in OA

chondrocytes and synovial fibroblasts [126]. Phase II clinical trials in OA have demonstrated that JAK inhibitor treatment decreases IL-6 levels in synovial fluid, suppresses chondrocyte hypertrophy, and improves knee pain without significant side effects over six months [75].

The selective STAT3 inhibitor Stattic blocks STAT3 dimerization and nuclear translocation [127]. In a mouse OA model induced by medial meniscus destabilization, Stattic protects cartilage by suppressing STAT3 activation, alleviating cartilage lesions, osteophyte formation, and synovitis mediated via the IL-6/STAT3 pathway [6]. In cartilage explant cultures, Stattic inhibits IL-6–induced STAT3 phosphorylation and proteoglycan degradation [6]. Additionally, Stattic suppresses osteoclast formation and bone resorption by downregulating STAT3 and NF-κB signaling activated by RANKL [128], highlighting its potential as a therapeutic STAT3 inhibitor for OA.

Another selective STAT3 inhibitor, STA-21, which blocks STAT3 dimerization, has completed phase I clinical trials for psoriasis [129]. In collagen-induced arthritis models, STA-21 modulates mRNA and protein levels of NF-κB p65, RORγt, IL-4, JAK1, and STAT3, leading to marked reductions in joint inflammation and bone erosion [130].

Other approaches to suppress STAT3 signaling include small molecules, peptides, small interfering RNAs, microRNAs, and oligonucleotides. Natural products have also shown promise in targeting STAT3 for OA therapy [131].

4.2 Clinical Prospects and Limitations

Although several STAT3 inhibitors have been shown to effectively block STAT3 activation, translating these therapies into clinical practice remains challenging. Most studies to date have been limited to *in vitro* and *in vivo* experimental models. Systemic suppression of STAT3 carries the risk of off-target and adverse effects, highlighting the need for cell- or tissue-specific targeting strategies [132]. Clinical application of STAT3 inhibitors in OA is further constrained by factors such as unclear pharmacokinetics, low bioavailability, long-term safety concerns, inefficient targeted delivery, and compound instability. For natural compounds, the active ingredients and mechanisms of action remain largely unknown despite their multi-target effects. Therefore, further research is needed to develop STAT3-targeting strategies that overcome these limitations and enable safe and effective OA therapy.

5. Conclusions

Inflammation and mechanical stress act as bidirectional and reinforcing factors in the onset and progression of OA. STAT3 may exert a transient reparative role during the initial stage of the disease; however, as OA progresses, STAT3 signaling becomes a central regulator of disease pathogenesis. In chondrocytes, STAT3 activation upregulates MMP-13 and ADAMTS-5, promoting degradation of type II collagen and proteoglycans, respectively. Activated STAT3 also enhances the release of IL-6, IL-1β, and TNF-α from synovial fibroblasts, amplifying local inflammation and further stimulating STAT3 activity in chondrocytes and macrophages.

In macrophages, STAT3 activation promotes phagocytosis and the secretion of proinflammatory factors, creating a vicious cycle that sustains chronic inflammation. Excessive bone resorption and microstructural damage in subchondral bone contribute to cartilage degeneration in early OA, suggesting that subchondral bone is a potential therapeutic target [133]. STAT3 signaling in OA disrupts subchondral bone homeostasis, leading to abnormal sclerosis. These structural changes, in turn, activate STAT3 in chondrocytes through mechanical stimulation, establishing a positive feedback loop between cartilage and subchondral bone.

This STAT3-mediated network of multicellular interactions orchestrates disease onset and progression across the entire joint and represents a key pathological axis in OA development. A deeper understanding of the JAK/STAT3 pathway in OA pathogenesis may inform effective strategies for targeted intervention in OA management [75].

Author Contributions

TY contributed to the conceptualization of the study and to writing and reviewing the manuscript, gave final approval of the version to be published, and agreed to be responsible for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The author declares no conflicts of interest.

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