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REVIEW

Role of Interleukin-6 in Rheumatoid Arthritis-Associated Interstitial Lung Disease: Focus on the JAK/STAT Pathway and Macrophage Polarization

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Abstract: Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterized by chronic synovitis and extra-articular manifestations (EAMs), with interstitial lung disease (ILD) being a leading cause of mortality. Interleukin-6 (IL-6), a pivotal cytokine in RA pathogenesis, drives both articular and pulmonary inflammation through its involvement in immune dysregulation and fibrotic processes. This review elucidates the molecular mechanisms by which IL-6 contributes to rheumatoid arthritis-associated interstitial lung disease (RA-ILD) progression, particularly via the Janus kinases (JAK)/signal transducers and activators of transcription (STAT) signaling pathway and macrophage polarization. Additionally, we objectively evaluate current and emerging therapeutic strategies targeting IL-6 and downstream pathways.

Keywords: IL-6, RA-ILD, JAK/STAT signaling, macrophage polarization, targeted therapy

Introduction

Rheumatoid arthritis (RA) is a systemic, chronic, autoimmune disease.[1] The main feature of RA is symmetrical synovitis, typically involving the proximal interphalangeal joints, metacarpophalangeal joints, elbows, shoulders, wrists, and knees, while usually sparing the distal interphalangeal joints and the spine, except for the cervical spine. However, the prognosis of RA patients is usually closely linked to extra-articular manifestations (EAMs). Lung involvement represents the frequent EAMs in RA patients, and interstitial lung disease (ILD) is one of the leading causes of mortality in RA.[2–4]

The overall prevalence of ILD in patients with RA is about 10–19%,[5] but the exact prevalence is unknown and may be related to population, region, and measurement method. Approximately 10% of cases present with clinical manifestations such as persistent dry cough and malaise in the early stages and significant cardiorespiratory dysfunction in the later stages, and are the leading cause of death.[2,5] Raimundo et al demonstrated that 35.9% of patients died 5 years after the first diagnosis of rheumatoid arthritis-associated interstitial lung disease (RA-ILD), and in the United States, the median survival was 7.8 years,[6] with up to 7% of RA-related deaths associated with RA-ILD.[7] Early symptoms of RA-ILD are often overlooked because they are not specific, and the development of ILD is usually progressive, with limited options for medications that can be used to treat it later in life. Currently known drugs for the treatment of pulmonary fibrosis include pirfenidone and nintedanib.[8] However, due to their adverse effects and indications in China (idiopathic pulmonary fibrosis), clinicians tend not to use them prematurely, and the results are often very limited. Methotrexate (MTX) is not recommended for the treatment of RA-ILD due to its inherent pulmonary toxicity.[9] In this context, targeted therapy may be a good option.

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Accumulating clinical evidence has demonstrated significantly elevated Interleukin-6 (IL-6) levels in RA patients.[10] As a gp130 cytokine family member, IL-6 mediates inflammatory signaling through the gp130/ Janus kinases (JAK)/ signal transducers and activators of transcription (STAT) pathway.[11] Notably, substantial research has confirmed the crucial involvement of JAK/STAT signaling in pulmonary fibrogenesis, suggesting that IL-6 may exert central pro-fibrotic effects through this pathway in RA-ILD.[12] Furthermore, IL-6 has been shown to play pivotal roles in multiple immunological processes, including B-cell differentiation and antibody production,[13] CD4+ T-cell differentiation,[11] and macrophage polarization.[14] Specifically, B cells contribute to RA-ILD pathogenesis through the production of auto-antibodies such as rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA).[15,16] Th17 cell-derived IL-17 has been implicated in pro-fibrotic responses, while M2 macrophages have been identified as key effector cells in fibrotic processes.[17,18]

Because the clinical studies of targeted drugs for RA-ILD are insufficient, clinicians' indications are often limited to simple RA; therefore, it is important to understand the role of IL-6 in the pathogenesis of RA-ILD, which will help us to pay attention to the therapeutic effects of targeted drugs, promote the progress of clinical research, and help clinicians to decide whether or not to use targeted drugs at an early stage. This review provides a systematic examination of the potential pro-fibrotic mechanisms of IL-6 and summarizes some of the targeted therapeutic agents that are already in existence.

IL-6 in Rheumatoid Arthritis-Associated Interstitial Lung Disease

Inflammation Establishment and Maintenance

The pathogenesis of RA involves the production of autoantibodies, mediation by immune cells, and activation of inflammatory pathways.[19] RA begins with the production of autoantibodies, including RF and ACPA. The pathogenesis initiates through the combined effects of genetic variants, epigenetic modifications, and environmental factors (eg, smoking, pulmonary/oral/gut microbiota dysbiosis), leading to citrullination of arginine or glycine residues in native proteins (Figure 1).[15] These modified self-antigens are subsequently recognized by antigen-presenting cells (APCs), triggering B-lymphocyte activation and autoantibody production (including RF and ACPA), which form immune complexes with modified self-antigens. The resulting immune complexes recruit macrophages, B-cells, and synovial fibroblasts to joint sites, promoting the secretion of IL-6 (Figure 1).[15,19–21]

IL-6, predominantly secreted by synovial fibroblasts and B cells in RA patients, plays a pivotal role in establishing and maintaining inflammatory processes.[20] IL-6 signaling initiates upon binding to the gp130 receptor, triggering inflammatory cascades that induce acute-phase proteins including C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, and promote synovial fibroblast proliferation, survival, and tissue invasion[11,19] (Figure 1).

The inflammatory milieu in RA is further amplified through cytokine interactions. Tumor necrosis factor-α (TNF-α), primarily derived from macrophages and B cells, synergizes with IL-6 through nuclear factor-kappa B (NF-κB) pathway activation. This cytokine interplay enhances receptor activator of NF-κB ligand (RANKL) expression in synovial fibroblasts, driving osteoclast differentiation and subsequent bone erosion. Additionally, these cytokines facilitate the recruitment of inflammatory cells, including synovial fibroblasts and macrophages, which perpetuate IL-6 secretion, thereby establishing a self-sustaining inflammatory cycle. The stimulation of synovial fibroblasts with TNF-α through the NF-κB pathway to continuously secrete IL-6 is one of the features of RA[19,20] (Figure 1). Similarly, IL-1, predominantly secreted by macrophages in RA, promotes synovial fibroblast proliferation and IL-6 secretion. The elevated IL-6 in RA synovial fluid binds to the IL-6 receptor (IL-6R), activating gp130 and transducing inflammatory signals via the JAK/ STAT pathway, primarily through JAK1 and STAT3, in synovial fibroblasts.[19,22]

IL-6 also significantly influences T cell-mediated inflammation. It promotes CD4+ T cell differentiation, particularly enhancing Th17 cell development, which plays a critical role in the pathogenesis of RA. Th17-derived IL-17 further stimulates IL-6 secretion, creating a pro-inflammatory feedback loop (Figure 1).[11,23] Additionally, IL-6 suppresses the generation of regulatory T cells (Tregs) via the transforming growth factor-β (TGF-β) signaling, which plays a critical role in maintaining immune tolerance by inhibiting the activation of self-reactive T lymphocytes, thereby modulating immune responses and protecting against autoimmunity.[11,24] Thus, IL-6 acts as a key inflammatory mediator that

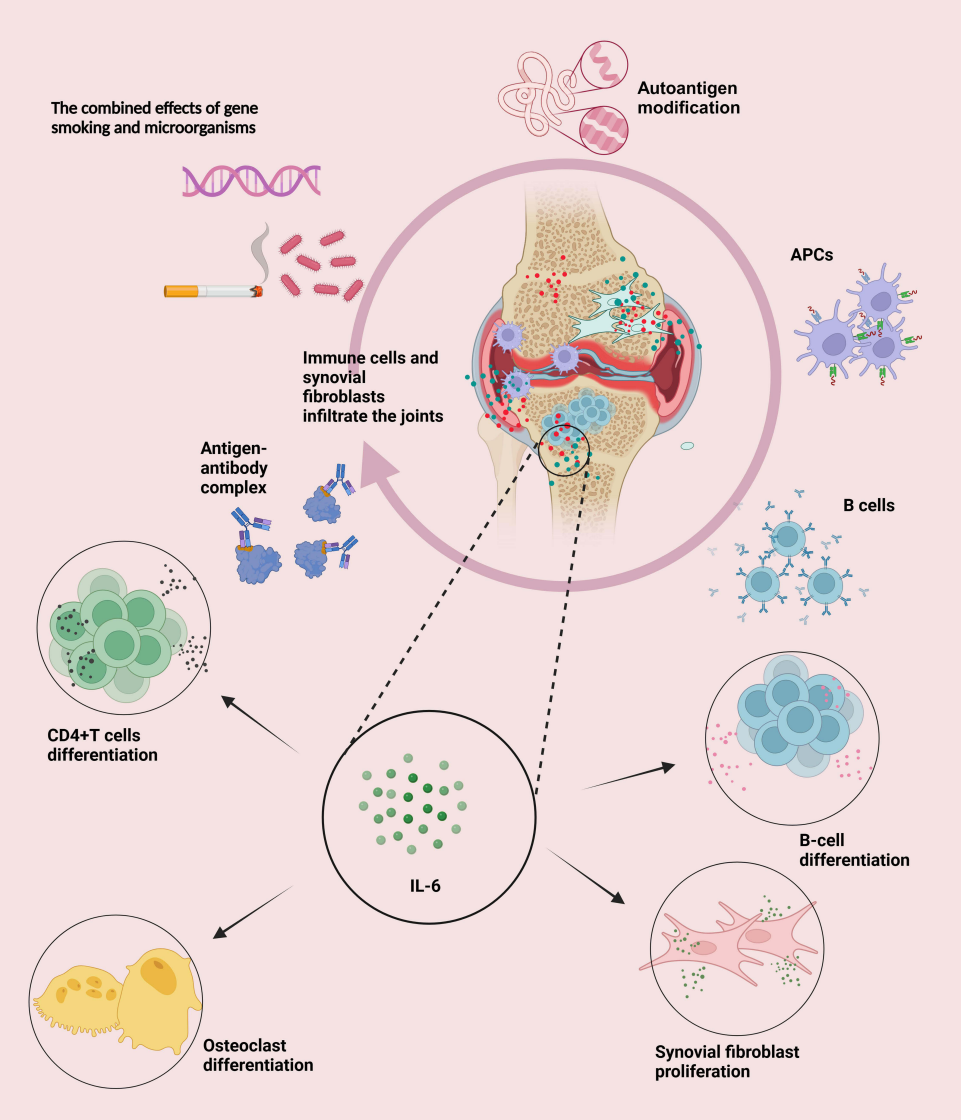

Figure 1 IL-6 plays a pivotal role in initiating and sustaining inflammation in RA. Antigen-antibody complexes trigger the accumulation of immune cells, including macrophages and B cells, as well as synovial fibroblasts, within the joints, leading to the release of IL-6. Created in BioRender. Yu, Z. (2025) https://BioRender.com/69itnxw.

promotes inflammation and fibrosis by impairing immune tolerance to reduce the ability of immune cells to distinguish between self and non-self.

Finally, IL-6 sustains inflammation by promoting B cell differentiation alongside its effects on T cells. Pathogenic antibodies in RA, such as RF and ACPA, are closely linked to B cells.[16,25] Moreover, IL-6—originally identified as B-cell stimulating factor 2 (BSF-2) due to its role in B-cell differentiation and antibody production (Figure 1).[13,26] Over the past decade, B-cell-targeted therapies, such as the anti-CD20 antibody rituximab, have demonstrated efficacy in RA.[27] Notably, in untreated RA patients, the frequency of citrullinated antigen-responsive B cells in peripheral blood often correlates with ACPA titers.[28]

IL-6 and the JAK/STAT Pathway

The JAK/STAT signaling pathway regulates numerous cellular processes essential for maintaining cellular homeostasis. This pathway primarily comprises JAKs and their downstream effectors, STATs. JAKs, a family of intracellular tyrosine kinases (JAK1, JAK2, JAK3, and TYK2), are crucial for signal transduction initiated by various membrane receptors.[29] Downstream of JAKs, STATs function as transcription factors and include seven members: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6.[30]

Distinct combinations of ligands, JAKs, and STATs contribute to cancer progression, inflammation, and autoimmune diseases, with the IL-6/JAK2/STAT3 axis playing a predominant role in lung fibrosis induction.[12] Notably, IL-6 alone cannot directly activate the JAK/STAT pathway. It must first form a complex with the IL-6R and subsequently bind to the gp130 receptor, inducing its dimerization to initiate downstream signaling.[22]

According to the presence of IL-6R, it can be classified into classical JAK/STAT signaling and trans-signaling. The membrane-bound IL-6R (mIL-6R) is expressed as a type-I transmembrane protein. The IL-6R consists of an Ig-like domain (D1), the cytokine binding module (CBM) domains (D2 and D3), and a 52-amino-acid-long flexible stalk region followed by the transmembrane and intracellular domains.[31] IL-6 classical signaling occurs on cells (mainly hepatocytes and leukocytes) that co-express mIL-6R and gp130, where IL-6 binds to mIL-6R and binds to gp130 to initiate an intracellular signaling cascade, which promotes an increase in inflammatory products. Soluble IL-6 receptor (sIL-6R) is produced either via the proteolysis of mIL-6R by the metalloprotease ADAM17 (A disintegrin and metalloproteinase-17) or less frequently, by the alternative splicing of IL-6R mRNA.[32] In trans-signaling, IL-6 and sIL-6R form a complex and then bind to gp130 to initiate a signaling cascade. The trans transactivation pathway can be activated in almost all cells because it is not restricted by mIL-6R expression. Studies have shown that trans-signaling plays an important role in pulmonary fibrosis and that the major cells involved are alveolar type II epithelial cells (ATII) and fibroblasts.[33,34] First, the closely linked JAKs are activated and undergo cross-phosphorylation. The activated JAK dimer phosphorylates tyrosine residues on the receptor, creating a docking site for STAT proteins. STATs are then phosphorylated, dissociate from the receptor, and dimerize through SH2 domain-phospho-tyrosine interactions. The dimer translocates from the cytoplasm to the nucleus, where it binds to specific promoters to regulate gene transcription.[35] This process induces fibroblast-to-mesenchymal transition (FMT) and epithelial-to-mesenchymal transition (EMT), also upregulates IL-6 expression in pulmonary tissues, driving excessive extracellular matrix (ECM) deposition, and ultimately contributes to ILD development[12,22,36] (Figure 2). However, unlike IL-6 secretion in the joint cavity, this may be mainly associated with ATII.[33]

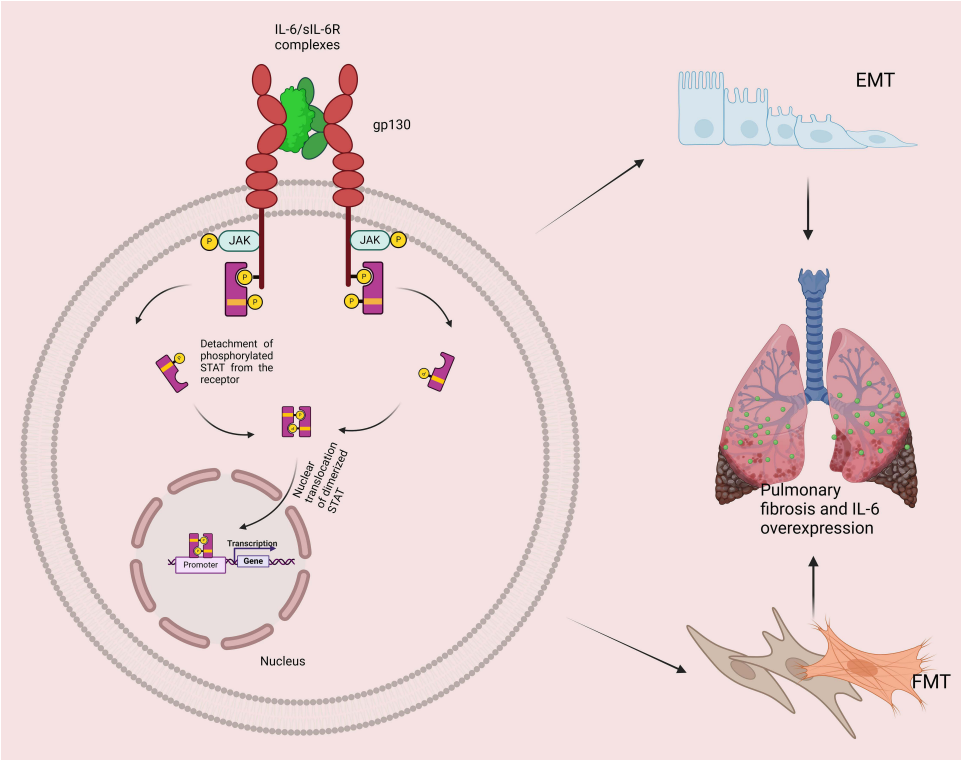

Figure 2 The IL-6 signaling cascade: the JAK/STAT pathway activated through the IL-6/sIL-6R/gp130 complex, driving transcriptional regulation of pro-fibrotic genes. Created in BioRender. Yu, Z. (2025) https://BioRender.com/z25hgmg.

In a combined murine model of collagen-induced arthritis (CIA) combined with bleomycin-induced pulmonary fibrosis (BLM), protein expression levels of IL-6, JAK2, STAT3, and phosphorylated STAT3 were significantly up-regulated in the ankle joints of RA-ILD mice compared to controls. Inhibition of the JAK2/STAT3 signaling pathway by Simiao pill, which is primarily composed of Phellodendri Chinensis cortex, atractylodes rhizome, achyranthis bidentatae radix, and Coicis Semen, alleviated both arthritis and pulmonary fibrosis.[37] Interestingly, emerging evidence suggests IL-6 exhibits a dual role in pulmonary fibrosis: it exerts anti-fibrotic effects during early inflammation but promotes fibrosis in later stages. Premature IL-6 blockade may paradoxically exacerbate inflammation and accelerate fibrotic progression, which may give a new vision for mastering the timing of the targeted therapeutics.[33]

Beyond its direct pro-fibrotic effects mediated through JAK/STAT signaling, IL-6 amplifies fibrogenesis via an indirect mechanism: it upregulates IL-4 receptor expression on macrophages, thereby potentiating IL-4-dependent STAT6 activation. This signaling axis drives M2 macrophage polarization—a pro-fibrotic phenotype characterized by excessive extracellular matrix deposition. polarization and function of M2 macrophages are detailed in Macrophage Polarization and Extracellular Matrix Deposition.[38]

Epithelial-Mesenchymal Transition (EMT)

EMT is a dynamic biological process wherein polarized epithelial cells, typically characterized by cuboidal morphology, tight intercellular junctions, and nonmotile, undergo phenotypic transformation into mesenchymal-like cells with migratory and invasive properties.[39] EMT is subclassified into three functionally distinct types: Type 1 (developmental EMT), Type 2 (fibrosis-associated EMT), and Type 3 (cancer-related EMT). In pulmonary fibrosis, Type 2 EMT predominates, marked by apoptosis resistance and pathological ECM deposition, primarily driven by inflammatory stimuli.[40]

TGF-β/SMAD pathway has been extensively studied as a prototypical pathway that drives EMT transcription factor (EMT-TF) gene expression and promotes the transformation of ATII into mesenchymal cells.[41] Notably, however, the JAK2/STAT3 pathway also plays an important role in EMT progression, for instance, Javier Milara et al demonstrated by in vitro isolation and culture of human ATII that the Combination of IL-6 and IL-13 not only stimulated ATII to increase the expression of p-JAK2 and p-STAT3 but also up-regulated the expression of mesenchymal markers such as Snail and Slug mRNAs.[42] Interestingly, this study also found that JAK2/STAT3 activation could be enhanced through the TGF-β-dependent SMAD pathway, potentially through two mechanisms: (1) TGF-β-induced upregulation of IL-6 and IL-13 expression in ATII, or (2) direct SMAD2/3-dependent STAT3 activation by TGF-β1.[42,43] Similarly, in peritoneal fibrosis, IL-6/JAK2/STAT3 was shown to be a pro-EMT pathway.[44]

Although accumulating evidence has demonstrated that even after undergoing EMT, these cells exhibit limited capacity for ECM gene expression, suggesting that the direct fibrotic contribution of EMT may be relatively modest,[45–47] the significance of EMT in fibrotic processes should not be underestimated. These studies have also revealed that mesenchymal-transformed ATII secrete various pro-fibrotic mediators, which subsequently induce fibroblast-to-myofibroblast differentiation,[45–47] which is called paracrine-mediated FMT. Given that fibroblasts possess significantly greater ECM-producing capacity compared to epithelial cells, this paracrine effect of EMT represents a crucial pro-fibrotic mechanism. Notably, these previous investigations were conducted in contexts independent of IL-6/JAK/STAT signaling regulation, and the secreted pro-fibrotic factors remain largely unexplored, with tissue-type plasminogen activator (tPA) being the only well-studied mediator. But these findings provide valuable insights for understanding RA-ILD. Is there also a paracrine role for EMT in RA-ILD? This is worthy of further study. Further investigation into this mechanism could significantly contribute to the development of targeted therapeutic strategies for RA-ILD.

Fibroblast-Mesenchymal Transition (FMT)

FMT is another critical process in pulmonary fibrosis, characterized by the loss of fibroblast differentiation and acquisition of a mesenchymal phenotype of myofibroblasts. This transition leads to the expression of α-smooth muscle actin (α-SMA) and abnormal ECM secretion.[12] Lung-resident fibroblasts are widely recognized as the primary source of myofibroblasts.[48]

TGF-β serves as a pivotal cytokine in the regulation of fibroblast-to-myofibroblast differentiation, exerting its biological effects through both canonical SMAD-dependent and non-SMAD signaling pathways.[49] We concisely outline the canonical SMAD signaling pathway here. The process initiates with TGF-β binding to and activating the TGF-β type

II receptor (TβRII), which subsequently recruits and phosphorylates the TGF-β type I receptor (TβRI). This receptor complex formation leads to the transphosphorylation and activation of the intracellular mediators SMAD2 and SMAD3. The phosphorylated forms of these proteins (p-SMAD2 and p-SMAD3) then form a complex with the common mediator SMAD4. This trimeric complex undergoes nuclear translocation to modulate the expression of various fibrotic genes, including those encoding extracellular matrix components and profibrotic mediators (Figure 3).

The rationale for including the TGF-β-activated SMAD signaling pathway in our discussion stems from the potential molecular crosstalk between this pathway and the JAK/STAT signaling cascade. Emerging evidence suggests that SMAD-dependent signaling in non-fibroblastic cells, particularly epithelial cells, can upregulate IL-6 secretion through a mechanism involving SMAD complex translocation and subsequent transcriptional activation. This paracrine IL-6 secretion may subsequently activate JAK/STAT signaling in neighboring fibroblasts, ultimately promoting fibroblast proliferation and their differentiation into myofibroblasts (Figure 3).[49] A transgenic mouse model utilizing keratin 5 promoter-driven TGFβ1 expression, developed by Li et al,[50] demonstrated a significant increase in IL-6 secreted by epithelial cells in severely fibrotic mice. Notably, this study simply emphasized the paracrine role of mouse epithelial cells without addressing their EMT. Thus, combined with the TGF-β-mediated EMT discussed in Epithelial-Mesenchymal Transition (EMT). We speculate that the TGF-β/SMAD signaling pathway also upregulates IL-6 expression in promoting EMT, which in turn promotes FMT (Figure 3). This is consistent with the idea that FMT is enhanced through paracrine secretion, and IL-6 expression is upregulated in ATII by TGF-β-induced in Epithelial-Mesenchymal Transition (EMT).

Furthermore, emerging evidence has demonstrated that elevated levels of IL-6 can significantly upregulate TGF-β1 expression, and high concentrations of IL-6 in bronchoalveolar lavage fluid (BALF) have been shown to potentiate TGF-β1-mediated Smad signaling in fibroblasts. This synergistic interaction between IL-6 and TGF-β1 pathways further supports the existence of crosstalk between these two critical signaling cascades in fibrotic processes.[14,51]

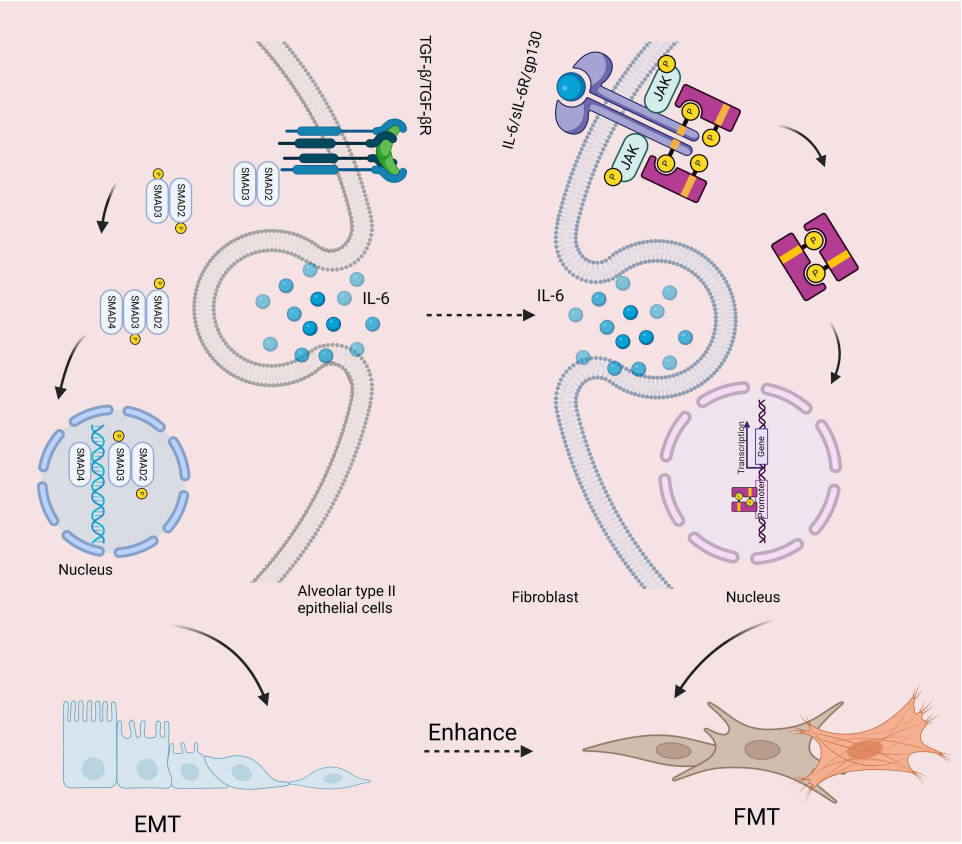

Figure 3 IL-6 may promote fibroblast proliferation and transformation through a non-fibroblast paracrine pathway. TGF-β binds to its receptor and regulates gene transcription via the Smad-dependent pathway, inducing non-fibroblasts to secrete IL-6, which stimulates fibroblast proliferation and their transformation into myofibroblasts. The dashed line indicates that FMT is enhanced through paracrine signaling. Created in BioRender. Yu, Z. (2025) https://BioRender.com/irwalcz.

Macrophage Polarization and Extracellular Matrix Deposition

ECM is a noncellular component present in all tissues and organs. Under normal conditions, it provides a physical scaffold for cellular components and initiates fibrotic repair mechanisms via fibroblasts in response to acute tissue injury. Tightly regulated feedback mechanisms, such as the balance between tissue inhibitors of metalloproteinases (TIMPs) and metalloproteinases (MMPs), as well as controlling the activity of enzymes like lysyl oxidase (LOX) enzyme and transglutaminases, prevent excessive ECM deposition, ensuring tissue homeostasis and fibrosis resolution.[52]

ECM comprises two main macromolecules: fibrous proteins and proteoglycans. Fibrous proteins, including collagens, elastins, fibronectins, and laminins, are the primary protein components for fibrotic repair after tissue injury. Proteoglycans consist of core proteins and glycosaminoglycans (GAGs), which bind to cytokines (eg, IL-6, IL-10, IL-4) and chemokines (eg, CXCL8, CXCL10), mediating pro-inflammatory and anti-inflammatory effects by recruiting inflammatory cells to injured tissues.[52–54] However, under pathological conditions, such as repeated injury or disrupted feedback mechanisms, ECM synthesis becomes dysregulated. Elevated mechanical stress from excessive ECM deposition further induces EMT and FMT. Myofibroblasts, highly contractile and capable of synthesizing ECM components, produce large, stiff collagen bundles, ultimately leading to aberrant fibrosis.[52]

The abnormal accumulation of ECM involves the polarization of macrophages in the repair of damaged tissues.[18] Under normal conditions, macrophages repair inflammation-induced tissue damage by polarizing into M1 and M2 macrophages and can degrade and absorb ECM produced during the repair process.[18,55,56]

During inflammation, bone marrow monocytes migrate to inflamed tissues and differentiate into macrophages. These macrophages are initially in a quiescent state, referred to as resting macrophages (M0).[57,58] With the help of pro-inflammatory factors such as interferon-γ (IFN-γ) and TNF-α, which are secreted by Th1, M0 macrophages can be activated to become classical macrophages (M1), which further release pro-inflammatory cytokines and chemokines (eg, IL-6, TNF-α) to mediate inflammation and produce ROS (reactive oxygen species) to clear pathogens, but this process leads fibroblasts to upregulate matrix-degrading enzymes to promote ECM degradation, slowing down repair of the surrounding tissue and causing tissue damage (Figure 4).[18,55,56,59]

In contrast, M2 macrophages release anti-inflammatory factors such as IL-4 and IL-10, promote fibroblast proliferation, and up-regulate a range of genes involved in cell-ECM interactions, thereby generating a highly aligned matrix that supports angiogenesis, rearrangement, and repair of damaged tissues (Figure 4).[18,55,56] M2 macrophages are further subdivided into four subtypes—M2a, M2b, M2c, and M2d—based on the specific inducing activation factors required, each exhibiting distinct characteristics.[60,61] Among these, M2a and M2c macrophages are primarily associated with fibrosis.[60,62] M2a macrophages are induced and activated by Th2 cytokines such as IL-4 and IL-13. The characteristic features of M2a macrophages include high expression of the CD206 mannose receptor on the cell surface and high expression of the anti-inflammatory factor IL-10. And upon activation, they participate in promoting fibrosis and anti-inflammatory responses.[60,62] M2c macrophages are typically activated by IL-10, characterized by high expression of the scavenger receptor CD163, arginase 1 (Arg1), and IL-10 on their cell surfaces. Upon activation, M2c macrophages exhibit enhanced collagen secretion capacity, playing a role in matrix remodeling.[60,61] During normal tissue repair, macrophage polarization goes through two stages and maintains a delicate balance, first polarizing into M1 macrophages, which play a strong proinflammatory role, and then M1 macrophages polarize into M2 macrophages, which play an anti-inflammatory and tissue repair role (Figure 4).[55,56]

However, if inflammation persists, the M1/M2 balance is disrupted, which may take many forms, causing ECM deposition eventually leading to fibrosis: (1) The sustained cytotoxic and pro-inflammatory effects of M1 macrophages exacerbate lung epithelial cell injury, leading to excessive M2 differentiation. This phenomenon is partly attributed to Th2 cell-derived pro-fibrotic factors (IL-4, IL-10, and IL-13) that drive M0 macrophage polarization toward the M2 phenotype. Additionally, macrophage polarization plasticity contributes to this process, whereby M1 macrophages can repolarize into M2 cells (Figure 4).[18,55,58,63] (2) M2 macrophages express mIL-6R and are a potential sIL-6R. Increased M2 macrophage populations enhance sIL-6R production, facilitating IL-6/sIL-6R complex formation and subsequent signaling[34] (Figure 4). (3) IL-6 secreted by M1 macrophages forms a complex with sIL-6R that persists EMT and FMT through continuous stimulation of the JAK/STAT signaling pathway. (4) Emerging evidence indicates that IL-6 synergistically interacts with IL-4 and IL-13 to potentiate M2 macrophage polarization, driving the development of a distinct

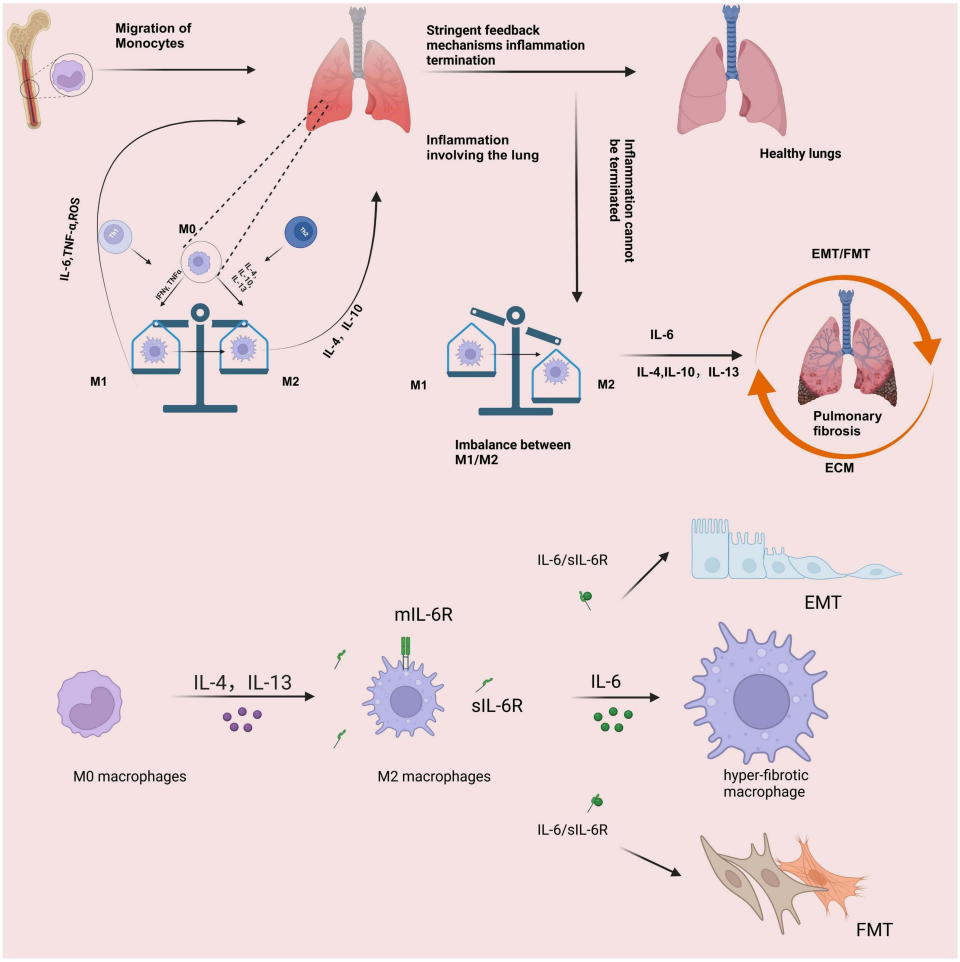

Figure 4 Differential functions of M1/M2 macrophage polarization in the repair of normal inflammatory injury. Role of M1/M2 polarization imbalance in pulmonary fibrosis. M2 macrophages induce IL-6/sIL-6 complex formation. IL-6 promotes hyperpolarization of M2 macrophages. Created in BioRender. Yu, Z. (2025) https://BioRender.com/xmv8jpk and Created in BioRender. Yu, Z. (2025) https://BioRender.com/f5oerjc.

pro-fibrotic macrophage phenotype. These highly activated macrophages, termed hyper-fibrotic macrophages, exhibit enhanced fibrogenic potential and play a crucial role in the progression of fibrotic disorders[14] (Figure 4).

Overall, inflammation-induced imbalance of MI and M2 macrophage differentiation and increased expression of cytokines are important causes of abnormal ECM accumulation and fibrosis.

Targeting IL-6 and JAK/STAT for ILD Treatment

Extensive evidence underscores the pivotal role of the IL-6 and JAK/STAT pathways in ILD, prompting the exploration of these pathways as therapeutic targets. Tocilizumab (TCZ), an IL-6 receptor antagonist, was first approved by the European Medicines Agency (EMA) in 2009 for RA in Europe, followed by the Food and Drug Administration (FDA) in 2010 for RA treatment in the United States.[64] However, the use of TCZ in RA-ILD remains controversial and is a central focus of this discussion. Other IL-6 and IL-6 receptor inhibitors, such as olokizumab (OKZ), sirukumab (SRK), levilimab (LVL), and vobarilizumab (VBR), are currently under development. To date, no clinical studies have evaluated their efficacy in RA-ILD, and thus, they are excluded from this review. Janus kinase inhibitors (JAKi), a novel class of oral small-molecule drugs, have emerged as promising RA therapeutics and are also being investigated for RA-ILD. Among JAKi, tofacitinib and baricitinib are the most extensively studied in RA-ILD and are a key focus of this review. The current major targeted drug researches are shown in Table 1.

Table 1 Overview of the Included Targeted Therapies

References	Publication Year	Study Design	Targeted Drug	Key Findings
Nakashita et al[65]	2012	Prospective study	TCZ	RA patients treated with TCZ exhibited no development of new ILDs, and pre-existing ILDs showed no progression.
Takao Koike et al[66]	2014	Prospective study	TCZ	The observed incidence of ILD in RA patients treated with TCZ significantly exceeded expectations.
Curtis et al[67]	2015	Retrospective cohort study	TCZ	TCZ failed to significantly reduce the incidence of ILD in RA patients or the hospitalization rate in RA-ILD patients.
Otsuji et al[68]	2018	Prospective study	TCZ	RA-ILD patients treated with TCZ demonstrated significant improvements in RA disease activity and KL-6 levels, along with prevention of ILD progression.
Sendo et al[69]	2019	Basic research	TCZ	Tofacitinib can alleviate pulmonary fibrosis in SKG mice
Khanna et al[70]	2020	Phase III trial	TCZ	FVC% remained more stable in TCZ-treated SSC-ILD patients compared to other treatment groups.
Manfredi et al[71]	2020	Multicenter retrospective study	TCZ	In TCZ-treated RA-ILD patients, pulmonary function tests demonstrated stability in FVC and DLCO in over 50% of cases during follow-up, with improvement observed in a minority. HRCT findings remained stable in the majority of patients.
Citera et al[72]	2021	Post Hoc Analysis	Tofacitinib	Tofacitinib treatment was associated with a significantly reduced incidence of ILD events in RA patients.
Kalyoncu et al[73]	2022	Prospective study	Tofacitinib	Tofacitinib significantly improved the mean predicted FVC% from baseline in RA-ILD patients.
Baker et al[74]	2023	Retrospective cohort study	Tofacitinib	RA patients receiving tofacitinib demonstrated the lowest incidence of ILD among treatment groups.
Caterina Vacchi et al[75]	2021	Case report	Tofacitinib	Tofacitinib exhibited significant therapeutic efficacy in patients with progressive RA-ILD.
Tobias Hoffmann et al[76]	2024			
Owen Cronin et al[77]	2021	Retrospective study	Baricitinib	Baricitinib treatment showed no increased risk of respiratory adverse events, respiratory-related hospitalizations, or mortality in RA-ILD patients.
Marika Tardella et al[78]	2022	Retrospective study	Baricitinib	Baricitinib maintained stable pulmonary status in the majority of RA-ILD patients during follow-up.
Vincenzo Venerito et al[79]	2023			
Haoming Yuan et al[80]	2023	Meta-analysis	Baricitinib	Baricitinib, either as monotherapy or in combination with other disease-modifying agents, stabilized pulmonary function and attenuated ILD progression in RA patients.
Kurushima et al[81]	2024	Retrospective study	Baricitinib	The combination of Baricitinib and MTX had a greater effect on EMT than Baricitinib alone.
Vincenzo Venerito et al[79]	2023	Retrospective study	Upadacitinib	Upadacitinib-treated RA-ILD patients maintained stable pulmonary imaging findings and lung function parameters.
Yuuya Nishii et al[82]	2023	Case Report	Upadacitinib	Upadacitinib demonstrated significant improvement in thoracic imaging findings and pulmonary function in refractory RA-ILD patients.

Targeting IL-6

TCZ is a recombinant humanized monoclonal immunoglobulin G1κ antibody that targets both soluble and membrane-bound IL-6 receptors.[64] Multiple large-scale randomized controlled trials (RCTs), involving >300 participants with ≥24-week follow-up durations, have consistently demonstrated the efficacy of intravenous TCZ. These studies, evaluating TCZ as both monotherapy and combination therapy with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), showed significant improvements in disease activity among adults with moderate-to-severe active RA.[83–88]

The therapeutic and preventive role of TCZ in RA-ILD remains controversial. A large retrospective cohort study by Curtis et al found no significant advantage of TCZ over TNF inhibitors (TNFi) in reducing ILD incidence in RA patients

or decreasing hospitalization rates in RA-ILD cases.[67] Furthermore, a Japanese post-marketing surveillance study of 7901 TCZ-treated RA patients reported an ILD incidence twice the initial estimate, raising concerns about TCZ's preventive efficacy against ILD development.[66]

However, recent evidence has re-evaluated TCZ's potential efficacy in RA-ILD management. Otsuji reported that TCZ-treated RA-ILD patients showed significant improvements in both disease activity and KL-6 levels. Moreover, chest CT scans revealed no ILD progression in the majority of patients after 1-year follow-up.[68] Nakashita et al demonstrated that TCZ-treated RA patients showed no new-onset ILD and progression of existing ILD compared to TNFi-treated patients.[65] In a separate study of 104 Systemic sclerosis-related interstitial lung disease (SSC-ILD), TCZ treatment resulted in more stable FVC% changes versus placebo at week 48. Although this phase III trial did not specifically target RA-ILD, its findings provide potential therapeutic insights.[70] Furthermore, a multicenter retrospective study revealed that after a median 30-month follow-up, most TCZ-treated RA-ILD patients maintained stable pulmonary function and HRCT findings, with some demonstrating improvement.[71]

In conclusion, while TCZ demonstrates potential protective effects against RA-associated ILD, its efficacy as first-line therapy requires further validation.

JAK/STAT Inhibitors

Currently, five JAK inhibitors are approved for RA treatment: tofacitinib, baricitinib, upadacitinib, filgotinib, and peficitinib.[89] Among these, tofacitinib and baricitinib are most extensively studied for RA-ILD management, while clinical evidence supporting upadacitinib remains limited.[90–92]

Tofacitinib

Tofacitinib, a second-generation selective JAK inhibitor, received FDA approval for RA treatment in April 2012.[93] Clinical trials, including Phase II, III, and long-term extension studies (up to 114 months), have demonstrated the efficacy and safety of tofacitinib as monotherapy or combined with csDMARDs, particularly methotrexate, in moderate-to-severe RA.[94–97]

Post-hoc analysis revealed significantly lower incidence rates (IR) of RA-ILD events in tofacitinib-treated patients compared to placebo (0.12 and 0.10 vs 0.32 per 100 patient-years for 5 mg, 10 mg, and placebo groups, respectively).[72] Comparative cohort studies indicate that tofacitinib-treated RA patients exhibit the lowest incidence of ILD among various biologic and targeted therapies, including adalimumab, abatacept, rituximab, and tocilizumab.[74] Additionally, basic research by Sendo et al has also demonstrated that Tofacitinib can alleviate pulmonary fibrosis in SKG mice (a mouse model of RA established by inducing point mutations in the gene encoding ZAP-70, leading to abnormal T cell differentiation), and further in vitro experiments have demonstrated that the mechanism may be related to Tofacitinib's ability to selectively inhibit the JAK1 and JAK3 pathways, thereby causing the expansion of myeloid-derived suppressor cells (MDSCs).[69]

Clinical evidence also supports tofacitinib's efficacy in established RA-ILD. For example, case reports by Vacchi et al[75] and Hoffmann et al[76] demonstrated successful management of progressive RA-ILD with tofacitinib after multiple treatment failures. Furthermore, a prospective real-world study of 18 RA-ILD patients showed significant improvement in predicted FVC% following tofacitinib treatment (79.8% vs 82.8%, p=0.014) after a median 12-month follow-up.[73]

Baricitinib

Baricitinib, a selective JAK1/JAK2 inhibitor with preferential JAK1/2 affinity, received EMA approval for RA treatment in February 2017 and FDA approval in May 2018.[98,99] Phase III trials have established its efficacy and safety as monotherapy or combined with methotrexate in active RA.[100]

While large-scale clinical trials specifically evaluating baricitinib in RA-ILD are lacking, retrospective studies by Tardella et al[78] and Venerito et al[79] suggest its therapeutic potential, demonstrating stable pulmonary status in most RA-ILD patients during follow-up. Similarly, A systematic review and meta-analysis by Yuan et al demonstrated that baricitinib, either as monotherapy or combination therapy, stabilized pulmonary function and attenuated ILD progression.[80] Safety analyses consistently support baricitinib's favorable profile in RA-ILD management. Cronin et al's retrospective study found no increased risk of respiratory adverse events, hospitalizations, or mortality compared

to rituximab.[77] Additionally, Salvarani et al[101] and Winthrop et al[102] reported that baricitinib primarily induced upper respiratory and urinary tract infections while reducing ILD incidence, further confirming its safety and efficacy. MTX has been contraindicated in previous studies in patients with severe respiratory disease or severe pulmonary fibrosis due to its pulmonary toxicity (which can induce EMT),[103,104] but in contrast to previous studies, a study by Kurushima et al[81] demonstrated that MTX inhibited IL-6-induced EMT. Interestingly, this study demonstrated that the combination of baricitinib and MTX had a greater effect on EMT than baricitinib alone, suggesting that combining JAKi and MTX may contribute to altering the pathogenesis of pulmonary fibrosis.

In conclusion, while baricitinib has demonstrated promising efficacy and safety in RA-ILD management based on retrospective studies, its therapeutic role requires further validation through large-scale prospective studies and randomized controlled trials.

Upadacitinib

Upadacitinib, a second-generation selective JAK1 inhibitor, obtained FDA approval for moderate-to-severe RA treatment in August 2019.[105,106] While its efficacy and safety in RA have been established through global phase II/III trials,[107,108] evidence regarding RA-ILD remains limited to case reports and retrospective studies. Venerito et al reported stable pulmonary imaging and function in three RA-ILD patients after a median 19.1-month follow-up.[79] Also, Nishii et al documented significant improvement in a refractory RA-ILD case following upadacitinib treatment (15 mg daily), with enhanced pulmonary function (FVC%: 105% to 117%; DLCO%: 54.3% to 69.7%) and HRCT findings after 29 weeks. Disease stability persisted even after dose reduction to 7.5 mg daily.[82]

Conclusion

This review systematically examines the dual aspects of RA-ILD pathogenesis and treatment. First, it consolidates evidence supporting IL-6's central role in disease progression through four principal mechanisms: (1) establishing and maintaining pro-inflammatory microenvironments conducive to ILD development; (2) modulation of fibrogenic gene transcription mediating EMT and FMT through the JAK/STAT pathway; (3) promoting FMT through TGF-β-induced paracrine signaling and JAK/STAT activation; and (4) macrophage polarization in inflammatory injury and repair processes. These mechanisms collectively lead to excessive ECM deposition and interstitial lesions.

Second, the review critically evaluates current targeted therapies for RA-ILD. While the efficacy of IL-6 receptor inhibitors (eg, tocilizumab) remains controversial, preliminary findings suggest potential clinical benefits. JAK inhibitors, including tofacitinib, baricitinib, and upadacitinib, have demonstrated promising therapeutic outcomes. However, the current evidence base primarily relies on retrospective studies with limited sample sizes, underscoring the need for large-scale, multicenter randomized controlled trials to further validate the efficacy of both IL-6-targeted therapies and JAK inhibitors in RA-ILD management.

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