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Pathogenesis And Treatment Of Rheumatoid Arthritis Based On Inflammation

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Abstract. Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent synovitis and joint destruction. Its pathogenesis involves complex interactions between genetic, environmental and immune system factors. In recent years, JAK/STAT and NF-κB signaling pathways have become the focus of research due to their central role in pro-inflammatory factor expression and immune cell activation. The continuous activation of JAK/STAT pathway can further aggravate inflammation and bone destruction by inhibiting apoptosis of synovial fibroblasts, promoting differentiation of Th17 cells and activating osteoclasts, while NF-κB pathway can regulate the expression of inflammatory factors such as IL-6 and IL-8 through classical and non-classical pathways, forming an amplified inflammatory network. Cross-regulation accelerates RA pathologies. In terms of therapeutic strategy, JAK inhibitors effectively reduce disease activity by blocking STAT phosphorylation, while a new generation of selective JAK3 inhibitors aims to reduce the risk of side effects. Against the NF-κB pathway, synthetic inhibitors such as BMS-345541 and natural compounds such as curcumin exert anti-inflammatory effects by inhibiting IKKβ activity or promoting IκBα degradation. Combination therapy has shown superior efficacy by synergizing inhibition of inflammatory response through multiple pathways. However, resistance and long-term safety issues still need to be overcome. Future research needs to integrate multi-omics data with artificial intelligence models to shift from "pathway inhibition" to "immune homeostasis reconstruction" to develop more precise and safe treatment strategies to improve the prognosis and quality of life of RA patients.

Keywords: Rheumatoid arthritis (RA); JAK/STAT; NF-κB; JAK inhibitors; NF-κB inhibitors.

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic synovitis and joint destruction. Its pathogenesis involves a complex interaction of genetics, environment and abnormal activation of the immune system. JAK/STAT and NF-κB pathways have become the focus of research in recent years because of their central role in regulating the expression of pro-inflammatory factors and the activation of immune cells. Excessive activation of these two pathways leads directly to synovial fibroblast proliferation, inflammatory cell infiltration, and bone erosion, ultimately leading to irreversible joint damage [1].

Since the 1990s, the role of JAK/STAT pathway in RA has been gradually revealed. Early studies found that STAT3 and STAT1 phosphorylation levels in synovial tissue of RA patients were significantly increased, and closely related to the secretion of cytokines such as IL-6 and TNF-α [2]. After 2000, gene knockout experiments confirmed that STAT3-deficient mice had significantly reduced arthritis symptoms, suggesting that STAT3 is a key factor driving chronic inflammation [3]. At the same time, the study of NF-κB pathway shows that its activation is directly related to the overexpression of IL-6, IL-8 and RANKL in RA synovium, and positively correlated with disease activity [4]. In 2012, the approval of the first JAK inhibitor, tofacitinib, marked a new era in RA therapy moving from "cytokine neutralization" to "intracellular signaling pathway targeting"[1].

This article will focus on the molecular mechanisms of JAK/STAT and NF-κB pathways, systematically analyze their cross-regulatory networks, and explore therapeutic strategies targeting

these two pathways based on the latest clinical evidence, including selective inhibitor development, combination drug regimens and epigenetic interventions.

2. The Core Inflammatory Pathway

2.1. Abnormal Activation of JAK/STAT Pathway

JAK/STAT signaling pathway is a signal transduction pathway stimulated by cytokines, which is widely involved in many biological processes such as cell proliferation, differentiation, immune regulation and inflammatory response. The core mechanism of this pathway is the regulation of gene expression through the binding of cytokines to their receptors, which in turn activates tyrosine kinase JAK (Janus kinase) family proteins, resulting in the phosphorylation and activation of STAT (signal transducer and activator of transcription) proteins. In the JAK/STAT signaling pathway, cytokines such as IL-6 and IFN-γ initiate signaling by binding to their specific receptors. For example, IL-6 binds to the IL-6 receptor (IL-6R) and activates JAK1 and TYK2, whereas IFN-γ activates JAK1 and TYK2 via the IFN-γ receptor (IFN-γ R). These JAK kinases then phosphorylate specific tyrosine residues of STAT proteins, causing them to dimerize and migrate into the nucleus, interacting with DNA binding sites such as ISRE/GAS, thereby regulating transcription of downstream genes. Specifically, cytokines such as IL-6 or IFN-γ bind to their receptors (e.g., IL-6R or IFN-γ R), causing receptor dimerization and activation of JAK kinases, which then phosphorylate specific tyrosine residues of STAT proteins, causing them to dimerize, whereupon phosphorylated STAT protein dimers enter the nucleus, bind to the promoter region of the target gene, and regulate gene transcription [5].

In RA, sustained activation of the JAK/STAT signaling pathway plays an important role in the pathological process. Synovial fibroblasts (SFs) are one of the core cells of arthritis. Activation of JAK/STAT signaling pathway can inhibit apoptosis of SFs, leading to abnormal proliferation and survival. For example, IFN-γ exerts an anti-apoptotic effect on SFs by activating the JAK-STAT pathway, causing them to secrete a large number of pro-inflammatory factors (such as TNF-α, IL-6 and IL-18), further aggravating arthritis and tissue damage [6]. Th17 cells are also key effector cells in RA, and their differentiation is closely related to JAK/STAT signaling pathway. Th17 cells promote synovial fibroblasts to produce RANKL by secreting cytokines such as IL-17, which in turn activates osteoclast formation and ultimately leads to bone destruction [7]. Second, osteoclasts are key mediators of bone destruction in RA. Continued activation of JAK/STAT signaling pathway promotes osteoclast maturation and activation. For example, inflammatory factors such as IL-6, TNF-α, and IL-17 induce RANKL expression via the JAK/STAT pathway, thereby activating differentiation of osteoclast precursors into mature osteoclasts [8]. These osteoclasts further accelerate the degradation of cartilage and bone matrix by releasing MMPs such as MMP-13, resulting in the destruction of joint structures.

Finally, abnormal activation of AK/STAT signaling pathway not only acts directly on synovial fibroblasts and osteoclasts, but also triggers systemic inflammatory response by secreting a large number of inflammatory factors (such as IL-6, IL-17, TNF-α, etc.). These inflammatory factors further promote the infiltration and activation of immune cells, forming a vicious cycle that exacerbates arthritis and bone destruction [9].

2.2. Regulation of NF-κB Pathway

NF-κB is involved in RA inflammation through classical and nonclassical pathways. In the classical pathway, TNF-α and IL-1 are two important inflammatory factors that initiate signaling by binding to their receptors. TNF-α binds primarily through the TNFR1 receptor, whereas IL-1 binds through the IL-1R1 receptor. Activation of these receptors recruits a range of signaling molecules, such as TRADD, TRAF2, RIP1, etc., that ultimately activate the IKK complex (composed of IKKα, IKKβ, and NEMO). The activated IKK complex then phosphorylates IκBα specifically, primarily at the two N-terminal serine sites (Ser32 and Ser36) of IκBα. This phosphorylation results in ubiquitination of

IκBα and degradation via the 26S proteasome pathway. After degradation of IκBα, NF-κB (p50/p65) subunits are released. NF-κB is a transcription factor that usually exists as a p50/p65 heterodimer. The released NF-κB enters the nucleus and binds to cis-acting elements (such as NF-κB sites) of target genes, thereby activating transcription of downstream genes. NF-κB activates the expression of a variety of inflammation-related genes in the nucleus, including pro-inflammatory factors IL-6, IL-8 and anti-apoptotic protein Bcl-2. Expression of these genes further promotes inflammatory response and cell survival [10].

Similarly, the non-classical NF-κB signaling pathway is an important immune and inflammatory regulatory mechanism, and its core lies in the activation of NF-κ B-induced kinase (NIK) through specific signaling molecules (such as LT β receptor, CD40 ligand, B cell activating factor BAFF, etc.), thus triggering downstream signaling cascades. This pathway is characterized by independent of the classical trimeric IKK complex (composed of IKKα and IKKβ), but by unique molecular mechanisms that regulate p100 processing and p52/RelB heterodimer formation, ultimately promoting inflammation and transcription of related genes. Here, receptors such as LTβR activate NIK via TRAF2-and TRAF3-mediated signaling complexes. NIK is subsequently phosphorylated and activates IKKα, leading to ubiquitination and degradation of p100, resulting in the active p52 subunit. p52 binds to RelB to form a p52/RelB heterodimer, which is then transferred to the nucleus and activates transcription of target genes, including chemokine genes (e.g., CCL21, CCL19) and other inflammation-related genes [11].

3. Treatment Strategies and Combination Treatment Potential

3.1. Abnormal Activation of JAK/STAT Pathway and Intervention Strategy

In the first generation of JAK inhibitors tofacitinib (JAK1/3 inhibitor) and baritinib (JAK1/2 inhibitor) block STAT phosphorylation by competitively binding to the ATP pocket of JAK, significantly reducing disease activity (DAS28 score) and radiological progression [1]. However, the new generation of selective JAK inhibitors Filgotinib and Decernotinib have significant advantages in treating autoimmune diseases. Filgotinib is a highly selective JAK1 inhibitor with IC50 values of 10 nM for JAK1 and up to 28 nM for JAK2, showing approximately 30-fold selectivity. This selectivity allows Filgotinib to inhibit pro-inflammatory cytokine signaling while reducing the risk of side effects such as anemia due to JAK2 inhibition. In addition, Filgotinib preferentially inhibits the JAK1 pathway by interfering with IL-6 signaling, thereby avoiding interference with the JAK2-dependent erythropoietin (EPO) and thrombopoietin (TPO) pathways.

Decernotinib is a new generation of JAK3 selective inhibitors with a Ki value of 2.5 nM for JAK3, which is more than 4 times more selective than JAK1, JAK2 and TYK2. Decernotinib showed significant inhibition of Th17 cell differentiation in animal models, indicating its potential in modulating immune responses. However, Decernotinib should be cautious about metabolic toxicity in clinical application because it may cause adverse reactions such as lymphopenia [12]. At the same time, nanoparticle-encapsulated JAK inhibitors target synovial tissue via a local delivery system, significantly reducing systemic exposure and reducing the risk of infection. This strategy not only improves the safety and effectiveness of treatment, but also opens up new possibilities for the treatment of diseases such as RA [13].

3.2. NF-κB Pathway Regulation and Inhibition Strategies

Synthetic inhibitors and natural compounds have different mechanisms of action in inhibiting IKKβ and its downstream signaling pathways such as NF-κB. Among synthetic inhibitors, IKKβ inhibitors (e.g., BMS-345541) are highly selective IKKβ inhibitors that inhibit inflammation by blocking IKKβ activity, preventing phosphorylation of IκBα and activation of NF-κB [4]. There is also a synthetic inhibitor, triptolide derivative (LLDT-8), a derivative of triptolide that significantly reduces the expression of inflammatory factors such as IL-6 by inhibiting IκBα degradation and nuclear translocation of p65. Compared to conventional DMARDs, LLDT-8 showed better tolerability and

potential efficacy in RA patients in preclinical studies. For example, LLDT-8 can inhibit the expression of NF-κB signaling pathway and its downstream inflammatory factors IL-6 and IL-8 in synovial cells of RA patients induced by TNF-α and IL-17 [14]. In addition, LLDT-8 did not cause liver and kidney dysfunction in animal experiments, indicating that it has high safety [14].

Curcumin is the main representative of natural compounds. Curcumin is a natural compound that inhibits NF-κ B-dependent gene transcription by directly blocking IKK beta kinase activity. This mechanism of action makes it valuable in anti-inflammatory therapy. Clinical trials have shown that curcumin in combination with methotrexate improves ACR20 response rates, indicating its potential in RA treatment [4]. In addition to curcumin, other natural compounds such as triptolide have also been shown to exert anti-inflammatory effects by inhibiting NF-κB signaling. For example, triptolide inhibits RA-associated inflammatory responses by reducing IL-6 and TNF-α expression [15]. Therefore, synthetic inhibitors (such as BMS-345541 and LLDT-8) and natural compounds (such as curcumin and triptolide) exert anti-inflammatory effects by inhibiting IKKβ and its downstream signaling pathways. However, synthetic inhibitors face safety and tolerability challenges in clinical development, while natural compounds show greater potential due to their lower toxicity and higher bioavailability [16].

3.3. Pathway Cross-regulation and Combination Therapy Potential

JAK/STAT and NF-κB pathways significantly intersect in RA. In positive regulation, there is an interaction between STAT3 and NF-κB and a role for IL-6. STAT3 is a signal transducer and activator of transcription, which can enhance the transcriptional activity of NF-κB through various mechanisms. STAT3 promotes acetylation of the RelA subunit of NF-κB via acetyltransferase p-300, thereby prolonging its nuclear residence time and enhancing its activity [17]. This interaction creates a positive feedback mechanism that allows NF-κB to continue to activate and further enhance the inflammatory response. Meanwhile, IL-6 is an important signal molecule linking STAT3 and NF-κB. IL-6 activates the JAK/STAT signaling pathway through its receptor (gp130), leading to activation of STAT3. IL-6 is also one of the downstream target genes of NF-κB, and activation of NF-κB promotes the expression of IL-6. Thus, IL-6 forms a positive regulatory loop between STAT3 and NF-κB: NF-κB activates IL-6, which in turn enhances NF-κB activity by activating STAT3, thus forming an inflammation amplification loop [17]. Furthermore, JAK/STAT signaling pathway is a central part of IL-6 signaling. IL-6 binds to receptors on the cell surface and activates JAK kinase, which in turn activates STAT3. Activated STAT3 enters the nucleus and regulates the expression of various inflammatory factors including IL-6. Therefore, STAT3 forms a positive regulatory loop between NF-κB activity and IL-6 as a key mediator, which ultimately leads to activation of JAK/STAT pathway and continuous secretion of inflammatory factors. This process creates an inflammatory amplification loop that further exacerbates the inflammatory response [17].

Combined inhibition strategies also play a significant role in RA treatment. JAK/NF-κB dual-target inhibitors and epigenetic intervention are two important joint inhibition strategies. TAK-242 acts as a JAK/NF-κB dual-target inhibitor, a small molecule inhibitor that targets both TLR4 and JAK1, thereby exhibiting synergistic anti-inflammatory effects in animal models of RA. Specifically, TAK-242 inhibits TLR4-mediated inflammatory responses by binding to the intracellular domain of TLR4 and blocks the interaction between TLR4 and adaptive molecules [18]. TAK-242 also inhibits JAK1 activity, thereby blocking the JAK/STAT signaling pathway and reducing the production of pro-inflammatory factors such as IL-6 and IL-10. This dual mechanism of action allows TAK-242 to have significant synergistic effects in anti-inflammatory therapy.

Epigenetic intervention works through modification mechanisms that regulate gene expression, such as histone acetylation. HDAC inhibitors such as Givinostat inhibit activation of NF-κB signaling pathway by increasing acetylation of IκBα, while also inhibiting phosphorylation of STAT3, thereby doubly blocking inflammation-related pathways [19]. Givinostat, for example, is a potent HDAC1 and HDAC3 inhibitor with IC50 values of 198 and 157 nM, respectively, demonstrating the ability to regulate multiple inflammation-related signaling pathways. Therefore, these two combined

inhibition strategies work synergistically through different mechanisms to inhibit key inflammatory pathways in RA. JAK/NF-κB dual-target inhibitors (e.g. TAK-242) reduce pro-inflammatory factor production by directly blocking TLR4 and JAK1 signaling pathways, while HDAC inhibitors (e.g. Givinostat) indirectly affect NF-κB and STAT3 signaling pathway activity through epigenetic regulation. This multi-target, multi-tiered treatment strategy is expected to provide more effective treatment options for RA patients.

4. Conclusion

JAK/STAT and NF-κB pathway are the core hubs of RA inflammatory network, and their targeted therapy has moved from "broad spectrum inhibition" to "precise regulation". Although drugs such as tofacitinib have significantly improved patient outcomes, there are still challenges that need to be addressed, such as resistance mechanisms and long-term safety. In the context of resistance mechanisms, JAK/STAT signaling pathways may maintain inflammatory or disease states through compensatory activation in the event of TNF inhibitor failure. TNF inhibitors act primarily by blocking TNF binding to its receptors, but when these inhibitors fail, other signaling pathways may be activated to compensate for their effects. For example, the JAK/STAT signaling pathway can be reactivated by activation of cytokines (e.g., IL-6, IL-10, etc.), resulting in persistence or exacerbation of inflammatory responses. Therefore, exploring the molecular mechanism of JAK/STAT compensatory activation after TNF inhibitor failure is helpful to understand the causes of disease progression and drug resistance formation, and provides theoretical basis for developing new therapeutic strategies.

For long-term safety, JAK inhibitors have shown significant efficacy in treating a variety of diseases, but their potential side effects (such as infection risk and cardiovascular adverse events) limit their safety for long-term use. For example, JAK inhibitors may increase the risk of infection by suppressing the immune response, while excessive inhibition of STAT3 may lead to loss of cardiac protection, thereby increasing the risk of cardiovascular disease. Meanwhile, studies targeting cardiovascular risk suggest that JAK inhibitors may interfere with cardioprotective signaling pathways by affecting STAT3 activity. Therefore, by developing tissue-specific delivery systems and optimizing the selectivity of JAK inhibitors, infection and cardiovascular risks of their long-term use can be effectively reduced, thereby improving patient quality of life and treatment compliance. Future research is expected to achieve RA treatment from "pathway inhibition" to "immune homeostasis reconstruction". This will not only provide patients with safer and more effective treatment options, but will also promote the development of precision medicine, ultimately improving the prognosis and quality of life of RA patients.

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