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Review

The role of IL-6 in rheumatoid arthritis comorbidity and implications for therapy

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ABSTRACT

Immune-mediated inflammatory diseases (IMIDs) are complex conditions commonly associated with alterations in cytokine biology. In rheumatoid arthritis (RA), the systemic activities of cytokines, such as interleukin (IL)-6, have led to the clinical introduction of targeted medicines that greatly improve patient outcomes. However, the beneficial effects of these therapies extend beyond improvements in joint pathology and often affect a range of RA-associated comorbidities that influence a patient's quality of life. For IL-6, these include impacts on cardiovascular risk, metabolic diseases, neuropsychiatric conditions, pain, fatigue, and altered tissue homeostasis. Reviewing the involvement of classical IL-6R signalling and IL-6 trans-signalling in these processes, we will examine the mechanistic basis for these comorbidities and consider the implications for therapy in RA and related IMIDs.

1. Introduction

Rheumatoid arthritis (RA) is an immune-mediated inflammatory disease (IMID) characterized by painful inflammation of peripheral joints (synovitis). However, IMIDS are complex conditions and patients with RA often display comorbidities, including cardiovascular, metabolic, pulmonary, and neuropsychiatric conditions as well as anaemia (Fig. 1, Table 1). Significant advances in the treatment of RA have resulted in the introduction of biological inhibitors of cytokine signals, with clinical experience illustrating that these medicines work beyond the inflamed joint to improve the quality of life of patients [1,2]. One cytokine that has been successfully targeted by biologic medicines is interleukin-6 (IL-6). High concentrations of IL-6 are present in synovial fluid and serum of RA patients, with levels correlating with disease activity scores [3] and clinical indices of RA-associated comorbidities [4].

The clinical efficacy of the IL-6 receptor (IL-6R) blocker tocilizumab in RA has raised the profile of IL-6 as a clinical target [5–8] and has inspired the development of antibody-based therapies against IL-6 and IL-6R (Fig. 2). Some of these therapies improve drug pharmacokinetics or pharmacodynamics, whilst others inhibit selective aspects of IL-6 bioactivity [6]. However, blocking IL-6 or its receptor is accompanied by broad immune suppression, and similar to other targeted therapies, often give rise to clinical complications. These include risk of infections (particularly at barrier surfaces, e.g., skin, gut, and respiratory or urinary tract) and adverse outcomes impacting physiological processes (e.g., gastric perforation) controlled by IL-6 in health [9]. Indeed, diseases that remain refractory of inhibitors of IL-6 typically include indications where IL-6 is required to maintain barrier immunity or tissue physiology. Thus, IL-6 plays critical roles in health and disease, and these involvements form the basis for comorbidity, and adverse outcomes or contraindications associated with IL-6 blockers. These illustrate the complex nature of IL-6 biology.

IL-6 is a pleiotropic cytokine known for its role in inflammation and the regulation of immune responses and has been classified as a keystone cytokine in chronic inflammatory conditions and autoimmune diseases such as RA [9].

The biological activities of IL-6 are elicited through two mechanistically distinct signalling pathways. These are termed, classical IL-6R signalling, working via the membrane-bound IL-6 receptor cassette, and IL-6 trans-signalling requiring the soluble IL-6 receptor (sIL-6R) (Fig. 3 A, B). The sIL-6R is a determinant of IL-6 bioactivity and enhances the bioavailability of IL-6 by prolonging its circulating half-life. The importance of sIL-6R in governing inflammatory outcomes comes from early studies demonstrating its role in transition from innate to adaptive immunity in acute inflammatory settings [10]. These activities become central to the role of IL-6 in chronic inflammation, where it

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supports processes leading to retention of activated immune cells, with effector functions linked to the development of tissue pathology [11–14]. Once formed, the IL-6:sIL-6R complex supports IL-6 signalling in cell types inherently non-responsive to IL-6 itself. In order words, cells lacking the cognate IL-6R. Given the systemic nature of IL-6 signalling in IMIDs, it is anticipated that the biological action of IL-6 in driving the comorbidities seen in RA will rely on both modes. It is also worth noting that a third mode of IL-6 signalling has been identified, termed IL-6 trans-presentation [15] (Fig. 3 C). Further work is however required to ascertain the significance of this mode of signalling in IMIDs and it is not discussed in the context of this review.

Correlation studies and some experimental data suggest that elevated serum IL-6 levels contribute to cardiovascular complications, including endothelial dysfunction, coagulation and atherosclerosis, which are a leading cause of patient mortality in RA [16,17]. With effects on glucose metabolism, IL-6 contributes to the increased prevalence of metabolic syndrome and type 2 diabetes in RA patients. Beyond these conditions, IL-6 influences the quality of life of patients by affecting psychiatric disorders, including mood, fatigue, depression, sleep quality, and anhedonia, and physiological processes such as changes in body temperature, general activity, and appetite [18,19]. In the pulmonary system, IL-6 trans-signalling facilitates inflammatory processes that significantly impact respiratory function and patient outcomes [20,21]. Furthermore, IL-6 is a principal driver of anaemia of chronic disease, the most common comorbidity in RA [22,23]. Understanding the mechanistic basis of IL-6 involvement in these comorbidities is critical for assessing the potential therapeutic benefits and adverse consequences of targeting IL-6 signalling pathways with selective biological medicines.

This review aims to explore IL-6 signalling and its blockade in various comorbidities of RA and, where possible, consider the role of IL-6 trans-signalling vs. classical IL-6R signalling.

2. The relevance of IL-6 biology in RA

Interleukin 6 belongs to a family of cytokines that includes IL-6, IL-11, IL-27, LIF (leukaemia inhibitory factor), OSM (oncostatin M), CNTF (ciliary neurotrophic factor), CT-1 (cardiotrophin-1) and CLC (cardiotrophin-like cytokine), which share common and distinct involvements in health and disease [24]. IL-6 was first identified as B-cell stimulating factor (BSF-2) by Hirano et al., in 1986 [25]. Simultaneously, others identified IL-6 as interferon-beta 2 (IFN-β2) due to its interferon-like antiviral activities and hepatocyte-stimulating factor, accounting for the regulation of acute-phase proteins like C-reactive protein (CRP) [26–28]. Subsequent investigations have revealed that IL-6 exhibits pleiotropic functions extending far beyond its initial characterization, encompassing critical roles in inflammatory responses and immune regulation, as well as tissue homeostasis, bone metabolism, haematopoiesis, reproductive biology, and the aging process. IL-6 remains one of the most highly regulated cytokines and is produced by both immune and stromal tissue cells in response to activation of innate sensing pathways, certain inflammatory cytokines, growth factors and bioactive lipids [30–32]. These pleiotropic activities require tight control, with various regulatory mechanisms governing the bioactivity and

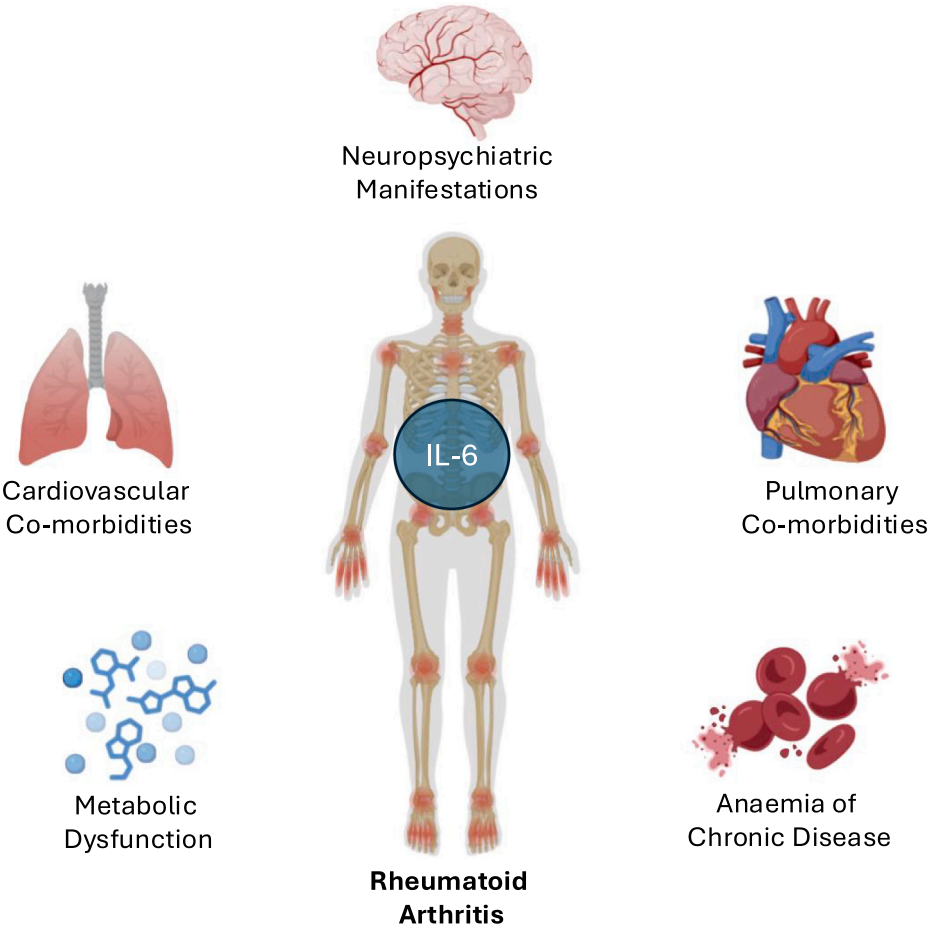


Fig. 1. Comorbidities associated with rheumatoid arthritis.
Representative image showing comorbidities of RA driven by IL6: cardiovascular disease, metabolic disorders and diabetes, anaemia, pulmonary and neuropsychiatric diseases. Made with Biorender.

bioavailability of IL-6 and receptor components.

2.1. Classical IL-6R signalling

Classical IL-6R signalling is generally associated with the physiological maintenance of tissue regeneration and turnover (e.g., in bone, liver, gut) and immune homeostasis [33]. However, this mode of signalling also initiates certain inflammatory processes, including the acute phase response consistent with its role as a hepatic-stimulating factor, and as a lymphokine promoting the proliferation, survival and effector properties of lymphocytes (e.g., Th17 and Tfh cells). Due to the cellular distribution of IL-6R, classical IL-6R signalling is limited to hepatocytes, certain leukocyte subsets, megakaryocytes, and some specialised epithelial cells. The initial trigger arises from the binding of IL-6 to its membrane-bound receptor IL-6R. Following their ligation, the IL-6-IL-6R complex binds the signal-transducing molecule gp130, which acts as the β-receptor signalling subunit for all IL-6-related cytokines [35]. This interaction triggers the activation of tyrosine kinases, leading to the downstream activation of signal transducer and activator factor 1 (STAT1), STAT3, and signalling intermediates activated through the

Table 1
Summary of RA comorbidities Influenced by IL-6 and Impact of IL-6 inhibition.

Comorbidity	Prevalence in RA	Key IL-6-mediated mechanism	Evidence of trans-signalling involvement	Impact of IL-6 inhibition	References
Cardiovascular Disease	Leading cause of mortality; significantly elevated risk vs. general population	• Promotion of atherosclerosis via smooth muscle cell proliferation • Increased intimal-medial thickness • Regulation of CRP production • Induction of oxidative stress and endothelial dysfunction via AT1R upregulation	**Strong preclinical evidence:** • Blocking gp130 reduced CCL2 and sVCAM-1 levels • Restored vascular function in arthritis mouse model upon trans-signalling blockade • L-6 trans-signalling is required for Ang II-dependent hypertension	**Mixed results:** • Tocilizumab associated with increased lipid density levels vs. etanercept • Tocilizumab treatment increases LDL-C, but alters HDL-C to anti-inflammatory composition • Cardiovascular benefits not yet fully demonstrated in clinical trials	[77,78,164,165]
Metabolic Dysregulation (Diabetes)	Increased prevalence vs. general population	• Impaired hepatic insulin sensitivity • Reduced peripheral glucose uptake in muscle and adipose tissue • Hyperinsulinemia, hyperglycaemia, and hyperlipidaemia	**No evidence**	**Positive effects:** • Decreased insulin levels in non-diabetic RA patients • Improved insulin resistance • Better glycemic control • Sarilumab (Il-6 receptor blocker) improves glucose metabolism	[91,92,95,96]
Pulmonary Complication (Interstitial Lung Disease)	~45% of RA patients affected	• Neutrophil mobilization from bone marrow and recruitment to lungs • Increased CXCL1 production • Fibroblast to myofibroblast transformation via JAK/STAT3 • Epithelial fluidization affecting repair vs. fibrosis balance	**Strong preclinical evidence:** • Inhibition of trans-signalling attenuated pulmonary fibrosis in mice • sIL-6Rα from pulmonary macrophages drives fibrosis • Neutralization reduced myofibroblasts, fibronectin, and collagen	**Promising preclinical results:** • Reduced fibrosis in animal models • Decreased inflammatory markers	• Clinical trial data in RA-ILD currently limited
Neuropsychiatric Conditions (Depression, Fatigue)	>40% affected by depression	• Disruption of HPA axis: excessive CRH production, impaired negative feedback, altered cortisol circadian rhythm • Neurotransmitter dysregulation • Crossing BBB during inflammation • Signalling through peripheral nerves	**Moderate preclinical evidence:** • sgp130 facilitated recovery from LPS-induced sickness behaviour in mice • Reduced hippocampal IL-6 levels • *trans*-Presentation by dendritic cells may occur in brain	**Positive effects:** • Improved emotional wellbeing • Reduced depression symptoms, particularly in patients with elevated IL-6 • Better quality of life scores	[126,127,133,135]
Anaemia of Chronic Disease	Most prevalent extra-articular comorbidity in RA	• Upregulation of hepcidin synthesis in liver • Hepcidin binds ferroportin, causing internalization and degradation • Restricted iron release from macrophages • Reduced iron availability for erythropoiesis	**Mechanism involves soluble signalling:** • Direct evidence for trans-signalling role not specifically established	**Strong positive effects:** • Increased haemoglobin levels • Reduced hepcidin levels • Superior efficacy vs. TNF-α inhibitors	[155,158,159]

Ras-Raf pathway [36]. The tyrosine kinases supporting these signals are Jak1, Jak2 and Tyk2. How these individual Janus kinases are selected to signal via gp130 is currently unknown, but emerging evidence suggests these individual Jak proteins may orchestrate unique patterns of STAT transcription factor signalling [37]. Thus, their biological properties may instruct or modify IL-6 signalling in different cell types or activation states and are potentially relevant to the use of Jak inhibitors in clinical practice.

2.2. IL-6 trans-signalling

IL-6 trans-signalling provides an alternative mechanism that extends IL-6 responsiveness beyond cells expressing membrane-bound IL-6R. Not long after the discovery of IL-6, Taga et al., demonstrated that a recombinant variant of the IL-6R, lacking the transmembrane and intracellular domains, retained IL-6 binding capacity and could directly activate cells expressing membrane-bound gp130 [38]. This process was later termed IL-6 trans-signalling [39]. The relevance of these findings to human physiology and pathophysiology began to take shape with the identification of the soluble IL-6R (sIL-6R) in urine, plasma, tears, and breast milk [40–43], with the importance of sIL-6R driven by three seminal findings. First, the early identification that physiological activators of IL-6R shedding promote sIL-6R production during inflammation [44]. Second, the IL-6-sIL-6R shares structural homology resembling heterodimeric cytokines, such as IL-12, IL-23, and IL-27 [45]. Third, that soluble variants of gp130 (sgp130) antagonise the in vivo and in vitro activities of IL-6 trans-signalling [46]. These studies inspired the development of olamkicept, an engineered Fc-fusion with sgp130 [9,11,47–51], which blocks IL-6 trans-signalling by binding IL-6 in complex with sIL-6R, preventing its signalling through gp130. The generation of sIL-6R in mice is due to the shedding of IL-6R by ADAM10 and ADAM17 [52]. The sIL-6R binding of circulating IL-6 promotes interaction with membrane-bound gp130 and activation of the Jak/STAT pathway, coordinating inflammatory outcomes [33,51]. Interestingly, interleukin 11 (IL-11) displays a similar trans-signalling mechanism to IL-6, with the IL-11-sIL-11R complex activating gp130 signalling in cells lacking the cognate IL-11R [53]. Although IL-11 protects tissues against adverse chronic injury, recent discoveries identify roles for IL-11 in driving fibrotic processes, including hypercellular proliferation [54]. Given the structural relationship of the IL-11 receptor to the IL-6 receptor, it is important to note that sgp130 and olamkicept also block IL-11 signalling. Thus, olamkicept possesses a dual action on IL-6 and IL-11-trans-signalling [55,56]. The significance of this biology requires further investigation.

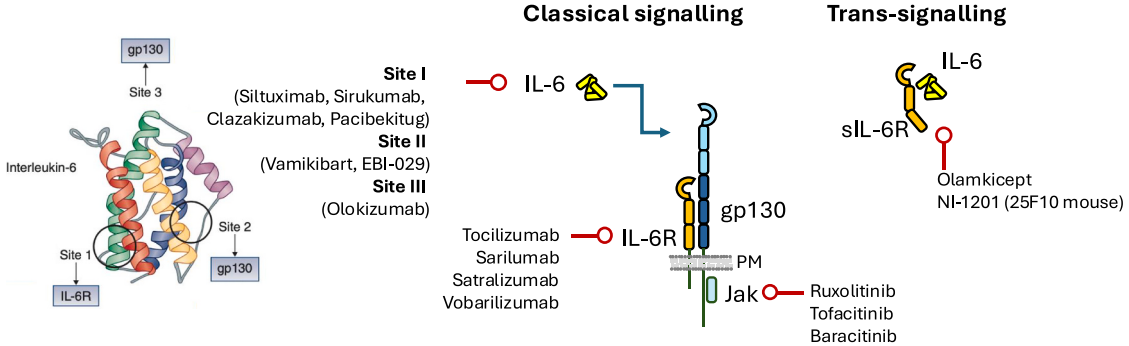
Several lines of evidence show that IL-6 and sIL-6R drive inflammatory diseases, including RA. In patients with RA, IL-6 and sIL-6R levels are high in both synovial fluids and serum and correlate with disease status, synovial leukocyte infiltration, and joint destruction [57]. Animal studies of collagen- and antigen-induced arthritis underline the importance of IL-6 in synovitis. Il6$^{-/-}$ mice display a protected or pauci-immune joint pathology, with the synovitis showing a lack of immune cell infiltration [58,59]. Later work subsequently revealed that synovial IL-6 activity relies on IL-6 trans-signalling, with joint tissue cells predominantly lacking IL-6R expression. These activities closely parallel those in humans with RA. Reviews by Srirangan & Choy and Hashizume & Mihara show that IL-6 drives key features of RA and its comorbidities, underpinning the success of IL-6-targeted therapies [61]. In the following section of this review, we will comprehensively describe some of these comorbidities, their association with IL-6, and the effect of RA treatments on them.

3. IL-6 and cardiovascular comorbidities

Cardiovascular disease (CVD) is the leading cause of patient mortality in RA, with patients showing significantly elevated risks compared to the general population [16,17]. Given the established role of IL-6 as a pivotal driver of RA pathogenesis, it is notable that elevated IL-6 levels have been consistently associated with increased risk of cardiovascular risk, including thrombocytosis [62], myocardial infarction, coagulation and stroke [63,64]. This convergence of inflammatory and cardiovascular pathology in RA patients highlights the complex interplay between IMIDS, autoimmunity and cardiovascular complications.

Multiple lines of evidence highlight elevated coagulation markers and thrombocytosis in RA patients [62,65]. In 2016, Dakhil et al. demonstrated a clear association in RA patients between elevated serum IL-6 levels and increased platelet count with consequences for thrombocytosis, linking this pleiotropic cytokine to disease presentation. Evidence from *Il6*-deficient mice and patients treated with tocilizumab suggests a role for IL-6 in thrombopoiesis [66], but the underlying mechanism remains incompletely characterized. In 2024, Costa et al. reported that IL-6 regulates changes in circulating pro-coagulant lipids generated from platelet membranes in mice with antigen-induced arthritis [67]. The direct link between pro-coagulant lipids and coagulation markers was also demonstrated in humans [67]. The role of IL-6 in contributing to thrombopoiesis is further supported by the efficacy of the anti-IL-6R drug tocilizumab in reducing prothrombotic markers [68].

While the precise aetiology of CVD in RA patients remains incompletely understood, accumulating evidence points to systemic inflammation as a central pathogenic mechanism, operating independently of



Hunter, CA. & Jones, SA. Nat. Immunol. 16:448 (2015)
Jones, SA. & Jenkins, BJ. Nat. Rev. Immunol. 18:773 (2018)

Fig. 2. Biologics alleviating comorbidities associated with rheumatoid arthritis.
Shown are examples of biologic medicines used for the treatment of RA that also improve comorbidities associated with the disease.

traditional cardiovascular risk factors such as age, sex, body mass index (BMI), hypertension, and cigarette smoking [69,70]. Studies have demonstrated that RA patients experience a high incidence of cardiovascular events that cannot be fully explained by conventional cardiac risk factors alone, suggesting that disease-specific inflammatory processes contribute substantially to cardiovascular risk [69]. Furthermore, cardiovascular risk factors may not confer equivalent risk in RA patients compared to non-RA individuals, underscoring the unique nature of cardiovascular pathology in this population [70,71].

The mechanistic connection between RA and CVD became clearer with the discovery that IL-6 plays a direct role in atherosclerosis, one of the primary pathological processes underlying cardiovascular disease. Specifically, IL-6 is produced by smooth muscle cells within the intima-media layer of blood vessels, where it promotes smooth muscle cell proliferation and contributes to increased intimal-medial thickness, a well-established marker of atherosclerotic disease progression [72,73].

The involvement of IL-6 in atherosclerosis is further substantiated by its regulation of C-reactive protein (CRP), fibrinogen, and serum amyloid-A, as key inflammatory biomarkers of systemic inflammation, coronary artery disease, and coagulation. Elevated CRP levels are strongly associated with increased cardiovascular disease risk, establishing an additional pathway through which IL-6 may promote cardiovascular pathology [73]. Moreover, IL-6 signalling has been shown to induce oxidative stress and endothelial dysfunction by upregulating the angiotensin II type 1 receptor, thereby compromising vascular health through multiple mechanisms [74–76].

Recent experimental evidence has provided compelling support for the role of IL-6 signalling in cardiovascular dysfunction associated with inflammatory arthritis. In a landmark 2021 study, Davies and colleagues demonstrated in a mouse model of arthritis that sgp130Fc reduced arthritis severity and decreased serum levels of CCL2 and sVCAM-1, both recognized markers of cardiovascular disease [77]. Critically, this intervention also restored vascular function, providing direct evidence that IL-6 signalling contributes to cardiovascular dysfunction in arthritis.

These findings suggest a novel therapeutic strategy, whereby selective inhibition of IL-6 trans-signalling may offer some therapeutic advantage over a more global blockade of IL-6 (e.g., with tocilizumab). This distinction may be particularly important given that clinical trials evaluating the cardiovascular safety of current RA treatments have not demonstrated substantial improvements in CVD comorbidity. A more selective approach targeting trans-signalling mechanisms might offer superior cardiovascular protection while maintaining therapeutic efficacy against arthritis.

In 2020, Giles and colleagues conducted a randomized controlled trial investigating the cardiovascular safety of tocilizumab against etanercept (a lymphotoxin-α and TNF-α inhibitor based on soluble TNF receptor 2) in patients with RA. Compared to etanercept, tocilizumab treatment elevated circulating lipids (e.g., total cholesterol, LDL-C, and HDL—C) [78]. Changes in circulating lipids are not uncommon in patients receiving biological or targeted medicines. However, the more pronounced changes seen under IL-6R inhibition may reflect an improved control of CRP by IL-6 inhibitors. A phenomenon known as the 'lipid paradox', with systemic increases in CRP as a response to inflammation often suppressing circulating lipids [79]. Significantly, biochemical studies evaluating the changes in lipid composition as a response to tocilizumab treatment identified that IL-6 blockade may positively influence the balance between anti-atherogenic high-density lipoprotein (HDL) cholesterol and pro-atherogenic low-density lipoprotein (LDL) cholesterol circulating lipids [80].

This paradoxical finding highlights the challenges in translating mechanistic understanding into improved cardiovascular outcomes. While IL-6 clearly contributes to atherosclerosis and cardiovascular dysfunction, broad IL-6 blockade may have unintended metabolic consequences that complicate the cardiovascular risk profile. These results underscore the need for more nuanced therapeutic approaches, such as selective targeting of pathogenic IL-6 signalling pathways while preserving beneficial homeostatic functions.

The relationship between IL-6, RA, and cardiovascular disease is multifaceted and clinically significant. While IL-6 clearly plays a central role in promoting atherosclerosis and cardiovascular dysfunction in RA patients through multiple mechanisms—including smooth muscle cell proliferation, CRP regulation, and endothelial dysfunction—current therapeutic approaches targeting IL-6 have not yet delivered the anticipated cardiovascular benefits. The promising preclinical data suggesting that selective targeting of IL-6 trans-signalling may offer superior cardiovascular protection warrant further investigation in clinical trials. Understanding and addressing the cardiovascular burden in RA patients remains a critical unmet need, requiring continued research into both disease mechanisms and therapeutic strategies that can safely and effectively reduce cardiovascular risk in this vulnerable population.

4. IL-6 and metabolic dysregulation

Multiple inflammatory factors present in rheumatoid arthritis (RA) promote insulin resistance and diabetes mellitus (DM) [82]. These include cytokines, autoantibodies, and adipokines [83], and high C-reactive protein (CRP) levels, where CRP involved in bone remodelling correlates with disease activity scores and IL-6 levels in RA patients [84–86]. In their recent review article, Li et al. comprehensively examined studies linking RA and DM, highlighting the substantial evidence base for this association [82]. Multiple studies have demonstrated the impact of inflammatory markers in driving DM development [87–89]. Among the inflammatory mediators implicated in RA-associated diabetes, IL-6 plays a particularly significant role. IL-6 contributes to insulin resistance through multiple interconnected

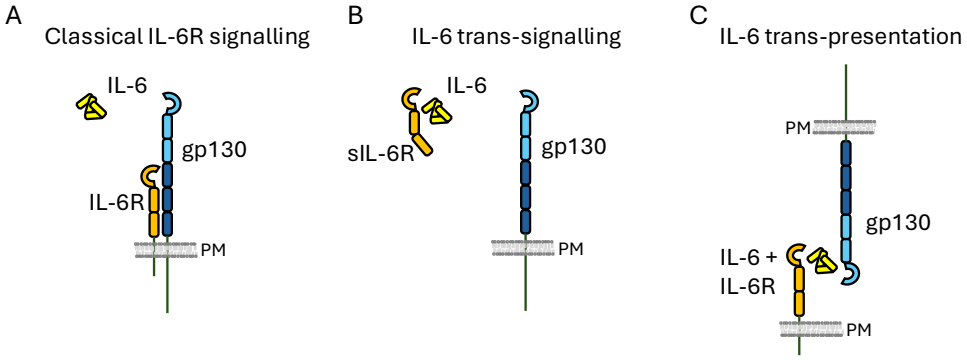


Fig. 3. Different modes of Il-6 signalling.
A. Classical IL6-signalling with a membrane bound Il-6 receptor, B. IL-6 trans-signalling with a soluble Il6:Il6Ra-complex and C. Il6 trans-presentation between two cells are shown. Only one gp130 and one Il6Ra of the hexametric complex is depicted.

mechanisms that disrupt normal glucose homeostasis.

IL-6 directly impairs hepatic insulin sensitivity, reducing the liver's ability to respond appropriately to insulin signalling [18]. This hepatic insulin resistance leads to continued glucose production by the liver despite elevated insulin levels, contributing to persistent hyperglycaemia [82,90]. IL-6 also interferes with peripheral glucose uptake, particularly in muscle and adipose tissue. By disrupting insulin signalling pathways in these tissues, IL-6 prevents efficient glucose clearance from the bloodstream, exacerbating hyperglycaemia [90]. The combined effects of reduced hepatic insulin sensitivity and decreased peripheral glucose uptake result in a cascade of metabolic disturbances, including sustained hyperinsulinemia (as the pancreas attempts to compensate), hyperglycaemia, and hyperlipidaemia [82,90].

The causal role of IL-6 in insulin resistance has been convincingly demonstrated through therapeutic intervention studies. Treatment with tocilizumab significantly decreased insulin levels in non-diabetic RA patients, providing direct evidence for IL-6 in glucose metabolism and insulin dysregulation [91]. These findings identify IL-6 as a driver of insulin resistance and highlight the therapeutic benefit of IL-6-targeting drugs (e.g., tocilizumab, sarilumab) on diabetes management in RA [92–96].

The evidence collectively demonstrates that IL-6 plays a critical mechanistic role in linking RA with diabetes mellitus by altering hepatic and peripheral insulin sensitivity. The therapeutic success of IL-6-targeted interventions in improving glycaemic control provides both validation of this pathophysiological mechanism and promise for dual management of rheumatic and metabolic disease in affected patients.

5. IL-6 and pulmonary comorbidities

Pulmonary complications represent a significant burden in rheumatoid arthritis, affecting approximately 45% of patients [20] and contributing substantially to both morbidity and premature mortality [97–99]. The spectrum of lung involvement in RA is diverse and includes interstitial lung disease, airways disease, rheumatoid nodules, and pleural effusions, with interstitial lung disease being among the most prevalent conditions [99]. This heterogeneity in pulmonary pathology necessitates individualized treatment strategies, and the effects of biologic therapies on lung disease in RA remain complex, with evidence suggesting both beneficial and potentially adverse outcomes [97].

IL-6 appears to play a significant role in the pathogenesis of rheumatoid arthritis-associated interstitial lung disease (RA-ILD) [100], a group of fibrotic lung disorders characterized by progressive fibrosis, interstitial inflammation, and aberrant cellular proliferation [101].

IL-6 promotes pulmonary inflammation through several key mechanisms. First, studies in mice overexpressing IL-6 in the lungs demonstrated elevated neutrophil egress from bone marrow and exaggerated neutrophil recruitment to the lungs, resulting in pulmonary vascular remodelling [102]. Systemic IL-6 enhances pulmonary CXCL1 (a neutrophil-activating chemokine with CXCL8-like activities in humans) production via trans-signalling, promoting neutrophil infiltration and lung tissue injury [103]. Functional inhibition of IL-6 has been shown to reduce both systemic and pulmonary neutrophilia in experimental models [104].

Second, IL-6 promotes the transformation of fibroblasts into myofibroblasts through the JAK/STAT3 signalling pathway, with IL-6-deficient mice showing attenuated fibrosis following bleomycin administration compared to wild-type controls, and IL-6 overexpression increasing the fibrotic response, including collagen production [105].

Third, IL-6 influences epithelial cell function, though its effects appear context-dependent. IL-6-dependent epithelial fluidization plays a critical role in coordinating the balance between homeostatic lung repair and fibrotic airspace remodelling [106], and blocking IL-6 at the early inflammatory stage of lung injury affects epithelial injury-based mechanisms of lung fibrosis [107].

Supporting the association between IL-6 and RA-ILD, a 2014 preclinical study demonstrated that inhibition of IL-6 trans-signalling attenuated pulmonary fibrosis in a murine model, with evidence suggesting that soluble IL-6 receptor alpha (sIL-6R) in the diseased lung may be derived from pulmonary macrophages. Subsequent research has shown that neutralization of IL-6 trans-signalling reduces the activation of lung myofibroblasts, limiting fibronectin and collagen production. These findings underscore the importance of the IL-6 trans-signalling in driving both articular and pulmonary inflammation in RA via Jak-STAT signalling and macrophage polarization [100].

6. IL-6 and neuropsychiatric conditions

Neuropsychiatric conditions constitute a major category of RA comorbidities. Depression alone affects over 40% of patients [109], underscoring the substantial mental health burden associated with IMIDs. Notably, depression in RA correlates with elevated serum IL-6 levels, disease activity score (DAS), visual analogue scale (VAS) score for pain, and CRP levels, and is associated with worse disease outcomes [110].

Under physiological conditions, locally produced IL-6 in the brain is essential for neuronal recovery after injury and plays a crucial role in normal brain function and development. However, emerging evidence indicates that systemic IL-6 and sIL-6R may cross the blood-brain barrier (BBB) when its permeability is increased by inflammatory conditions [111,112]. IL-6 can dysregulate neurotransmitters, disrupt the hypothalamic–pituitary–adrenal (HPA) axis, and signal through peripheral nerves [113–116], leading to neuropsychiatric conditions like fatigue and depression [114,117].

The HPA axis represents the body's primary stress response system and plays a central role in regulating mood, insomnia, anxiety, digestion/appetite, immune function, and inflammation [118]. Under normal conditions, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH). ACTH then triggers the adrenal cortex to produce cortisol, a glucocorticoid, that elicits broad immunosuppressive and anti-inflammatory effects while also providing negative feedback to the hypothalamus and pituitary to maintain homeostasis.

IL-6, which is systemically elevated in RA patients, disrupts this finely tuned system with several studies associating IL-6 levels with changes in hormone production. First, IL-6 has been correlated with excessive CRH production in the hypothalamus, leading to hyperactivation of the HPA axis [119,120]. Furthermore, IL-6 interferes with the negative feedback mechanisms that normally restrain HPA axis activity, resulting in sustained hypercortisolaemia [121,122]. Chronic cortisol elevation is strongly associated with depression, cognitive impairment, and hippocampal atrophy [123]. Additionally, IL-6 may also influence the circadian control of cortisol secretion, disrupting the normal diurnal pattern essential for mood regulation and energy homeostasis [124,125].

Multiple studies now associate treatment with IL-6 signalling-inhibiting drugs and improvement not only in joint inflammation but also emotional well-being (mood, sleep) and neuropsychiatric comorbidities such as depression and anxiety, particularly in patients with elevated serum IL-6 levels [115,126–130]. Patient-reported outcome measures frequently show the potential benefits of IL-6 inhibition in reducing signs of depression, anxiety, and anhedonia [131]. However, new research is required to understand whether these benefits correlate with an overall improvement in disease activity, or arise through direct actions on the brain, neuroendocrine system, pain, or inflammation-associated anaemia.

Given that IL-6 is already present constitutively within the brain, the critical question is whether IL-6 trans-signalling specifically drives neuroinflammation in this context. This distinction is particularly relevant in the brain, where not all cells express membrane-bound IL-6R [132]. Burton et al. (2011) demonstrated that sgp130 facilitated recovery from LPS-induced sickness behaviour (a model of depression-like

symptoms) in mice. This recovery was accompanied by reduced IL-6 receptor signalling and decreased IL-6 mRNA and protein levels in the hippocampus [133]. Campbell et al. (2014) concluded from their murine studies that many neuropathogenic effects of IL-6 are mediated through trans-signalling [134], and a Mendelian randomisation study in 2021 provided evidence for a causal effect of sIL-6R on depression in humans [135]. An additional mechanism of interest is IL-6 trans-presentation (akin to that seen in the IL-15 system), whereby a specific subset of dendritic cells (DCs) presents their own membrane-bound IL-6-IL-6R complex to gp130 on target cells. This process could occur within the brain parenchyma and would represent a juxtacrine mode of signalling that does not require circulating sIL-6R [15].

It is important to note that these findings derive predominantly from animal studies, and it remains unclear whether and to what extent IL-6 trans-signalling plays a role in the development of mood disorders in RA patients. An important conceptual distinction may need to be drawn between neuropsychiatric symptoms such as fatigue, low mood, and depression that emerge as comorbidities secondary to systemic inflammation and elevated serum IL-6 levels – potentially representing "inflammation-driven" affective disturbance - and depression as a primary psychiatric disorder that develops through brain-intrinsic mechanisms independent of peripheral inflammatory influences. Determining whether these represent distinct etiological pathways or points along a continuum, and identifying which patients are most likely to benefit from broad or trans-signalling specific IL-6-targeted therapies for neuropsychiatric symptoms, remain important areas for future investigation.

6.1. IL-6 and pain

Although pain is per se not a neuropsychiatric disorder, the psychological status of RA patients influences pain perception and is tied to peripheral and central pain processing [136].

Indeed, pain represents one of the most common symptoms of RA and has been reported as a top priority for treatment by patients [137–139]. However, even when chronic inflammation in the peripheral joints affected by RA resolves or significantly improves, a substantial percentage of patients report residual pain for which joint destruction appears to be only minimally responsible [140–143]. Moreover, pain is not limited to the joints but also affects diffuse sites throughout the body. This type of pain has been characterized by Sebba et al. as non-inflammatory pain [144]. Evidence from preclinical studies demonstrates that synovial IL-6 expression can promote long-lasting peripheral sensitization to stimulations (e.g., painful movement), suggesting a role for IL-6 in central pain [145,146]. Neurons and glial cells in the central nervous system express gp130 and are responsive to IL-6 trans-signalling, accounting for changes in nociceptive plasticity and increased nerve fibre growth [144,147,148]. However, a key question is how sIL-6R (often released by activated immune cells during inflammation) levels are increased in the CNS of patients with IMIDs. Here, damage to the blood-brain barrier as a consequence of systemic inflammation may increase vascular leakiness into the brain and CNS, while the role of IL-6 trans-presentation requires further consideration. Taken together, the persistent local neuronal activity and the susceptibility of the CNS to trans-signalling can lead to altered pain processing and, ultimately, chronic pain. It has been suggested that pain in RA should be treated as its own entity – maybe even a comorbidity - rather than as something that will resolve once inflammation is controlled.

7. IL-6 and anaemia

Anaemia represents the most prevalent extra-articular comorbidity associated with rheumatoid arthritis (RA), typically developing within the first years following disease onset. In the context of RA, anaemia manifests as anaemia of chronic disease (ACD), characterized by reduced haemoglobin levels [149]. Importantly, RA patients presenting with ACD tend to exhibit more severe disease manifestations and greater functional impairment [22,23]. This relationship between anaemia and disease severity underscores the clinical significance of understanding and addressing this comorbidity in RA management. Multiple studies have established a compelling association between elevated IL-6 levels and the development of anaemia in RA patients, strongly suggesting that IL-6 plays a causative role in this comorbidity [150,151]. The mechanism underlying this relationship centres on hepcidin, a key regulatory protein in iron metabolism. Patients with ACD in the setting of RA demonstrate elevated hepcidin levels, which provide the critical mechanistic link between IL-6 signalling, the acute phase response, and anaemia [151].

Hepcidin functions as the master regulator of systemic iron homeostasis, primarily by inhibiting iron transport and release from macrophages [152]. This regulatory mechanism has profound implications for erythropoiesis, as hepcidin restricts iron availability to the bone marrow. At the molecular level, hepcidin exerts its effects by binding to ferroportin, the sole known cellular iron exporter, leading to ferroportin internalization and degradation [153].

The direct link between IL-6 and hepcidin expression was elegantly demonstrated through multiple experimental approaches. When human hepatoma cells were stimulated with IL-6, hepcidin expression increased substantially. Further supporting this relationship, IL-6 knockout mice exhibited markedly reduced hepcidin levels accompanied by elevated tissue iron concentrations. Clinical studies corroborated these findings, showing that IL-6 infusion in patients resulted in increased circulating hepcidin levels [153,154]. Mechanistically, Nemeth and colleagues demonstrated that IL-6 upregulates the transcription of the gene encoding hepcidin, thereby establishing the molecular pathway through which inflammatory cytokines lead to iron restriction and subsequent anaemia [155].

While numerous clinical studies have documented improvements in anaemia following treatment with tumour necrosis factor-alpha (TNFα) inhibitors [156,157], the central role of IL-6 in driving anaemia in RA patients suggests that therapies specifically targeting IL-6 should demonstrate even greater efficacy in addressing this comorbidity. This hypothesis has been validated in clinical practice. Song and colleagues showed that tocilizumab effectively alleviated anaemia in RA patients, with efficacy superior to that observed with the anti-TNF-α inhibitor infliximab [158]. These findings were corroborated by Isaacs and colleagues in 2013, who reported significant improvements in haematological markers in RA patients treated with tocilizumab, providing further evidence that IL-6 signalling plays a pivotal role in the pathogenesis of RA-associated anaemia [159].

The evidence clearly establishes IL-6 as a key mediator of anaemia in RA through its regulation of hepcidin expression and subsequent iron restriction. Understanding this pathway not only illuminates the pathophysiology of this important comorbidity but also provides a strong rationale for the use of IL-6-targeted therapies in RA patients with anaemia. The superior efficacy of tocilizumab compared to TNFα inhibitors in improving anaemia supports a targeted therapeutic approach based on the underlying mechanisms of disease. However, there are serious gastrointestinal complications associated with tocilizumab therapy, including gastric perforations and diverticulitis [160–162]. While these adverse events are rare, they warrant particular attention as they may present with nonspecific symptoms and can lead to secondary anaemia through gastrointestinal bleeding, potentially confounding the assessment of treatment response in RA-associated anaemia.

8. Final remarks and conclusion

In this review, we have examined the role of IL-6 in driving the most common comorbidities associated with RA, identifying IL-6 as a key mediator linking joint inflammation to systemic disease manifestations. While we have concentrated our discussion on patients with RA, the underpinning biological mechanisms likely have relevance to patients

with other IMIDs or multimorbidity, where signs of cardiovascular risk, psychiatric complications, and altered metabolic processes are common comorbidities. These processes highlight the unique burden of symptoms experienced by patients with IMIDs like RA and reinforce the need for early and targeted therapeutic intervention.

The introduction of biological and targeted medicines against IL-6 signalling has significantly improved not only joint inflammation but also key comorbidities. Clinical evidence confirms improvements in insulin resistance, anaemia, and certain neuropsychiatric symptoms following IL-6 blockade. While this validates the pathogenic role of IL-6 in comorbidity development, the clinical picture of RA remains complex and marked by a lack of uniformly positive clinical outcomes, with around 50% of patients not responding to intervention with certain biological drugs.

A promising future therapeutic development is the selective targeting of IL-6 trans-signalling while preserving classical signalling pathways. IL-6 trans-signalling extends inflammatory effects to cells lacking membrane-bound IL-6 receptors and has been implicated in pathological inflammation across multiple organ systems. Some preclinical studies, particularly in cardiovascular and pulmonary models, suggest that selective inhibition of IL-6 trans-signalling with agents such as olamkicept may offer improved therapeutic benefits by targeting pathogenic inflammation while maintaining the homeostatic functions of IL-6, such as tissue regeneration, acute phase responses, and immune regulation. However, definitive evidence for the contribution of trans-signalling to the manifestation of comorbidities in RA patients remains limited, particularly for neuropsychiatric and metabolic dysfunctions, highlighting a critical gap in our understanding.

Several key research priorities emerge from this review. First, there is an urgent need for predictive biomarkers that identify patients at risk of developing specific IL-6-driven comorbidities and which patients most likely benefit from IL-6-targeted therapies. This would facilitate early intervention strategies and personalised treatment approaches. Second, long-term studies are needed to fully characterize the effects of IL-6 inhibition on comorbidity development and progression, particularly regarding cardiovascular complications, where current evidence remains unclear. Third, mechanistic studies are needed to establish the contribution of IL-6 trans-signalling versus classical signalling to specific comorbidities in RA, and there is a pressing need to move beyond animal models to patient-derived evidence. Fourth, the recent discovery that human IL-6 can bind and signal through the IL-11 receptor adds further complexity to therapeutic decision-making. The cross-reactivity between the two cytokines suggests that cytokine-blocking therapies (siltuximab, clazakizumab, olokizumab) may offer broader pathway inhibition compared to receptor-blocking agents (tocilizumab, sarilumab). This is particularly relevant given the role of IL-11 in fibrosis and aging-related processes that commonly affect RA patients [163].

In conclusion, the inflammation associated with IMIDs such as RA is complex, with mechanisms accounting for local synovitis within inflamed joints and systemic inflammation affecting disease-associated comorbidities. The therapeutic targeting of IL-6 improves both arms of the disease, but further research is required to improve treatment outcomes through better patient stratification, clinical decision-making, and understanding of adverse reactions and contraindications. With advances in precision medicine, integrating individual comorbidity risk factors and profiles into treatment strategies will be essential for improving disease outcomes and overall quality of life for patients living with RA.

CRediT authorship contribution statement

Federica Monaco: Writing – review & editing, Writing – original draft, Conceptualization. **Sandra Dimonte:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Simon A. Jones:** Writing – review & editing, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors formulated the structure and wrote the manuscript content. They acknowledge using Elicit and Claude.ai to support literature reviews and proofreading for grammatical errors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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