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REVIEW

# Key Role of STAT3 in Osteoarthritis: From Pathogenic Mechanisms to Targeted Therapy

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**Abstract:** Osteoarthritis (OA) is a multifactorial degenerative disease characterized by articular cartilage degeneration. Currently, the underlying mechanisms of its pathogenesis remain unclear, and effective treatment options are limited. Signal transducer and activator of transcription 3 (STAT3) is a key transcription factor involved in various physiological and pathological processes, and recent evidence suggests its association with the pathogenesis of OA. Janus kinase (JAK)/interleukin-6/STAT3 signaling pathway plays an important role in STAT3 involved in disease occurrence. This review summarizes the common signaling pathways involving STAT3 in OA and its roles in different cell types. Additionally, we systematically discuss the latest therapeutic approaches targeting STAT3 for OA treatment, aiming to identify drugs that can enhance delivery efficiency and binding affinity. By discussing molecular mechanisms and treatment methods, this review provides a foundation for subsequent research on the STAT3 signaling pathway and OA.

**Keywords:** STAT3, JAK, osteoarthritis, signaling pathway, targeted therapy

## Introduction

Osteoarthritis (OA) is a common degenerative joint disease worldwide, which is fundamentally characterized by cartilage loss that eventually leads to pain and physical dysfunction.[1] According to The Lancet Rheumatology (2023), an estimated 595 million people worldwide were living with OA in 2020, accounting for 7.6% of the global population.[2] In addition to its impact on individuals through pain, disability, and reduced quality of life, OA also imposes a substantial burden on productivity and healthcare systems,[3] However, effective curative treatments for OA remain lacking to date. Although interventions such as physical therapy, oral nonsteroidal anti-inflammatory drugs (NSAIDs), and paracetamol can be employed in the early stages of OA, these available strategies are limited to pain relief and fail to fundamentally halt or reverse disease progression.[4] Joint replacement surgery is an effective treatment for symptomatic end-stage OA, but functional outcomes may be poor, prosthesis lifespan is limited, and patients may face significant financial burdens.[5] This situation is primarily attributable to our limited understanding of the mechanisms underlying the onset and progression of OA. Therefore, to expand the therapeutic landscape and available interventions for OA, it is crucial to elucidate the molecular pathogenesis of the disease and to develop novel therapeutic targets amenable to clinical application.[6] Currently, several signaling pathways have been implicated in the onset and progression of OA, including the Wnt/β-catenin, NF-κB, hypoxia-inducible factors (HIFs), TGF-β/BMP, and FGF signaling pathways. Key regulatory factors involved in these processes include AMPK, mTOR, and RUNX2.[7]

Signal transducer and activator of transcription 3 (STAT3) is one of the transcription factors in the STAT family, including STAT1, 2, 3, 4, 5a, 5b, and 6. Members of the STAT family share structurally conserved functional domains and are involved in a wide range of physiological processes, including cell differentiation, proliferation, immune responses, and apoptosis.[8,9] As a transcription factor, STAT3 is involved in various inflammatory and tumorigenic processes. It can be activated by multiple signaling pathways triggered by a diverse array of molecules, including



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cytokines and oncogenes.[10,11] STAT3 has been extensively studied in the context of immune disorders and cancer.[6,12] Previous research has shown that STAT3 signaling is involved in multiple oncogenic pathways, where it regulates the expression of immunomodulatory factors and recruits immunosuppressive cells to establish a tolerogenic tumor microenvironment (TME), and connecting tumor cells with the TME at different levels of crosstalk to enhance tumor-induced immune suppression.[13–15] Due to its pivotal roles in tumor initiation, metastasis, and therapeutic resistance, the STAT3 signaling pathway has long been regarded as a promising therapeutic target in cancer treatment.[16,17] In addition to cancer, increasing evidence suggests that STAT3 also plays an important role in various bone related diseases, including osteoporosis, OA, and rheumatoid arthritis.[18–20] Hyperactivation of STAT3 signaling is observed in the majority of OA patients and has been associated with poor clinical outcomes. By modulating key processes such as macrophage polarization, mesenchymal stromal cell differentiation, angiogenesis, and bone degradation, STAT3 contributes to the progression of bone-related diseases.[21–23]

Although several studies have explored the role of STAT3 in OA, a comprehensive understanding of its molecular mechanisms and therapeutic implications remains lacking. This gap largely stems from the inherent complexity of OA pathogenesis, which is driven by the interplay of mechanical stress, chronic inflammation, metabolic dysregulation, and epigenetic remodeling—all contributing to progressive joint degeneration.[1,24,25] In recent years, single-cell sequencing technology has further revealed the heterogeneous responses of cartilage, synovium, and immune cells in OA, underscoring that the same signaling pathway may exert markedly divergent effects across different cell types.[26–28] Against this backdrop, hub molecules capable of integrating multiple signaling pathways—such as STAT3—have increasingly emerged as promising targets to overcome therapeutic bottlenecks. Moreover, with advances in targeted therapies and immunotherapies, up-to-date comprehensive reviews summarizing disease mechanisms, treatment progress, and future directions are critical to advancing OA research.[29]

This review aims to provide a systematic and in-depth discussion of the dual roles of STAT3 in OA, thereby offering further insights to inform clinical applications, with a particular focus on STAT3 regulatory functions and targeted therapeutic strategies. We explore mechanistic insights into STAT3 signaling, encompassing both the canonical and non-canonical pathways, their roles in the pathogenesis and progression of OA, as well as the translational potential of targeting STAT3 for therapeutic intervention.[11,30,31] Additionally, we analyze therapeutic approaches targeting STAT3, including Janus kinase (JAK) inhibitors (such as tofacitinib and stattic),[32,33] natural compounds (eg, curcumin and resveratrol),[34,35] Small interfering RNA[36] and microRNA[37] (Figure 1).

# Biological Functions and Regulatory Mechanisms of STAT3

## Fundamentals of the STAT3 Signaling Pathway

### The STAT3 Canonical Signaling Pathway in OA

STAT3 is a protein composed of 770 amino acids and its protein structure consists of several distinct structural domains from the N-terminal to the C-terminal, including the amino-terminal domain (NH2), the coiled-coil domain (CCD), the DNA-binding domain (DBD), the linker domain, the SRC homology 2 (SH2) domain, and the transactivation domain (TAD). Among these, the SH2 domain is the most highly conserved region within STAT proteins and plays a crucial role in signal transduction by binding to specific phosphotyrosine motifs.[38] Interleukin-6 (IL-6) serves as the principal upstream activator of STAT3. The extracellular ligand IL-6 binds to its corresponding membrane receptor, leading to the formation of a heterohexameric complex composed of IL-6, IL-6R, and the transmembrane protein IL-6R subunit-β (gp130). This subsequently activates the STAT3 activation pathway, causing a conformational change in the receptor, activating the JAK tyrosine kinase, which in turn catalyzes the phosphorylation of the tyrosine residue Tyr705 in STAT3, forming a specific phosphotyrosine motif. Phosphorylated STAT3 recognizes and binds to the phosphorylated tyrosine docking site on phosphorylated gp130 via its SH2 domain, which then binds to the phosphorylated Tyr705 site on another STAT3 molecule. This mediates the formation of a dimer and its translocation into the cell nucleus. The phosphorylated dimer in the nucleus binds to DNA to regulate the expression of downstream genes, thereby promoting and activating the transcription of multiple genes that control cell differentiation, proliferation, and survival in various cell types,[38–40] which is also a canonical signaling pathway of STAT3.

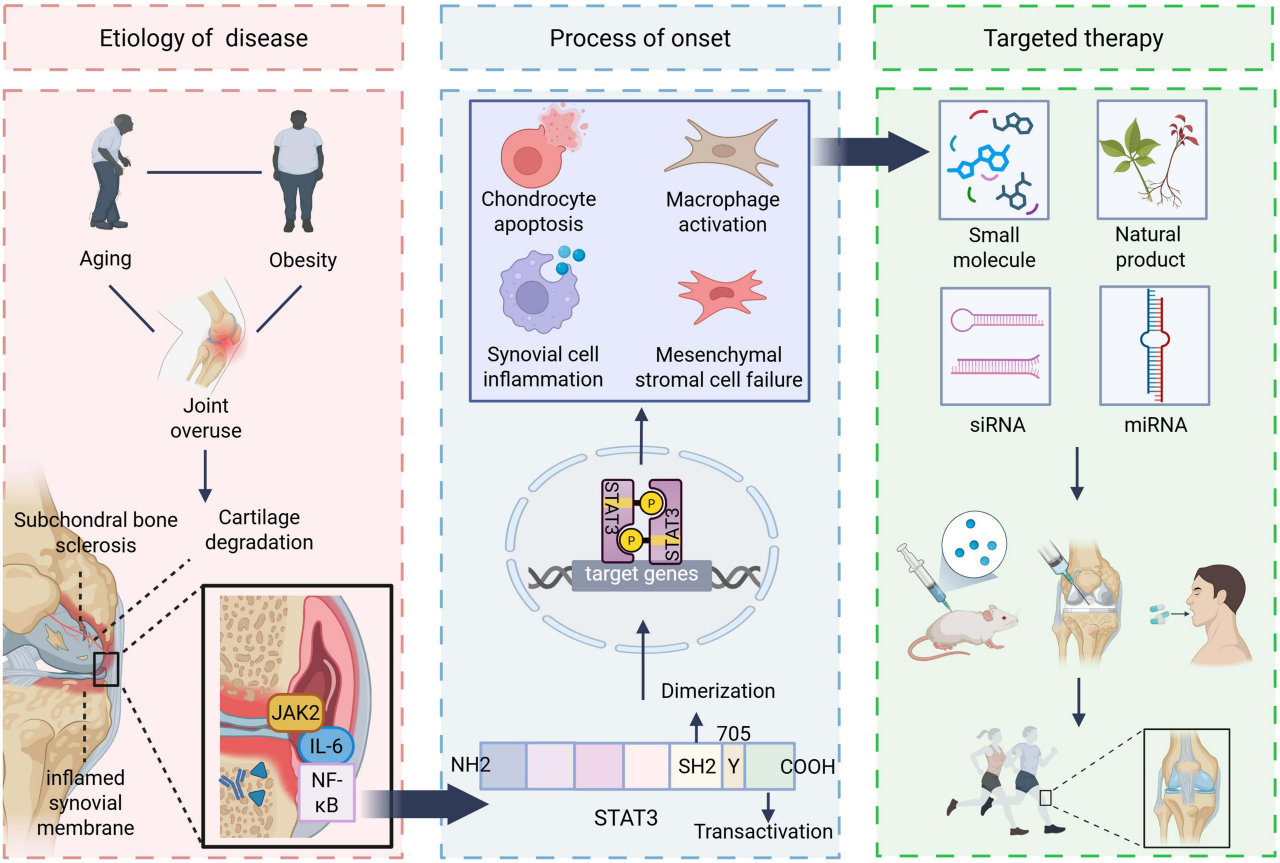


**Figure 1** Schematic overview of the role of STAT3 signaling in the pathogenesis and therapeutic targeting of OA. Aging, obesity, and joint overuse contribute to subchondral bone sclerosis, cartilage degradation, and synovial inflammation. These pathological changes lead to the upregulation of IL-6, which activates the JAK2/STAT3/NF-κB signaling axis. Phosphorylated STAT3 undergoes dimerization and nuclear translocation, promoting the transcription of downstream target genes. This contributes to key pathological events in OA, including chondrocyte apoptosis, macrophage activation, synovial cell inflammation, and mesenchymal stromal cell dysfunction. Multiple therapeutic strategies—such as small molecule inhibitors, natural compounds, siRNAs, and miRNAs—aim to suppress aberrant STAT3 activity. These interventions have shown promise in preclinical models and hold translational potential for future OA treatment. Created with Biorender.com.

STATs were initially discovered through their ability to mediate IFN and IL-6 receptor signaling after binding to homologous cytokines. Cytokine receptors typically lack intrinsic tyrosine kinase activity; instead, they rely on the activation of receptor-associated tyrosine kinases, most notably members of the Janus kinase (JAK) family—JAK1, JAK2, JAK3, and TYK2.[12] Previous studies have shown that the JAK/STAT3 signaling pathway plays a crucial role in mediating the effects of IL-6 on tumor cell proliferation, survival, invasion, metastasis, and its immunosuppressive actions against tumor immunity.[41] As mentioned earlier, OA is an inflammatory disease characterized by cartilage loss. Among inflammatory factors, interleukins (ILs) and interferons (IFNs) are the main proinflammatory factors involved in the pathogenesis of OA. Since these factors are considered stimulators of JAK/STAT signal transduction, the pathogenesis of OA is closely related to the JAK/STAT pathway. Recent studies have suggested that IL-6 and STAT3 are closely linked and can form a related signaling pathway that affects OA progression by influencing processes such as chondrocyte proliferation.[37,42] This highlights the potential therapeutic value of STAT3-related signaling pathways in OA and underscores their significant research implications.

JAK is a non-transmembrane tyrosine kinase in the JAK family, which consists of JAK1, JAK2, JAK3, and Tyk2.[43] The JAK/STAT pathway is an evolutionarily conserved signaling pathway that can be stimulated by various cytokines, hormones, growth factors, and other related molecules, regulating cellular metabolism, differentiation, and immune responses. It promotes cytokine-mediated cellular activation through a convenient and efficient mechanism by triggering a response to fully transmembrane receptor-nuclear signaling.[44,45] Inflammatory factors can act as initiators of the JAK/STAT pathway and play a role in the pathophysiological processes of chondrocytes.[44] Previous studies have shown that,


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compared to normal cartilage tissue, the JAK2/STAT3 pathway is aberrantly activated in OA cartilage. Inhibition of JAK2 affects the expression of its downstream molecule STAT3, which significantly reduces aggrecan (AGG) loss and chondrocyte structural damage, indicating that the JAK2/STAT3 signaling pathway is involved in the imbalance of cartilage homeostasis in OA.[46] IL-1β increases the phosphorylation levels of JAK1 and STAT3, and this effect is significantly reduced after inhibition of hematopoietic cell kinase (Hck), suggesting that Hck induces OA progression by activating the JAK/STAT3 pathway.[47] Additionally, the regulatory role of STAT3 in long non-coding RNAs (lncRNAs) is becoming evident. METTL14-mediated lncRNA-FAS-AS1 activates the JAK/STAT3 signaling pathway by recruiting FMR1, promoting chondrocyte apoptosis and extracellular matrix (ECM) degradation in OA.[48] In addition, Zhang et al found that OA is associated with chronic inflammation and autophagy defects in chondrocytes. Tofacitinib can reduce inflammation by inhibiting IL-1 β - induced activation of the JAK1/STAT3 signaling pathway and restore autophagy to protect ECM.[49] Another study also suggests that STAT3 phosphorylation significantly alters the JAK/STAT3 inflammatory pathway, thereby promoting ECM degradation and leading to the development of OA.[50] Zhang et al's research identified that CXCL8/11 might promote chondrocyte apoptosis and inhibit proliferation via the JAK/STAT pathway, exacerbating the OA disease course.[51] In summary, promoting JAK/STAT3 signaling can advance OA progression by inducing chondrocyte apoptosis, ECM degradation, and disrupting cartilage homeostasis. Therefore, further investigation of the molecular mechanisms of JAK/STAT3 in ECM and cartilage homeostasis is crucial for the development of effective treatments for OA.

IL-6 is a direct target gene of NF-κB in human chondrocytes and a key mediator of several chondrocyte pre catabolic metabolic factors involved in OA. Previous study has found that the overactivated STAT3 signaling pathway in cancer can stimulate the production of IL-6, thereby forming a positive feedback pathway,[41] indicating a close relationship between IL-6 and STAT3. Similar to cancer patients and those with Castleman disease, elevated levels of IL-6 have been observed in patients with arthritis. In chondrocytes, IL-6 promotes catabolism while inhibiting anabolism in articular cartilage. Therefore, inhibition of the IL-6 signaling pathway may provide a potential therapeutic approach for OA. IL-6 induces the JAK/STAT signaling pathway in various diseases, a concept that may also apply to OA.[52] And a study found that STAT3, as a downstream effector of IL-6 signaling, is an indispensable part of the pathogenesis of OA. For example, upregulation of phosphorylated STAT3 (p-STAT3) in cartilage and synovium after joint injury is associated with the worsening of OA symptoms.[53] This has prompted interest in exploring the molecular mechanisms of IL-6 and STAT3 in OA. Liang et al indicated that blockade of the orphan receptor α (RORα) might inhibit the IL-6/STAT3 pathway by directly binding to STAT3 or interacting with the IL-6 promoter, thus improving the matrix catabolism of OA chondrocytes.[54] IL-1β activates Cdc42/p21-activated kinase (Pak), which induces IL-6 production. IL-6 then activates JAK/STAT3 in articular cartilage cells, further contributing to OA. Additionally, IL-6 induces STAT3 and ERK1/2 pathways in chondrocytes and upregulates the production of major proteases involved in the pathogenesis of OA, leading to cartilage degradation. The involvement of STAT3 in IL-6-induced cartilage catabolism appears to be specific. Further experimental results indicated that the IL-6/STAT3 pathway may be another important mediator of mechanical stress-induced catabolic and inflammatory effects in OA-related cartilage damage, acting downstream of many catabolic cytokines or transcription factors in chondrocytes.[33] Mima et al discovered that IL-6 increases the production of inflammatory cytokines in mouse chondrocytes by activating JAK2/STAT3, and after injection of tyrphostin AG490 (a JAK inhibitor), it can reduce cartilage degeneration and arthritis pain to prevent OA progression and improve OA prognosis.[55] Another study found that miR-141/200c targeted SIRT1, acetylating histones on the IL-6 promoter, thereby activating the IL-6/STAT3 pathway and exacerbating OA.[56] Mesenchymal stromal cells (MSCs), which can differentiate into chondrocytes, play a crucial role in maintaining cartilage homeostasis through self-repair mechanisms. In one study, it was found that the activation of the IL-6/STAT3 signaling pathway positively regulates chondrogenic differentiation during the process of human MSCs differentiating into chondrocytes.[57] These studies suggest that the IL-6/STAT3 pathway plays a critical role in OA progression, potentially through its influence on chondrocyte catabolism.

The activation of STAT3 also opens up a negative feedback pathway involving SHP phosphatase and cytokine signaling inhibitory factor 3 (SOCS3).[58] In unstimulated cells, STAT3 is tightly regulated by negative modulators to maintain its inactive state in the cytoplasm. These regulators include protein inhibitors of activated STAT (PIAS), members of the SOCS family, protein tyrosine phosphatases (SHP1, SHP2, PTPN1, PTPN2, PTPRD, PTPRT, and

DUSP22), and members of the ubiquitin ligase family.[41] SOCS3 functions by binding to gp130, preventing JAK kinase-mediated phosphorylation of gp130, and thus inhibiting STAT3 phosphorylation.[59] Yuan et al demonstrated that miR-222-3p promotes macrophage polarization towards an anti-inflammatory phenotype and alleviates inflammation by activating the SOCS3/JAK2/STAT3 pathway.[60] In addition, Jiang et al found that SOCS3 acts as a negative feedback inhibitor in leptin signaling, enhancing its expression to attenuate JAK2/STAT3 pathway activation, potentially contributing to the suppression of OA progression.[61] However, the mechanisms through which SOCS3 and STAT3 signaling influence OA progression still require further experimental validation and exploration.

### The STAT3 Non-Canonical Signaling Pathway in OA

The function of STAT3 extends beyond canonical inflammation-driven mechanisms, encompassing regulation at the levels of cellular metabolism and epigenetics, thus revealing the multi-dimensional role of this pathway in OA. The discovery of the non-canonical STAT3 pathway has expanded the functional dimensions of STAT3, which can influence mitochondrial function and thereby regulate apoptosis. The hallmark of the STAT3 non-canonical signaling pathway is its β-catenin-independent mechanism, involving intracellular signaling and target gene regulation.[29] Recent studies have identified a non-canonical STAT3 signaling mechanism induced by phosphorylation at serine 727 (S727).[62] LPS-induced STAT3 specifically affects mitochondrial-endoplasmic reticulum contact (MERC) protein BAP31 and the mitochondrial membrane protein TOM40, providing new insights into the role of STAT3 in mitochondrial-endoplasmic reticulum interactions under inflammatory conditions.[63] These findings offer a fresh perspective on the pathogenesis and potential therapeutic strategies targeting STAT3 in OA. Moreover, mitochondrial-localized STAT3 (mtSTAT3) regulates the activity of respiratory electron transport chain complex I, influencing ROS generation and ATP synthesis,[64,65] suggesting that STAT3 may exacerbate oxidative stress in OA chondrocytes. Non-phosphorylated STAT3 can also dimerize and participate in various cellular activities. It can directly or indirectly regulate gene expression through mechanisms such as DNA methylation and histone modifications, thereby affecting the cell's epigenetic state. One study revealed a novel role of STAT3 in regulating DNA methylation, where the loss of STAT3 in chondrocytes led to increased expression of DNMT3B in knee joint cartilage cells in vivo, exacerbating post-traumatic OA progression induced by medial meniscus instability (DMM).[66] STAT3 can be acetylated at lysine 685 by its co-activator p300/CREB-binding protein, and cytokine treatment, such as IL-6, induces this acetylation.[67] Acetylation stabilizes STAT3 dimers, augments DNA binding and transcriptional activation, and subsequently upregulates inflammatory genes including IL-6 and OSM. These findings underscore the potential impact of the STAT3 non-canonical signaling pathway in OA, providing new avenues for targeted therapeutic interventions. Figure 2 illustrates the mechanisms of canonical and non-canonical STAT3 signaling pathways.

## Cell-Specific Functions of STAT3

As a common downstream signaling protein of many cytokines, STAT3 is involved in regulating cell proliferation and intercellular interactions. STAT3 directly influences the progression of bone-related diseases by modulating osteoclast activation, macrophage polarization, mesenchymal stromal cell differentiation, and cartilage degradation.[68] Investigating the specificity of STAT3 in different cell types and its interactions offers potential strategies for the treatment of OA (Table 1).

### Chondrocytes

Chondrocytes are the only cell type in articular cartilage and play a crucial role in the onset and progression of OA, surrounded by a collagen-rich ECM. ECM damage, increased expression of matrix-degrading proteases, and chondrocyte apoptosis are the primary causes of cartilage degradation in OA.[85] Therefore, understanding how STAT3 mediates OA in chondrocytes is essential.

Zhang et al discovered that inhibition of miR-375 enhances the ability of chondrocytes to counteract oxidative stress, maintaining ECM metabolic homeostasis. By activating the JAK2/STAT3 pathway, miR-375 inhibition protected chondrocytes, thereby alleviating OA.[69] Wu et al demonstrated that exposing rat knee joints to Benzophenone-3 significantly increased IL-6 transcription levels in chondrocytes and enhanced phosphorylation of JAK2 and STAT3. This activation upregulated catabolic genes such as MMP13, promoting ECM degradation and exacerbating chondrocyte damage.[50] Parathyroid hormone (PTH) (1–34), clinically used for the treatment of osteoporosis, attenuates chondrocyte apoptosis

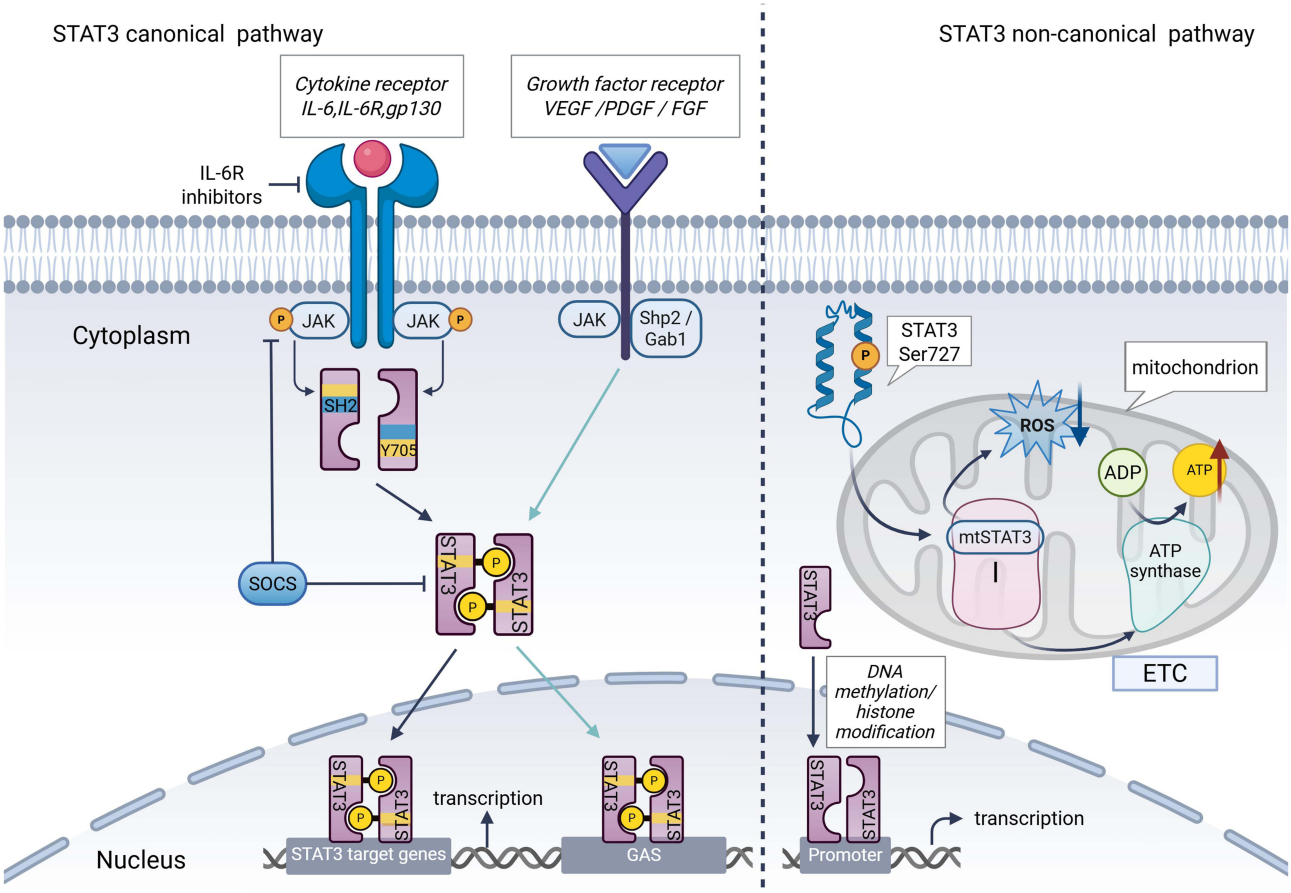


**Figure 2** Schematic illustration of the canonical and non-canonical STAT3 signaling pathways. In the canonical pathway (left), extracellular cytokines (eg, IL-6) bind to their receptor complex (IL-6R/gp130), activating JAK kinases and triggering phosphorylation of STAT3 at Tyr705, while certain members of the SOCS family can inhibit JAK kinase activity, thereby preventing STAT3 dimerization. Phosphorylated STAT3 dimerizes via SH2 domains and translocates into the nucleus, where it binds GAS elements or target gene promoters to drive transcription. Growth factor receptors (eg, VEGF, PDGF, FGF) can also activate STAT3 through intermediates such as Shp2 and Gab1. Additionally, nuclear STAT3 can modulate gene expression through epigenetic mechanisms like DNA methylation and histone modification.In the non-canonical pathway (right), STAT3 is phosphorylated at Ser727 and translocated into mitochondria (mtSTAT3), where it regulates electron transport chain (ETC) activity, enhances ATP production via ATP synthase, and modulates mitochondrial ROS levels. These mitochondrial functions of STAT3 are essential for cellular bioenergetics and redox homeostasis. In addition, unphosphorylated STAT3 is capable of forming dimers via epigenetic mechanisms, such as DNA methylation and histone modifications, thereby modulating gene expression. Created with Biorender.com.

and preserves cartilage metabolic homeostasis in OA models by downregulating the JAK2/STAT3 pathway and consequently enhancing aggrecan (AGG) expression.[70] These findings suggest that regulation of upstream JAK2 leads to changes in downstream STAT3, resulting in the imbalance of chondrocyte homeostasis in OA. However, JAK2 regulation may also cause unrelated side effects.[19,55] Consequently, some studies have shifted focus to the specific regulatory role of downstream STAT3. A study found that knockdown of the focal adhesion protein kindlin-2 (K2) promoted mitochondrial oxidative stress and activated STAT3. This in turn increased the expression of the downstream target protein Runx2, leading to enhanced chondrocyte catabolism and aggravated OA. This suggests that STAT3 might influence OA progression by mediating chondrocyte catabolism. The study also revealed that this process does not involve JAK2 activation of STAT3 but is partially triggered by elevated reactive oxygen species (ROS) levels in chondrocytes.[53] Another study confirmed that IL-6 mainly activates STAT3 to induce the synthesis of MMPs and aggrecanases in chondrocytes, thereby degrading the ECM.[33] Zeng et al demonstrated that FOXM1 induces activation of the JAK1/STAT3 signaling pathway in chondrocytes, leading to increased STAT3 phosphorylation and nuclear translocation. Moreover, FOXM1 directly interacts with STAT3 to upregulate the expression of multiple inflammatory mediators, including IL-1β, IL-6, and TNF-α.[71] In conclusion, whether through upstream STAT3 regulation or downstream targets, both can lead to ECM degradation and chondrocyte damage, disrupting chondrocyte homeostasis and accelerating OA progression.

**Table 1** Upstream Activators, STAT3 Targets, and Cellular Roles of the STAT3 Signaling Pathway in OA

| Cell Type | Upstream Activator | STAT3 Downstream Target(s) | Functional Effect | Reference |
|---|---|---|---|---|
| Chondrocyte | miR-375 inhibition | AGG (Aggrecan) | Protects chondrocyte by activating the JAK2/STAT3 pathway | Zou et al[69] |
| Chondrocyte | Benzophenone-3 | MMP13 | Promotes extracellular matrix degradation and exacerbates chondrocyte damage by elevating IL-6 levels | Wu et al[50] |
| Chondrocyte | Parathyroid hormone (PTH) (1–34) | AGG | Attenuates chondrocyte apoptosis and preserves cartilage metabolic balance by suppressing the JAK2/STAT3 pathway | Shao et al[70] |
| Chondrocyte | Kindlin-2 | Runx2 | Enhances chondrocyte catabolism | Wu et al[53] |
| Chondrocyte | Interleukin(IL)-6 | MMPs, aggrecanases | Induces ECM degradation through catabolic enzyme synthesis | Latourte et al[33] |
| Chondrocyte | FOXM1 | IL-1β, IL-6, TNF-α | Promotes the production of inflammatory cytokines and reduces chondrocyte survival | Zeng et al[71] |
| Macrophage | HMGB1, TLR4 | IL-1β, IL-6, IL-17A | Releases inflammatory mediators via the TLR4/STAT3 pathway | Feng et al[72] |
| Macrophage | LOXL1 | IL-6, IL-1β, TNF-α | Promotes M1 macrophage polarization, releases inflammatory mediators | Jiang et al[73] |
| Macrophage | IL-1β | NF-κB, IL-6 | Enhances IL-6 secretion through a positive feedback loop | Limagne et al[74] |
| Macrophage | Nrf2 | Small heterodimer protein (SHP) | Inhibits M1 polarization and promotes M2 polarization, downregulates the transcriptional activity of STAT3 | Wang et al[75]<br>Gong et al[76] |
| Macrophage | IL-13, IL-4 | 15-LO, CD36 | Induces the DNA-binding activity of STAT3 | Bhattacharjee et al[77] |
| Macrophage | Angelicin | CD9, gp130, IL-1β, TNF-α | Conducts CD9/gp130 to repolarize toward M2 macrophages | Tian et al[21] |
| Synovial Cell | Quercetin | HIF-1α | Reduces secretion of pro-inflammatory mediators, inhibits synovial cell migration and invasion | Zhang et al[78] |
| Synovial Cell | SMILE (Small heterodimer partner-interacting leucine zipper protein) | AMPK | Inhibits pain, cartilage destruction and immune cell differentiation (Th17, Th2, Treg) via the AMPK/STAT3 signalling pathway | Moon et al[79] |
| Synovial Cell | Leptin | IL-6, CD14, TLR4 | Promotes expression of pro-inflammatory proteins | Jiang et al[61]<br>Xiong et al[80] |
| Mesenchymal Stromal Cells (MSCs) | IL-10 | NLRP3 | Inhibits inflammasome activation, promotes M2 macrophage polarisation | Jiang et al[81]<br>Ma et al[82] |
| MSCs | miR-148a | iNOS, IL-10 | Targets KLF6, promoting M1 to M2 polarisation via the JAK/STAT3 pathway | Tian et al[83] |
| MSCs | MiR-216a | - | Promoting chondrocyte proliferation and migration whilst inhibiting apoptosis | Rong et al[84] |

## Synovial Cells

The synovial membrane consists of two layers: the inner layer primarily comprises synovial macrophages and synovial fibroblasts, while the outer layer is composed of various types of connective tissue, playing a crucial role in maintaining joint homeostasis.[86] The intercellular interactions between different cell populations in the synovium are key to triggering synovitis.[87] The synovium secretes a large number of inflammatory cytokines, including IL-1, IL-6, tumor necrosis factor α (TNF-α), and IL-8. These cytokines diffuse into the cartilage through the synovial fluid, leading to abnormal synovial cell growth and increased inflammatory responses. Traditionally, OA was considered a result of mechanical stress-

induced cartilage wear; however, recent studies have shown that synovial inflammation plays a crucial role in the onset and progression of OA. The histology of synovium in OA patients is characterized by synovial intimal hyperplasia, inferior intimal fibrosis, and stromal vascular formation.[88] Increasing evidence suggests that synovitis and the associated pro-inflammatory mediators are central to the pathogenesis of OA and significantly affect articular cartilage.[89] As a key signaling and transcriptional activator, STAT3 plays a core role in synovial cell-mediated chronic inflammation.

Zhang et al found that quercetin reduced IL-6-induced energy metabolism and oxidative stress in synovial fibroblasts, inhibiting the JAK1/STAT3/HIF-1α signaling pathway. This suggests that quercetin may regulate energy metabolism through the JAK1/STAT3/HIF-1α pathway, thereby reducing the secretion of pro-inflammatory mediators, inhibiting synovial cell migration and invasion, and ultimately slowing the destruction of bone and joints.[78] Another study showed that overexpression of Small heterodimer partner-interacting leucine zipper protein (SMILE) inhibited pain and joint cartilage destruction in a mouse OA model. Further research revealed increased expression of phosphorylated AMPK (p-AMPK) in synovial tissue and decreased expression of p-STAT3, suggesting that SMILE expression activated the AMPK signaling pathway while inhibiting STAT3 expression. Flow cytometry analysis also demonstrated that SMILE overexpression inhibited OA progression and the differentiation of immune cells such as Th17, Th2, and Treg through the AMPK/STAT3 signaling pathway.[79] Obesity is considered a risk factor for OA, and leptin is one of the most relevant factors secreted by adipose tissue.[61] Leptin exerts potent effects on immunity and inflammation by binding to its specific receptor (Ob-Rb). Xiong et al found that leptin can activate the JAK2/STAT3 signaling pathway and bind to Ob-Rb in synovial fibroblasts, upregulating IL-6 production in vitro, thereby exacerbating OA.[80] Another study also suggested that leptin promotes OA progression by inducing the JAK2/STAT3 pathway, leading to increased expression of pro-inflammatory proteins such as CD14 and TLR4.[61] These studies suggest that STAT3-related pathways primarily influence synovial cells in two ways: by regulating synovial cell metabolism and proliferation, and by controlling inflammatory responses. Firstly, STAT3-related pathways regulate the production of inflammatory cytokines, such as TNF-α and IL-6, leading to intensified inflammation in synovial tissue.[90] Secondly, STAT3-related pathways participate in regulating the function and activity of immune cells, such as macrophages, T cells, and B cells.[91–93] Synovial tissue is a rich region of immune cells, and the STAT pathway regulates the intensity and duration of immune responses by controlling the number of immune cells.[94]

## Macrophages

Macrophages are the most common immune cells in the synovial joints, and are major players in chronic synovial inflammation, osteophyte formation, subchondral bone remodeling, and cartilage damage. They are also the primary innate immune effector cells that trigger the initial inflammatory response in OA.[75,95,96] Macrophages impact bone in every stage of the inflammatory response. During the progression of arthritis, fibroblast-like synoviocytes (FLS) can promote macrophage polarization, driving cartilage matrix degradation and bone proliferation. During the recovery phase, M2 phenotype macrophages secrete various tissue repair-promoting factors, such as vascular endothelial growth factor (VEGF), and participate in bone tissue regeneration and remodeling.[97,98] Macrophage polarization in OA is regulated by multiple environmental stimuli. The involvement of M1 phenotype macrophages promotes cartilage cell damage and synovial inflammation, releasing pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), IL-1β, and IL-6.[99] Feng et al found that ferroptotic M2 macrophages release HMGB1, which activates the Toll-like receptor 4 (TLR4)/STAT3 signaling pathway in M1 macrophages through phosphorylation at serine 727, promoting an inflammatory response that may mediate OA progression.[72] Furthermore, Jiang et al discovered that LOXL1 increased the expression of NF-κB p-p65 and p-STAT3, primarily activating M1 macrophages via the NF-κB/STAT3 pathway. This activation promoted the secretion of inflammatory cytokines, including IL-6, IL-1β, and TNF-α, and advanced OA pathogenesis.[73] STAT3 can influence the phenotype and function of macrophages by regulating the expression of various inflammatory factors. One study showed that IL-1β activation of NF-κB induces IL-6 secretion, which then triggers STAT3 activation in macrophages. STAT3 subsequently upregulates IL-6 secretion, thereby forming a pro-inflammatory feedback loop.[74] Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that encodes various antioxidant enzymes and has anti-inflammatory effects. Upon activation, Nrf2 can suppress M1 polarization and promote M2 polarization via the STAT3 signaling pathway.[75,76] Additionally, IL-13 and IL-4 can activate M2 macrophages by

activating the JAK2/STAT3 signaling pathway, with JAK2 involved in regulating the STAT3 DNA-binding activity in response to IL-13 stimulation.[77] Tian et al found that angelicin maintained M2 polarization under LPS/IFN-γ conditions and downregulated the expression of inflammatory mediators like IL-1β and TNF-α. At the molecular level, angelicin activates the p-STAT3/STAT3 pathway via CD9/gp130 signaling to repolarize M2 macrophages, thereby alleviating OA progression.[21] In summary, inducing macrophage differentiation via STAT3 may serve as a promising therapeutic strategy for OA by regulating macrophage polarization and modulating inflammation.

### Mesenchymal Stromal Cells (MSCs)

Increasing evidence indicates that MSCs are pluripotent stem cells isolated from various tissues such as bone marrow, adipose tissue, placenta, and umbilical cord, possessing the potential for multidirectional differentiation and self-renewal, and exhibiting close associations with macrophages.[100] Stem cell therapy has become a research hotspot in many medical fields, and recent studies have pointed out that under certain conditions, stem cells can be induced to differentiate into chondrocytes, thereby maintaining the function and stability of cartilage.[101] Furthermore, MSCs derived from various tissues have not shown significant adverse effects in OA treatment, suggesting that MSCs have the potential to alleviate clinical symptoms and promote cartilage regeneration.[102]

Nie et al confirmed both in vivo and in vitro that placental mesenchymal stem cells (pMSCs) activate the STAT3 signaling pathway through the secretion of IL-10, leading to increased phosphorylation and nuclear translocation of STAT3. This inhibits NLRP3 inflammasome activation, promotes M2 macrophage polarization, and suppresses the inflammatory response. The study demonstrated that MSC-derived exosomes (MSC-EXOs) have the ability to promote chondrocyte proliferation, induce macrophage polarization towards the M2 phenotype, and regulate the inflammatory response, ultimately alleviating OA.[81,82] Tian et al found that MSC-EXOs improved the inflammatory microenvironment by promoting the transition of macrophages from the M1 to the M2 phenotype, thereby repairing inflammatory damage.[83] Further experiments showed that EXO-loaded miRNA (miR-148a) directly targeted and reduced the expression of DNA-binding transcription factor KLF6, which lowered p-STAT3 levels and modulated the JAK/STAT3 signaling pathway to alter macrophage polarization. Additionally, Liu et al demonstrated that under hypoxic conditions, MSCs transfer their exosome miR-126 to endothelial cells, promoting cell proliferation, angiogenesis, and migration, thereby accelerating fracture healing.[103] Previous studies have indicated that increased levels of the pro-angiogenic factor VEGF can alleviate pain and OA symptoms.[104] Another study revealed that HIF-1α may induce the release of small extracellular vesicles (sEVs) from hypoxic bone marrow mesenchymal stem cells (BMSCs), enhancing the production of miR-216a-5p. miR-216a-5p upregulated the expression levels of JAK2 and STAT3, and through mediating the miR-216a-5p/JAK2/STAT3 signaling pathway, promoted chondrocyte proliferation, migration, and apoptosis inhibition, ultimately achieving therapeutic effects for OA.[84] Numerous experiments have verified the positive roles of MSCs and their exosomes in promoting macrophage polarization, inhibiting inflammatory signaling pathways, and improving chondrocyte function, providing strong support for the application of stem cell therapy in OA treatment. Figure 3 shows the mechanism of action of the STAT3 signaling pathway in OA in different cell types.

## Interactions of STAT3 with Other OA-Related Pathways

The pathological progression of OA is a complex network involving the interaction of multiple tissues and factors, regulated by various signaling pathways.[7,105] As a multifunctional transcription factor, the study of how STAT3 interacts with other key signaling axes and jointly drives the pathological process of OA holds significant scientific and clinical importance.

NF-κB is a core transcription factor that regulates inflammatory responses and can be activated by various stimuli such as IL-1β and TNF-α. There exists a multi-level interaction between NF-κB and STAT3.[106] On the one hand, the activation of NF-κB signaling produces cytokines, such as IL-6 and IL-1β, that can activate the STAT3 pathway.[107] Moreover, certain kinases induce NF-κB transcription, thereby activating STAT3 and recruiting it to specific target genes.[108] On the other hand, JSI-124 (a STAT3 inhibitor) activates the NF-κB pathway, and the phosphorylated NF-κB induces the expression of SOCS3, which acts as a negative regulator of STAT3, thus inhibiting subsequent STAT3 activation.[109] IL-10, through binding to IL-10Rβ, increases its affinity, allowing STAT3 to be more effectively activated.[110] An increase in STAT3 may lead to more p50/p50 NF-κB homodimers being activated and translocated

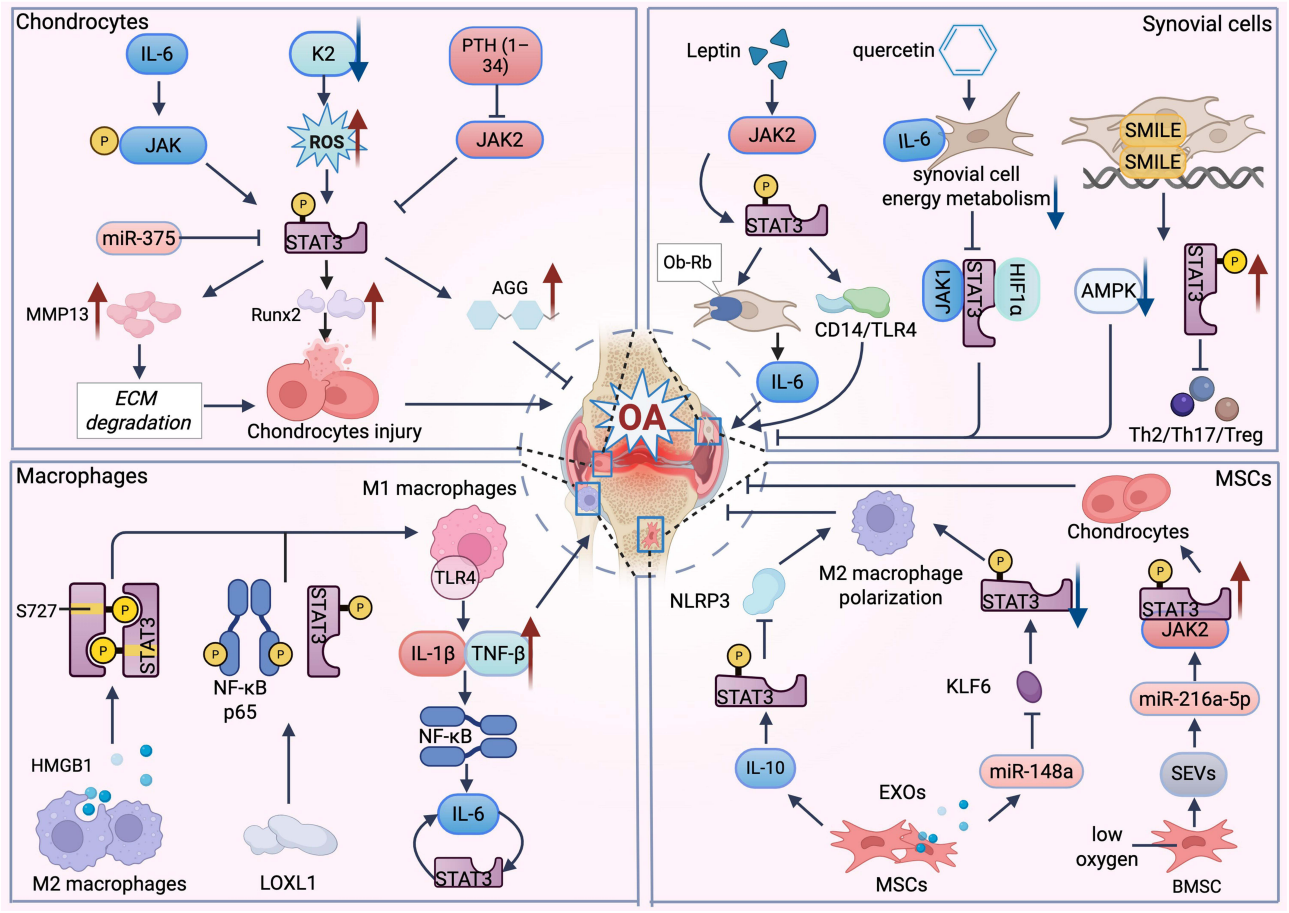


**Figure 3** Schematic representation of STAT3 signaling pathways in various cell types contributing to OA pathogenesis. In chondrocytes (top left), the IL-6/JAK signaling pathway induces STAT3 activation, which subsequently upregulates MMP13 expression and promotes ECM degradation. Knockdown of K2 elevates intracellular ROS levels, leading to increased expression of the downstream target protein Runx2 and enhanced chondrocyte catabolism, thereby aggravating the progression of OA. Conversely, PTH (1–34) suppresses the expression of JAK2 and STAT3, resulting in elevated levels of AGG and attenuation of OA pathology. miR-375 negatively regulates STAT3, indirectly reducing cartilage catabolism. In synovial cells (top right), leptin triggers JAK2/STAT3-mediated IL-6 expression via CD14/TLR4, while quercetin suppresses IL-6-driven metabolic activation. STAT3 also mediates energy metabolism and immune polarization (Th2/Th17/Treg) through AMPK signaling, while SMILE expression may modulate synovitis symptoms by downregulating AMPK and upregulating p-STAT3 expression. In macrophages (bottom left), ferroptotic M2 macrophages can trigger M1 activation via the HMGB1/TLR4/STAT3 (Ser727) axis. LOXL1 further enhances the M1 response through the NF-κB/STAT3 pathway. Activated M1 macrophages release pro-inflammatory cytokines (TNF-α and IL-1β) to promote synovitis and cartilage degradation. And the released pro-inflammatory factors promote the formation of a positive feedback loop between IL-6 and STAT3 through NF-κB. In MSCs (bottom right), STAT3 participates in immune regulation and cartilage repair. EXOs deliver IL-10 and miR-148a: IL-10 enhances STAT3 phosphorylation, thereby suppressing NLRP3 inflammasome activation and attenuating inflammatory responses, whereas miR-148a downregulates KLF6 to reduce p-STAT3 levels and modulate macrophage polarization. Under hypoxic conditions, sEVs transport miR-216a-5p, which upregulates JAK2 and p-STAT3 expression, consequently influencing STAT3 activity in chondrocytes. Collectively, STAT3 serves as a central hub orchestrating inflammatory and reparative responses in OA across multiple joint-resident cell types. Created with Biorender.com.

into the nucleus, suggesting that activated STAT3 promotes NF-κB activation.[111] Furthermore, both pathways are crucial during OA progression and treatment. Zhang et al first predicted through network pharmacology that Bergenin modulates both NF-κB and STAT3 pathways. Subsequent experiments demonstrated that Bergenin inhibited the activation of both NF-κB and STAT3 pathways in IL-1β-treated chondrocytes, thereby reducing chondrocyte apoptosis and extracellular matrix degradation in OA.[112] Another study showed that Xanthatin reversed the changes in MMP3 and aggrecan levels in cartilage matrix induced by IL-1β through the STAT3/NF-κB signaling pathway, alleviating cartilage degeneration and showing potential therapeutic effects for OA.[113] Huang et al discovered that the membrane protein Receptor tyrosine kinase-like orphan receptor 1, which is upregulated in OA cartilage, forms a positive feedback loop with STAT3, leading to the activation of the NF-κB signaling pathway and causing an imbalance between anabolic and catabolic processes in chondrocytes, thus exacerbating OA.[114]

In addition to the above pathways, many studies have shown that the c-Jun N-terminal kinase (JNK) signaling pathway is also associated with the pathogenesis and progression of human OA. JNKs are encoded by three genes (JNK1, JNK2, and

JNK3) and are a sub-group of mitogen-activated protein kinases (MAPK).[115] The JNK signaling pathway plays a critical role in cell proliferation, osteoclastogenesis, cartilage degeneration, and inflammation.[116,117] Yang et al investigated the role of immune factors in OA and found that CXCL8/11 stimulation induced high expression of phosphorylated STAT3 and JNK. Their experimental results suggest that CXCL8 and CXCL11 may exacerbate OA by promoting cell apoptosis and inhibiting chondrocyte proliferation through the JAK/STAT3 and JNK MAPK signaling pathways.[51] Another study revealed that sphingosine kinase 1 (SPHK1) promotes inflammation via the NF-κB/IL-6/STAT3 signaling pathway, which leads to JNK phosphorylation and activates the JNK/PTX3 signaling pathway, mediating inflammation and promoting glioblastoma (GBM) growth. SPHK1 and PTX3 further form a positive feedback loop, further promoting the progression of inflammation.[118] Additionally, earlier research showed that STAT3 is phosphorylated upon JNK activation, indicating that JNK is an upstream regulator of STAT3 signaling.[119] Ning et al found that nanosecond pulsed electric fields (nsPEFs) pre-treatment activated JNK and cAMP-response element-binding protein (CREB), leading to downstream STAT3 phosphorylation, significantly enhancing chondrocyte gene expression and the chondrogenic differentiation ability of MSCs.[120] In summary, the interaction between JNK and STAT3 signaling pathways holds therapeutic potential in OA. However, related research is still relatively sparse, and further exploration is needed.

## Targeting the STAT3 Pathway for OA Treatment

STAT3 is a well-established inflammatory mediator that is often overexpressed and/or overactivated in OA, primarily through the regulation of inflammatory responses, cartilage degradation, and cell invasion, which are generally associated with poor prognosis. As a key molecular hub in the OA-driving network, STAT3 is activated by cytokines such as IL-6 and upstream regulators like FOXM1, making it an essential target for therapeutic development. Therefore, identifying and developing STAT3 inhibitors for clinical use has become critically important (Table 2).

**Table 2** Therapeutic Candidates, Mechanisms of Action, and Developmental Progress of STAT3 Inhibitors

| Candidate | Mechanism of Action | Developmental Status | Representative References |
|---|---|---|---|
| Dehydrocorydoline (DHC) | Inhibits phosphorylation of JAK1 and STAT3 | Preclinical (in vitro) | Sha et al[121] |
| RCGD-423 | Prevents IL-6–mediated heterodimerization, and inhibits ERK1/2 and NF-κB activation | Preclinical (in vitro/in vivo) | Shkhyan et al[122] |
| Alantolactone (ALT) | Inhibits IL-1β–induced STAT3 phosphorylation and nuclear translocation | Preclinical (in vivo and in vitro) | Pei et al[123] |
| STX-0119 | Inhibits STAT3 phosphorylation, blocks nuclear translocation | Preclinical (in vivo and in vitro) | Lu et al[124] |
| Stattic | Prevents STAT3 dimerization and nuclear translocation | Preclinical (in vivo and in vitro) | Li et al[125] |
| Xanthatin (XA) | Inhibits STAT3 Tyr705 phosphorylation | Preclinical (in vivo and in vitro) | Xu et al[113] |
| AG490 | Blocks JAK2/STAT3 activation | Preclinical (in vitro) | Zhang et al[126] |
| Artesunate (ART) | Promotes the lipoxin A4, restrains JAK2/STAT3 signaling | Preclinical (in vivo and in vitro) | Zhao et al[127] |
| Tofacitinib, Baricitinib | Decreases STAT3 phosphorylation | Approved | Paulissen et al[128] |
| Resveratrol (RES) | Inhibits JAK2/STAT3 phosphorylation | Preclinical (in vitro and in vivo) | Jiang et al[34] |
| Hederagenin (HE) | Suppresses IL-1β-induced p-JAK2 and p-STAT3 | Preclinical (in vitro and in vivo) | Shen et al[129] |
| STEP (skipjack tuna elastin peptides) | Inhibits JAK2/STAT3 activation and inflammatory cytokines | Preclinical (in vitro and in vivo) | Wu et al[130] |
| si-STAT3 | Delivers siRNA targeting STAT3 and anti-CD44 aptamers to cartilage tissue, silently the expression of matrix metalloproteinases | Preclinical (in vitro and in vivo) | Lv et al[36] |
| si-p21 | Knockdown of p21 increases STAT3 phosphorylation | Preclinical (in vitro and in vivo) | Hayashi et al[131] |
| si-LOXL1 | Reduces p-NF-κB p65 and p-STAT3 expression | Preclinical (in vitro) | Jiang et al[73] |

(*Continued*)

**Table 2** (Continued).

| Candidate | Mechanism of Action | Developmental Status | Representative References |
|---|---|---|---|
| si-RPL38 | Restores SOCS2 via METTL3/m6A regulation, suppresses JAK2/STAT3 signaling | Preclinical (in vitro and in vivo) | Shi et al[132] |
| miR-182-5p | Targets TNFAIP8 to regulate the autophagy process in chondrocytes | Preclinical (in vitro) | Ji et al[133] |
| miR-125a-5p, miR-125b-5p | Regulates apoptotic signalling, transcriptional controls | Early exploratory | Li et al[134] |
| let-7a-5p | Inhibits STAT3 phosphorylation | Preclinical (in vitro and in vivo) | Shao et al[42] |
| miR-653-5p | Mitigates chondrocyte senescence and cartilage degradation via the IL-6/JAK/STAT3 pathway | Preclinical (in vitro and in vivo) | Lin et al[37] |
| miR-224-5p | Reduces JAK2/STAT3 phosphorylation | Preclinical (nanoparticle and in vivo) | Zhang et al[135] |

## Small-Molecule Inhibitors

Previous studies have suggested that unlike tyrosine kinases and other molecular targets, transcription factors do not possess intrinsic enzymatic activity. This makes it difficult to develop small molecule inhibitors and may require alternative methods.[12] However, recent studies have identified small-molecule inhibitors that have shown promising results in various in vitro models,[136] with potential for clinical prevention and treatment of OA, particularly in the development of new drugs and effective therapeutic agents. For example, Sha et al discovered that the small molecule dehydrocorydoline (DHC) could inhibit the phosphorylation of JAK1 and STAT3 induced by TNF-α in human OA chondrocytes, and improve cell proliferation and ECM synthesis in chondrocytes through the JAK1/STAT3 pathway.[121]

Ruzanna Shkhyan et al found that signaling through glycoprotein 130 (gp130), a common receptor for the IL-6 cytokine family, could specifically affect cartilage cells. High-throughput screening identified a small-molecule gp130 modulator, RCGD 423, which promotes the formation of gp130 receptor dimers in the absence of cytokine ligands. This inhibitor prevents heterodimerization mediated by IL-6 cytokines, thereby inhibiting hypertrophic and catabolic effects mediated by ERK1/2 and NF-κB signaling pathways, presenting a therapeutic approach for OA.[122] Another STAT3 inhibitor, Alantolactone (ALT), limits nuclear translocation of STAT3 by inhibiting IL-1β-induced phosphorylation of STAT3, thereby protecting cartilage.[123] Zhang et al reported that the small molecule STX-0119 regulates the STAT3/PPAR γ signaling pathway to inhibit cartilage catabolism in OA. STX-0119 inhibits STAT3 phosphorylation, impairs its nuclear translocation, and upregulates peroxisome proliferator-activated receptor gamma (PPARγ) expression, preventing cartilage degradation in OA.[124] Stattic, a non-peptidic STAT3 inhibitor, specifically inhibits STAT3 dimerization and nuclear translocation.[125] In the DMM model of OA, the protective effect of orally administered Stattic is mediated by inhibiting STAT3 activation in cartilage, without affecting synovial or subchondral bone cells. In superficial cartilage explants, Stattic counteracted IL-6-induced proteoglycan loss and STAT3 phosphorylation.[33] Another study found that Stattic limits osteoclast generation and bone loss by interfering with RANKL-induced STAT3 and NF-κB signaling. These results suggest that Stattic may be a potential candidate drug for treating OA. In a study by Xu et al, xanthatin (XA), a small-molecule STAT3 inhibitor, inhibited STAT3 phosphorylation at Tyr705 and reduced cartilage cell degeneration and subchondral bone loss by suppressing the STAT3/NF-κB signaling pathway. XA also decreased the expression of pro-inflammatory factors such as IL-1β and TNF-α, highlighting its potential in OA treatment.[113] Moreover, the function of STAT3 depends on the phosphorylation status of its two sites Tyr705 and Ser727,[137] while XA does not affect the activation of Ser727. Therefore, the specific inhibitory effect of XA on Tyr705 blocks the bidirectional regulation of STAT3, thereby reducing potential side effects. Furthermore, another study found that another STAT3 inhibitor, AG490, significantly inhibited IL-1β-induced JAK2/STAT3 activation.[138] Zhang et al also demonstrated that AG490 reversed leptin-induced chondrocyte apoptosis and JAK2/STAT3 activation in OA models.[126] Artesunate (ART) is an important small molecule compound produced by Artemisia annua. A study found that ART can upregulate the expression of Metastatic tumor antigen 1 (MTA1), which then promotes the expression of an inflammatory

termination signal lipoxin A4 through transcription, thereby inhibiting the activation of the JAK2/STAT3 signaling pathway to improve cartilage damage in OA mice.[127] Since JAK and STAT3 constitute classic inflammatory signaling pathways, small-molecule inhibitors targeting JAK, such as tofacitinib and baricitinib, have been shown to significantly reduce p-STAT3 expression in OA fibroblast-like synoviocytes (FLS) and chondrocytes, confirming their efficacy in inhibiting the JAK/STAT3 pathway.[128] On another hand, STAT3, as a transcription factor (TF), has long been regarded as a challenging and "undruggable" target. Apart from nuclear receptors, most transcription factors lack well-defined small-molecule binding pockets and exhibit a high degree of intrinsic disorder, which hinders the formation of stable, high-affinity binding sites for conventional ligands.[139] Moreover, the high sequence homology between STAT3 and other STAT family members further complicates the development of selective inhibitors.[6] In addition to these structural challenges, potential toxicity remains a major concern. Previous studies have shown that small-molecule inhibitors designed to bind the SH2 domain of STAT3 may induce the formation of toxic protein aggregates, thereby impairing mitochondrial function and leading to cell death.[140] Furthermore, in patients treated with one of the clinically advanced STAT3 inhibitors, lactic acidosis was observed, suggesting possible systemic toxicity associated with STAT3 inhibition.[141] Moreover, pharmacokinetic limitations similarly impede the clinical translation of STAT3 inhibitors. Certain compounds exhibit poor solubility and low bioavailability, thereby constraining their therapeutic efficacy. For instance, although LLL12 selectively inhibits STAT3 phosphorylation and nuclear translocation, its poor water solubility and limited bioavailability necessitate high doses in in vivo studies to achieve therapeutic effects.[142,143]

In summary, these small-molecule inhibitors show promising therapeutic potential for OA. However, constrained by the structural limitations of STAT3, the shortcomings of conventional drug design methodologies, safety concerns, and the low bioavailability of drugs, clinical trial data remains insufficient at present. Further exploration is required to validate its clinical application value in the treatment of OA.[136]

## Natural Products and Their Derivatives

In recent years, another type of STAT3 inhibitor, including natural products and their derivatives such as Resveratrol (RES), Hederagenin (HE), skip jack tuna elastin peptides (STEP), and M13, has been found to delay the progression of OA by inhibiting STAT3 signaling.

Jiang et al found in vitro that co-incubation of chondrocytes with leptin significantly activated the expression of JAK2 and STAT3 proteins. However, treatment with RES significantly blocked the expression of P-JAK2 and p-STAT3, indicating that RES suppressed the JAK2/STAT3 signaling pathway and thereby reduced the progression of obesity-related OA.[34] Another study also showed that RES inactivated the NF-κB transcription factor via phosphorylation of its inactive form, thereby reducing IL-6 secretion. The lower IL-6 levels led to reduced STAT3 phosphorylation in macrophages, thus limiting STAT3 activation.[74] These findings suggest that RES has anti-inflammatory potential and may offer possibilities for the prevention and treatment of OA. HE is a pentacyclic triterpenoid saponin extracted from herb plants. One study showed that HE (6.25 and 12.5 μM) reduced IL-1β-induced increases in P-JAK2 and p-STAT3 levels in a dose-dependent manner. Moreover, co-treatment with HE and the JAK2 inhibitor AG490 enhanced the inhibitory effect of HE on the expression of MMP-1 and MMP-3 proteins. These data indicate that HE may resist OA progression partly through suppression of the JAK2/STAT3 pathway. However, AG490 also enhanced HE's inhibitory effect on P-ERK levels, suggesting possible crosstalk between the JAK2/STAT3 and MAPK pathways, which may affect the anti-OA effects of HE.[129] STEP is a bioactive peptide extracted from skipjack tuna. Wu et al found that three potential anti-inflammatory peptides in STEP reduced IL-1β-induced OA by regulating inflammatory cytokines and inhibiting the JAK2/STAT3 signaling pathway. These peptides also effectively inhibited ECM degradation and chondrocyte apoptosis. However, due to the limited availability of raw materials, STEP remains relatively costly.[130] In addition, M13 is a compound extracted from the traditional Chinese medicine Morinda officinalis. One study showed that M13 binds to the SH2 domain of STAT3, thereby inhibiting STAT3 phosphorylation and alleviating OA progression. Further in vivo experiments confirmed that oral administration of M13 reduced surgery-induced OA in mice, lowered OARSI scores, and decreased cartilage degradation.[144] However, several challenges remain in translating natural products into clinically viable STAT3-targeted therapeutics. Among them, one of the most prominent issues is that only a limited number of natural compounds exhibit strong binding affinity toward STAT3, while the majority show

relatively weak or nonspecific interactions. Therefore, further studies are needed to enhance the binding affinity of natural products for STAT3 and improve their therapeutic potential.[145]

Overall, the above natural products and their derivatives can reduce OA progression by inhibiting STAT3-related signaling pathways. But their specific molecular mechanisms and affinity for binding to STAT3 still require further investigation, and more studies are needed to identify cost-effective compounds with better binding properties. Moreover, many studies have found that natural compounds can exert anti-inflammatory effects via the STAT3 pathway in other diseases. For example, Zhang et al reported that total glycosides of paeony (TGP) can suppress inflammation in autoimmune diseases (AIDs) by inhibiting the JAK2/STAT3 pathway in immune cells.[146] Whether these compounds can also be effective in OA needs further validation.

## Small Interfering RNA (siRNA)

The STAT3 signaling pathway regulated by siRNAs has shown potential for reducing inflammation and cartilage degradation. A DNA origami-based chondrocyte-targeted delivery system designed by Lv et al can accurately deliver siRNA targeting STAT3 and anti-CD44 aptamers to cartilage infected with OA, silencing the expression of matrix metalloproteinases and reducing inflammation. In the OA rat model, it maintained cartilage integrity and promoted regeneration, achieving good results.[36] p21 was initially identified as a potent inhibitor of cell cycle progression, and it also plays a critical role in inflammation and vascular smooth muscle cell proliferation.[147,148] A study reported that transfection with p21-specific siRNA significantly increased MMP13 mRNA expression while decreasing aggrecan expression. Notably, silencing of p21 also led to elevated STAT3 phosphorylation in human OA chondrocytes. Therefore, the regulation of p21 siRNA may be a therapeutic strategy for OA.[131] Similarly, Jiang et al silenced LOXL1 using siRNA and co-cultured the transfected cells with chondrocytes. LOXL1 knockdown in chondrocytes reduced the expression of phosphorylated NF-κB p65 and STAT3 in co-cultured macrophages, thereby alleviating cartilage degradation and cell apoptosis.[73] Additionally, Shi et al obtained similar results. They first found that Ribosomal protein L38 (RPL38) was upregulated in OA cartilage. Further mechanistic investigations revealed that RPL38 directly interacted with methyltransferase-like 3 (METTL3) and inhibited SOCS2 expression through METTL3-mediated m6A methylation. Knockdown of SOCS2 activated the pro-inflammatory JAK2/STAT3 signaling pathway. Transfection of RPL38 siRNA (si-RPL38) into chondrocytes successfully suppressed this process, thereby reducing cartilage tissue damage and ECM degradation in OA mouse models.[132] Collectively, these findings highlight that both direct siRNA-based delivery to OA chondrocytes and gene-specific siRNA knockdown strategies can attenuate STAT3-driven inflammatory signaling, thereby offering promising therapeutic avenues for the treatment of OA. However, issues such as the instability of siRNA, challenges in delivery, off-target effects, and potential immune responses still need to be further explored and resolved.[149]

## microRNA (miRNA)

Significant progress has been made in the development of miRNA-based therapeutics, with promising candidates such as Miravirsen for hepatitis C and Cobomarsen for certain lymphomas currently undergoing clinical trials. However, miRNA research in OA remains largely at the experimental stage.[134] Previous mechanistic studies, particularly in oncology, have demonstrated that dysregulation of microRNAs (miRNAs) targeting STAT3 contributes to aberrant STAT3 activation in tumors.[41] In recent years, research on miRNAs in the context of OA has expanded. For example, Ji et al reported that miR-182-5p was significantly downregulated in the synovial fluid of OA patients, and by targeting TNFAIP8, it regulated autophagy in chondrocytes, highlighting its therapeutic potential.[133] This review aims to explore additional miRNAs with potential as therapeutic agents.

Using genome-wide association studies (GWAS) and other approaches, Li et al identified hsa-miR-125a-5p and hsa-miR-125b-5p as protective factors in OA, modulating apoptotic signaling and transcriptional regulation. These miRNAs interact with competing endogenous RNAs (ceRNAs) such as circ_0000254 and SPACA6P-AS, thereby regulating the expression of proteins including STAT3, which provides new directions for miRNA-based therapies.[134] In another study using RNA-seq analysis of $Exo^{BMSC}$ and $Exo^{PTH}$, three overexpressed miRNAs were identified, among which let-7a-5p was the predominant functional miRNA in $Exo^{PTH}$. Functional assays showed that let-7a-5p inhibited IL-6 expression and subsequent STAT3 phosphorylation, suggesting that it may enhance chondrocyte migration and proliferation by

suppressing the IL-6/STAT3 pathway, thereby mitigating OA progression.[42] Through high-throughput sequencing and qRT-PCR, Lin et al found that miR-653-5p was significantly downregulated in cartilage tissues and chondrocytes from OA patients, and IL-6 was identified as a direct target of miR-653-5p. Further studies revealed that upregulating miR-653-5p in OA can reduce chondrocyte senescence and cartilage degradation through the IL-6/JAK/STAT3 pathway. Subsequently, in a DMM animal model, intra-articular (IA) injection of miR-653-5p was demonstrated to be a potential method for the prevention and treatment of OA.[37] Zhang et al demonstrated that circ_PDE1C sponged miR-224-5p, thereby upregulating CCL2 and activating the downstream JAK2/STAT3 pathway, which exacerbated cartilage degradation and OA symptoms. Conversely, overexpression of miR-224-5p reduced JAK2 and STAT3 phosphorylation and alleviated ECM degradation and apoptosis in chondrocytes, identifying miR-224-5p as a potential therapeutic regulator.[135] Supporting this, Chen et al also confirmed the therapeutic role of miR-224-5p in OA and addressed its delivery challenges by designing a nanoparticle-based system (G5-AHP) to protect and efficiently deliver miR-224-5p. High-dose (9.09 mg/kg) G5-AHP/miR-224-5p treatment not only prevented ECM degradation but also reduced synovial inflammation and hyperplasia in OA.[150] Furthermore, hypoxia-induced delivery strategies for miRNAs have shown therapeutic promise. Li et al found that hypoxia-preconditioned M2 macrophage-derived exosomes (M2φ-Exos) significantly upregulated miR-124-3p, which binds to the 3′ untranslated region (UTR) of STAT3 in chondrocytes, thereby reducing its post-transcriptional expression and mitigating ECM catabolism and apoptosis.[151] A previous study also revealed that HIF-1α is crucial for miRNA expression under hypoxic conditions. Rong et al identified HIF-1α as a key transcription factor in this context. They found that sEVs derived from HIF-1α-induced hypoxic BMSCs reduced the levels of JAK2 and phosphorylated STAT3 (p-STAT3), while normoxic sEVs increased p-STAT3 levels. Further investigations suggested that hypoxia enhanced miR-216a-5p production via HIF-1α and modulated the JAK2/STAT3 pathway to promote chondrocyte proliferation and migration and to inhibit apoptosis. In addition, their research also showed that hypoxia also promoted the production and uptake of sEVs by MSCs and chondrocytes, respectively, offering a novel avenue for MSC-based OA therapies.[84] In conclusion, research on miRNAs in OA has advanced considerably in recent years, especially emerging strategies such as nanoparticle-based delivery and hypoxia conditioning have significantly enhanced the efficiency of drug targeting. Numerous studies have demonstrated that specific miRNAs play critical roles in OA pathogenesis by modulating key signaling pathways such as IL-6/JAK/STAT3. These findings support the potential of miRNAs as therapeutic agents, although most studies remain at the preclinical stage. Moreover, whether serving as therapeutic agents or molecular targets, the sensitivity, specificity, selectivity, and potential toxicity of miRNAs require comprehensive validation through further clinical investigations.[152] At the same time, additional studies are necessary to establish effective strategies for delivering miRNA-based therapies into the joint. Elucidating the interactions between miRNAs and their multiple target genes may be essential for maintaining joint homeostasis and regulating the pathophysiology of OA. Figure 4 depicts the targeted therapy of four substances on STAT3.

## Conclusion and Prospect

Currently, most degenerative diseases, including OA, lack effective treatments. Although certain approaches can alleviate symptoms to some extent, complete cure remains elusive. STAT3 is an essential protein present in all tissues, playing a crucial role in communication between cytokines and kinases and influencing the function of various physiological systems. Upon activation by growth factors or cytokines, STAT3 enhances the expression of genes involved in cell cycle regulation and proliferation. Dysregulated STAT3 activity, whether hyperactivated or inactivated, has been associated with various skeletal diseases and pathological processes, including joint inflammation, cartilage degradation, osteoclast activation, osteoblast differentiation, and macrophage polarization. Despite its potential as a therapeutic target for OA, current STAT3 inhibitors have shown limited efficacy and modest clinical benefit. Therefore, developing novel strategies to target STAT3 in OA remains a priority. In addition, some studies have suggested that activation of the STAT3 signaling pathway may suppress pro-inflammatory gene expression,[153] raising the possibility that STAT3 may have dual roles in OA, which warrants further investigation.

To date, multiple types of STAT3 inhibitors have been developed, including small molecules, peptides, miRNAs, and oligonucleotides, which can effectively block STAT3 dimerization and nuclear translocation. Since STAT3 signaling is regulated by molecules such as miRNAs and siRNAs, selectively targeting these pathways using small-molecule inhibitors

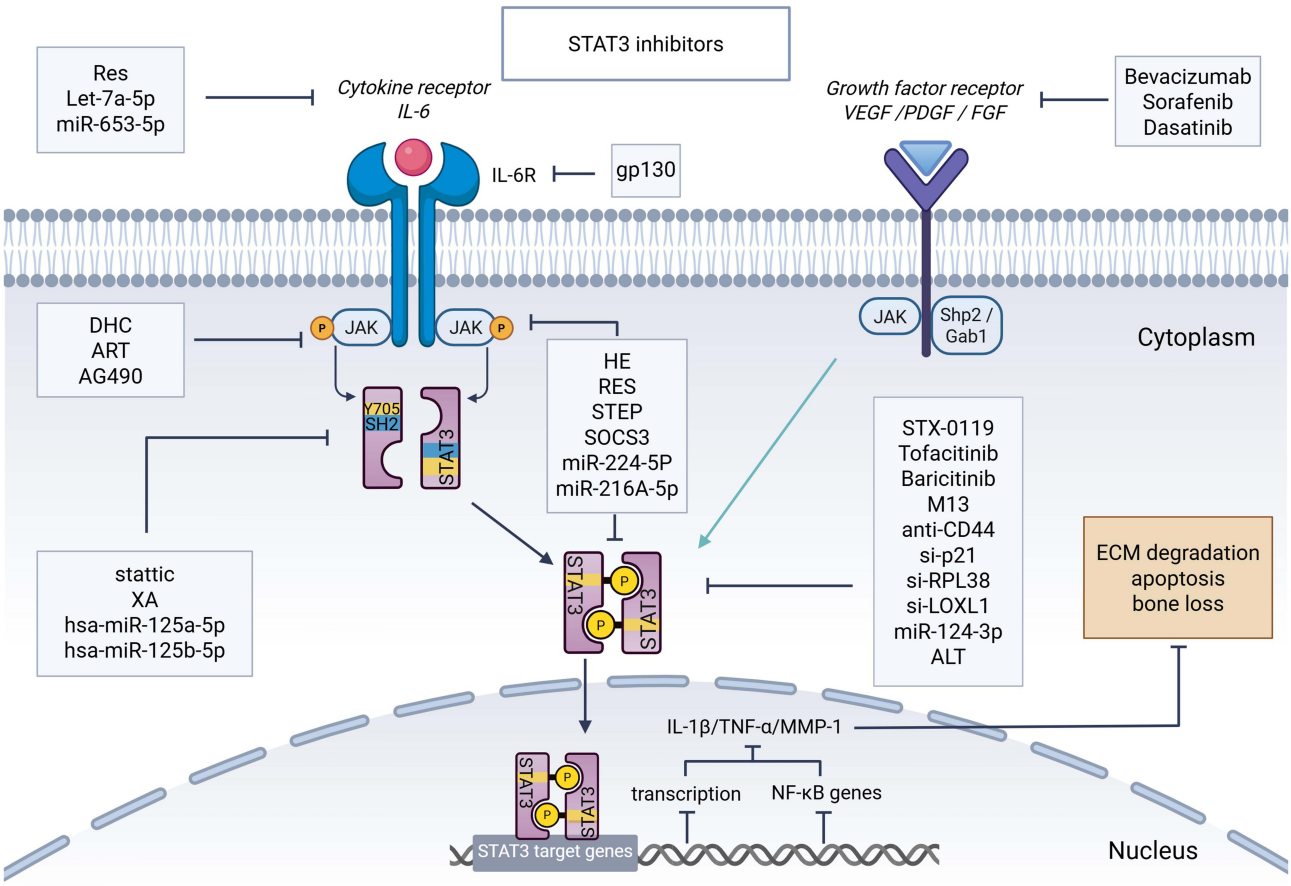


**Figure 4** Schematic illustration of therapeutic strategies targeting STAT3 signaling pathway in OA. Substances that inhibit IL-6 include Res, Let-7a-5p, and miR-653-5p. Gp130 inhibits IL-6R. DHC, ART, and AG490 inhibit JAK phosphorylation. STX-0119, Tofacitinib, Baricitinib, M13, anti-CD44, si-p21, si-RPL38, si-LOXL1, miR-124-3p, and ALT inhibit STAT3 phosphorylation. Meanwhile, HE, RES, STEP, SOCS3, miR-224-5P, and miR-216A-5p simultaneously inhibit JAK2 and STAT3 phosphorylation. Stattic, XA, hsa-miR-125a-5p, and hsa-miR-125b-5p inhibit the STAT3 dimerization process. Bevacizumab, Sorafenib, and Dasatinib reduce STAT3 phosphorylation by inhibiting the expression of growth factors. Created with Biorender.com.

may effectively suppress STAT3 activity and reduce inflammation. Natural products also represent a promising source for uncovering previously unexplored signaling pathways and inflammatory mechanisms,[154] offering a novel and under-researched approach for targeting STAT3 in OA therapy. However, previous studies on peptide- or oligonucleotide-based STAT3 inhibitors have mainly focused on cancer, with few investigations in the context of OA. Moreover, these inhibitors exhibit several limitations. For example, oligonucleotide-based STAT3 inhibitors suffer from low extracellular stability and rapid degradation, limiting their drug delivery efficiency. Peptide-based STAT3 inhibitors also face common challenges, such as instability, poor delivery efficiency, and suboptimal pharmacodynamics, which hinder their development.[155,156] Furthermore, some studies have reported that inhibitors like Bevacizumab, Sorafenib, and Dasatinib can reduce STAT3 phosphorylation by suppressing growth factor expression in various disease models.[157–159] however, systematic investigation of such mechanisms in OA is still lacking. Therefore, future research on STAT3-targeted inhibitors for OA should not only focus on identifying promising peptide or oligonucleotide inhibitors but also explore approaches to enhance their delivery efficiency and binding capacity, such as hypoxia-based delivery strategies.

In summary, instability, low bioavailability, side effects, and poor targeted delivery efficiency are common obstacles that need to be addressed. Researchers may consider designing novel delivery systems, such as nanoparticle-based carriers or co-delivery strategies. Co-loading oligonucleotide- and peptide-based inhibitors onto nanoparticles could enhance bioavailability, permeability, and retention effects to better target diseased tissues. Additionally, optimizing the dosage, targeted therapy, or combination treatment strategies may improve the efficacy of STAT3 inhibitors while

reducing adverse effects. Although various strategies have been explored to identify drugs capable of inhibiting STAT3 signaling, further research is required to optimize their efficacy and clinical applicability.

## Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## Author Contributions

SZ, HX, and JC jointly conceived and designed the study. SZ, HX, HZ, and SD performed the literature review. SZ drafted the initial manuscript. HX, YY, and ZL provided critical feedback, finalized the content, and completed the final version. Each author made significant contributions to this study, whether in the conception, study design, execution, data acquisition, analysis, and interpretation, or in all of these aspects. All authors approved the final version to be published, agreed to the submission, and accepted accountability for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest in this work.

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