Chapter

Cytokines in Autoimmune Diseases: Pathophysiological Roles and Therapeutic Targeting

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Abstract

Cytokines are critical intermediaries of immune and inflammatory responses and present a central role in the pathogenesis of numerous rare diseases. Dysregulated cytokine production and signaling contribute to disease onset, progression, and clinical heterogeneity, particularly in autoinflammatory, autoimmune, genetic, and neurodegenerative disorders. They are synthesized and secreted by numerous cell types, including monocytes, T- and B- lymphocytes, dendritic cells, natural killer cells, endothelial cells, fibroblasts, and epithelial cells. Auto-inflammatory and autoimmune diseases represent two major categories of immune-mediated disorders characterized by dysregulated immune responses. Although traditionally considered distinct, increasing evidence supports a continuum between innate and adaptive immune dysfunction. Auto-inflammatory diseases are driven primarily by aberrations in the innate immune system, without significant participation of antigen-specific T cells or autoantibodies. These conditions are often associated with genetic mutations affecting inflammasome components, leading to excessive activation of inflammatory pathways. Recent advances in molecular immunology have allowed the identification of disease-specific cytokine crosses and facilitated the advance of targeted biological therapies. Future research should therefore focus on identifying reliable biomarkers for treatment stratification, understanding mechanisms of therapeutic resistance, and developing safer and more effective immunomodulatory approaches. Continued progress in cytokine biology and precision immunology is expected to substantially improve outcomes and quality of life for patients with rare autoimmune and autoinflammatory diseases. This review delivers a comprehensive overview of cytokine biology, their involvement in rare diseases, and current and emerging cytokine-targeted therapeutic strategies. Additionally, it highlights the role of cytokines as biomarkers and discusses future perspectives in precision medicine.

Keywords: cytokines, autoimmune, therapeutic targeting, anti-inflammatory, autoinflammatory

1. Introduction

Cytokines are a heterogeneous group of small, low-molecular-weight, soluble signaling molecules that mediate communication among immune and non-immune cells and regulate inflammatory and immune processes. They play a fundamental role in the pathogenesis of a wide range of diseases, including those caused by infectious agents as well as disorders resulting from immune system dysfunction. They are synthesized and secreted by numerous cell types, including monocytes/macrophages, T- and B-lymphocytes, dendritic cells, natural killer cells, endothelial cells, fibroblasts, and epithelial cells, usually in response to immunological, inflammatory, infectious, or stress-related stimuli [1, 2]. Cytokines exert pleiotropic, redundant, synergistic, and antagonistic biological effects, thereby orchestrating highly complex regulatory networks involved in immune homeostasis and pathological inflammatory responses. Based on structural characteristics and functional properties, cytokines are generally classified into several major families, including interleukins (ILs), interferons (IFNs), tumor necrosis factors (TNFs), chemokines, colony-stimulating factors (CSFs), and transforming growth factors (TGFs). These mediators regulate diverse biological processes such as leukocyte activation and trafficking, antigen presentation, hematopoiesis, angiogenesis, apoptosis, cellular proliferation and differentiation, as well as tissue remodeling and repair. Cytokines may act in an autocrine, paracrine, or endocrine manner depending on their concentration, receptor distribution, and physiological context [2–4].

The biological activity of cytokines is mediated through specific membrane-bound receptors that belong to several structurally distinct receptor superfamilies, including type I and type II cytokine receptors, TNF receptor family members, immunoglobulin superfamily receptors, chemokine receptors, and receptor tyrosine kinases. Ligand-receptor binding induces conformational changes and receptor oligomerization, leading to the activation of intracellular signaling cascades such as the Janus kinase/signal transducer and activator of transcription (JAK/STAT), nuclear factor kappa B (NF-κB), mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), and SMAD pathways. The integration and cross-talk between these signaling networks ultimately determine the magnitude, duration, and specificity of cellular responses. Aberrant cytokine production, receptor dysregulation, or persistent activation of downstream signaling pathways contributes substantially to the pathogenesis of autoimmune, autoinflammatory, infectious, allergic, metabolic, and malignant disorders. Consequently, cytokines and cytokine receptors have become major therapeutic targets, leading to the development of monoclonal antibodies, receptor antagonists, and small-molecule kinase inhibitors aimed at modulating cytokine-driven inflammatory pathways [1–6].

Rare autoimmune diseases are defined in Europe as conditions affecting fewer than 1 in 2,000 individuals; however, collectively, they impact more than 300 million people globally. Many of these diseases are chronic, progressive, and lack effective therapeutic options [4].

In physiological conditions, cytokines contribute to the preservation of immune balance and the coordination of protective host responses against pathogens and tissue injury. However, dysregulation of cytokine production – whether excessive or insufficient – can disrupt this balance and initiate

pathological inflammatory processes. Pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, contribute to tissue damage and chronic inflammation, whereas anti-inflammatory cytokines, such as IL-10 and TGF-β, play essential roles in immune regulation [5, 6].

We are aware of the increasing number of molecular and genetic studies that investigate the implication of cytokines in multiple diseases and auto-inflammatory processes. Under normal conditions, cytokines are involved in host defense and the upkeep of tissue balance. However, cytokine dysregulation or altered production, characterized by imbalanced secretion – either increased or decreased – can initiate inflammatory processes that lead to disease development. IFNs, ILs, chemokines, CSFs, and growth factors belong to the family of cytokines. Pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 can impair tissue integrity, sustain inflammation, and promote the progression from acute to chronic disease, whereas IL-10 and TGF-β suppress immune functions or facilitate immune evasion as
anti-inflammatory cytokines. Due to their role in the pathology of diseases, their significance as targets for therapeutic intervention is increasing. Given their central role in disease mechanisms, cytokines have emerged as key therapeutic targets. Biological therapies targeting cytokines are increasingly used in the treatment of immune-mediated diseases. Importantly, many immunologic disorders exist along a continuum ranging from monogenic auto-inflammatory conditions to polygenic autoimmune diseases, highlighting the importance of tailored cytokine-targeted approaches [1–6].

This review summarizes the role of cytokines in rare autoimmune diseases, with a focus on auto-inflammatory and autoimmune conditions, and discusses current and emerging therapeutic strategies.

2. Brief overview of cytokine biology

Cytokines play a diverse role in upholding immune balance and are critically involved in the pathophysiology of autoimmune, metabolic, endocrine, and cardiovascular diseases, as well as cancer. Pro-inflammatory and inflammatory cytokines are key mediators of the immune response, playing essential roles in host defense and immune regulation. They are rapidly produced in response to infection, tissue injury, or immune activation and function to initiate and amplify inflammation (see **Table 1**). Major pro-inflammatory cytokines, including IL-1β, IL-6, TNF-α, and IFN-γ, promote leukocyte recruitment, activation, and the production of additional inflammatory mediators [1–3]. While these cytokines are crucial for effective immune protection, their excessive or prolonged production can lead to dysregulated inflammation and tissue damage. Such imbalances are central to the pathogenesis of numerous conditions, including autoimmune, metabolic, and cardiovascular diseases, as well as cancer. Therefore, tight regulation of pro-inflammatory cytokine activity is essential for maintaining immune homeostasis and preventing chronic inflammatory conditions.

Pro-inflammatory cytokines, like IL-1β, IL-6, IL-8, IL-12, TNF-α, and IFN-γ, are rapidly produced in response to infection or tissue injury. Depending on the nature of the stimulus and the stage of the response, additional cytokines are synthesized and secreted by recruited leukocytes, such as polymorphonuclear cells,

Class	Key examples	Main functions	Receptors	Major signaling pathways	Reference
Interleukins (ILs)	IL-1, IL-2, IL-4, IL-6, IL-10, IL-17	Immune regulation, inflammation, T/B cell activation, differentiation.	IL receptors (e.g., IL-1 R, IL-2 R)	JAK/STAT, NF-κB	[1, 5, 6]
Interferons (IFNs)	IFN-α, IFN – IFN-γ, IFN-λ	Antiviral defense, macrophage activation, immune modulation	IFNAR, IFNGR, IL-28 R	JAK/STAT (STAT1, STAT2)	[1, 4, 5]
TNF Superfamily	TNF-α, FasL, CD40L	Inflammation, apoptosis, immune cell activation	TNFR1, TNFR2, Fas (CD95)	NF-κB, MAPK	[1, 5, 6]
Chemokines	CXCL8 (IL-8), CCL2 (MCP-1), CCL5 (RANTES)	Chemotaxis (migration of immune cells)	CCR, CXCR (GPCRs)	GPCR signaling, MAPK	[5, 6]
Growth Factors	TGF-β, GM-CSF, VEGF	Cell growth, differentiation, angiogenesis, and tissue repair	TGF-βR, CSF receptors, VEGFR	SMAD, JAK/STAT, Tyrosine kinase pathways	[1, 5, 6]

Table 1.
Overview of cytokine biology.

macrophages, and lymphocytes [5, 6]. While this coordinated response is essential for host defense against infections, it may become harmful if it persists chronically. In cancer, the increased production and spread of pro-inflammatory cytokines, such as IL-1, IFN-γ, and TNF-α, can lead to disease progression. IFN-gamma is a crucial mediator in host defense against infections and is often elevated in autoimmune and inflammatory conditions. IFN-γ may likewise exert anti-inflammatory effects by inducing molecules such as IL-1 receptor antagonist and IL-18 binding protein, as well as by facilitating apoptosis. Anti-inflammatory cytokines function to suppress and regulate excessive inflammatory responses. Key anti-inflammatory mediators include IL-1 receptor antagonist, IL-4, IL-6, IL-10, IL-11, and IL-13. Anti-inflammatory cytokines, including IL-10, IL-4, and TGF-β, counterbalance these effects by suppressing immune activation and promoting the resolution of inflammation [2–6].

In autoimmune disease pathogenesis, the inflammatory cytokines further act as critical downstream amplifiers. For example, in systemic lupus erythematosus (SLE), immune complexes (ICs) containing nuclear antigens are recognized by FcγRIIa on myeloid dendritic cells (mDCs) and internalized into endosomes, where they activate Toll-like receptor (TLR-7 and TLR-9) signaling pathways, resulting in enhanced production of IFN-α. This process contributes to the typical "interferon signature," which plays an essential role in the loss of immune tolerance [2, 4–6].

Similarly, Syk and TAK1 kinases are activated by FcγRIIIb-mediated signaling in neutrophils, which leads to engagement of the MEK/ERK pathway. This signaling

cascade promotes the generation of reactive oxygen species (ROS) and the formation of neutrophil extracellular traps (NETs). NETs release pro-inflammatory mediators and also uncover autoantigens, thereby enhancing autoantibody production and IC formation in a self-perpetuating cycle. Consistent with this, patients with SLE show increased levels of many cytokines, including IL-6, IL-1, TNF-α, IL-17, and IL-21, which together support B-cell survival and T-helper cell activity.

Likewise, in rheumatoid arthritis (RA), ICs and cytokine networks – particularly TNF-α and IL-6 – act synergistically to sustain synovial inflammation and promote osteoclast activation, eventually driving progressive joint destruction [7, 8].

Overall, inflammatory cytokines not only amplify immune dysregulation; nonetheless, they can be considered important therapeutic targets. The clinical efficacy of biologic agents targeting cytokines such as IL-6, TNF-α, and IL-1β in reducing inflammation and delaying tissue damage progression further supports their central role in disease pathogenesis and highlights cytokine networks as key mediators in autoimmune disorders.

2.1 Brief overview of the cytokine signaling pathways

As a functionally and structurally diverse group of signaling molecules, cytokines can be classified according to the molecular architecture of their receptors. Major cytokine families include ILs, IFNs, TNFs, CSFs, TGFs, and various chemokines, each contributing to distinct aspects of immune regulation and cellular communication [1, 2]. Upon binding to their cognate receptors, either as monomeric or dimeric molecules, cytokines induce conformational changes that activate receptor-associated kinases and initiate intracellular signaling cascades. These signaling events culminate in the activation and nuclear translocation of specific transcription factors, which regulate the expression of target genes involved in immune responses, inflammation, cellular proliferation, differentiation, and survival [1–6].

The biological activity of cytokines is mediated through receptor-dependent signaling pathways that translate extracellular stimuli into specific cellular responses. Key pathways involved in cytokine signaling include the JAK/STAT pathway, the NF-κB signaling cascade, and MAPK pathways. Through coordinated regulation of gene transcription, these signaling systems control fundamental cellular processes such as inflammation, immune cell activation, proliferation, differentiation, and apoptosis (see **Figure 1**). Disruption of normal cytokine signaling can lead to sustained immune activation and has been implicated in the development of autoimmune diseases, autoinflammatory disorders, and cancer (see **Table 2**)

The most direct mechanisms of cytokine signal transduction, linking membrane receptor activation to nuclear gene transcription, are presented by the JAK/STAT pathway. Receptor-associated JAKs become activated upon cytokine binding, accompanied by phosphorylation of specific tyrosine residues, which enables recruitment and activation of STAT transcription factors. After activation, they translocate to the nucleus, where activated STATs regulate the expression of cytokine-responsive genes. The STAT pathway is utilized by a wide range of cytokines, including ILs, IFNs, and growth factors, and plays a key role in immune cell development, differentiation, and function. Tight regulation is achieved through negative feedback mechanisms, such as suppressors of cytokine signaling (SOCS)

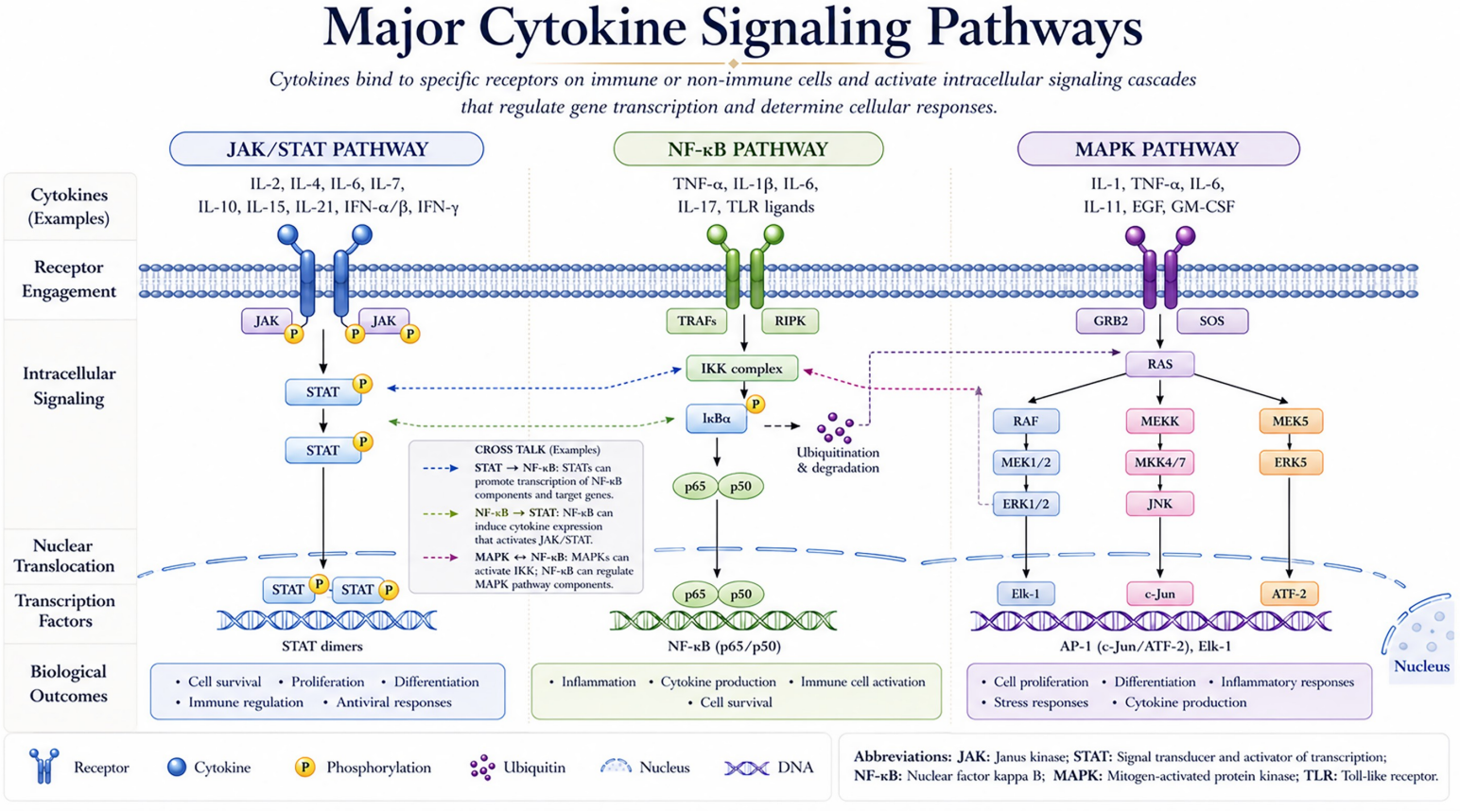

Figure 1.
Brief schematic and its cross-path presentation of the major signaling pathways. The image was created with the help of perplexity.

Pathway	Key components	Main cytokines involved	Biological functions	Clinical relevance	Reference
JAK/STAT	JAK1, JAK2, JAK3, TYK2; STAT proteins (STAT1–STAT6)	IL-2, IL-6, IL-10, IFNs	Signal transduction from membrane to nucleus; gene transcription; immune cell differentiation and proliferation.	Dysregulation linked to autoimmune diseases and cancers; target of JAK inhibitors (e.g., tofacitinib).	[7, 8]
NF-κB	IκB, IKK complex, NF-κB transcription factors	TNF-α, IL-1β, IL-6	Regulation of inflammatory gene expression, cytokine production, cell survival, and immune responses.	Chronic activation associated with inflammation, autoimmune diseases, and cancer.	[9]
MAPK (ERK, JNK, p38)	MAPKKK, MAPKK, MAPK (ERK, JNK, p38)	TNF-α, IL-1, growth factors	Controls cell proliferation, differentiation, apoptosis, and stress responses.	Implicated in inflammatory diseases, cancer progression, and stress-related signaling.	[10]

Table 2.
Overview of the signaling pathways of cytokines and their clinical relevance.

proteins, which prevent excessive or prolonged activation. Dysregulation of JAK/STAT signaling has been strongly associated with autoimmune diseases, malignancies, and chronic inflammatory conditions [7, 8].

The signaling cascade via the NF-κB represents one of the principal regulatory systems involved in cytokine-induced inflammatory responses. It is triggered by a diversity of stimuli, including pro-inflammatory cytokines such as TNF-α and IL-1β, as well as pathogen-associated molecular patterns. Activation of NF-κB leads to its translocation into the nucleus, and the transcription of numerous genes involved in inflammation, immune responses, and cell survival is induced. NF-κB signaling plays a central role in coordinating innate and adaptive immune responses and is critically involved in the regulation of cytokine production itself, thereby forming a positive feedback loop that amplifies inflammation. Persistent activation of NF-κB has been implicated in chronic inflammatory diseases, autoimmune disorders, and cancer, highlighting its importance as a therapeutic target [9].

ERK, JNK, and p38 signaling modules, part of MAPK pathways, constitute significant intracellular networks activated by cytokines and cellular stress stimuli. These pathways are triggered by cytokines, growth factors, and cellular stress signals, and they regulate a broad spectrum of cellular processes, including gene expression, proliferation, differentiation, and apoptosis. MAPKs act through a phosphorylation cascade, including MAP kinase kinase kinases (MAPKKKs), MAP kinase kinases (MAPKKs), and MAP kinases, ultimately leading to the activation of transcription factors that control inflammatory and stress responses. Importantly, MAPK pathways frequently interact with both JAK/STAT and NF-κB signaling, forming an integrated network that fine-tunes immune responses and determines the magnitude and duration of inflammation [10].

3. Cytokine dysregulation in rare diseases

3.1 Auto-inflammatory diseases, autoimmunity, and implicated cytokines

Auto-inflammatory and autoimmune diseases represent two major categories of immune-mediated disorders characterized by dysregulated immune responses. Although traditionally considered distinct, increasing evidence supports a continuum between innate and adaptive immune dysfunction. Auto-inflammatory diseases are driven primarily by aberrations in the innate immune system, without significant participation of antigen-specific T cells or autoantibodies. These conditions are often associated with genetic mutations affecting inflammasome components, leading to excessive activation of inflammatory pathways [11–14].

A key feature of auto-inflammatory diseases is the dysregulation of the NLRP3 inflammasome, resulting in increased production of IL-1β and IL-18. These cytokines mediate systemic inflammation and are responsible for clinical manifestations such as recurrent fever and tissue inflammation observed in conditions including CAPS, familial Mediterranean fever (FMF), and mevalonate kinase deficiency (MKD). IL-1β plays a central pathogenic role by promoting endothelial activation, leukocyte recruitment, and amplification of inflammatory responses. Additionally, TNF-α and IL-6 contribute to systemic inflammation and acute-phase responses. Until now, especially with advances in the field of genetics, the knowledge and identification of auto-inflammatory diseases have expanded (inflammatory bowel disease, gout, psoriasis, and some forms of RA) [12–14].

In contrast, dysregulation of the adaptive immune system, including autoreactive T and B lymphocytes and the production of autoantibodies, are properties of autoimmune diseases. Cytokines are a key part of shaping these adaptive immune responses and maintaining the balance between tolerance and immunity. SLE is a long-known autoimmune disease characterized by abnormal B and T lymphocyte activation. Other diseases where autoimmunity is involved include type 1 diabetes, Grave's disease, myasthenia gravis, and psoriasis. Key cytokines implicated in autoimmunity include IL-6, TNF-α, and IFNs, particularly IFN-alpha and IFN-gamma. These cytokines promote the differentiation and activation of pathogenic Th1 and Th17 cells as T helper cells, which are central to the development of autoimmune pathology. IL-6 is a pleiotropic cytokine that drives B-cell differentiation and antibody production, while also promoting Th17 cell differentiation. Diseases such as SLE and RA are characterized by increased IL-6 levels. TNF-α contributes to chronic inflammation by activating macrophages and endothelial cells, thereby sustaining tissue damage. IFN-α and other type I IFNs are strongly associated with SLE pathogenesis and other interferonopathies. These cytokines enhance antigen presentation, promote dendritic cell activation, and facilitate the survival of autoreactive lymphocytes. IFN-γ, on the contrary, is a key mediator of Th1 responses and contributes to macrophage activation and tissue inflammation [11, 12].

Importantly, overlap exists between auto-inflammatory and autoimmune conditions. IL-1 and IL-6 act at the interface of innate and adaptive immunity. Dysregulation of signaling pathways such as JAK/STAT and NF-κB further links these disease processes. The existence of an immunological spectrum between autoinflammatory and autoimmune disorders is illustrated by diseases that

incorporate characteristics of both innate and adaptive immune dysregulation, including systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease. These conditions are driven by complex cytokine networks in which IL-1, IL-6, and IL-18 function as major inflammatory mediators, linking innate immune activation with subsequent adaptive immune responses. Recognition of the pivotal contribution of these cytokines to disease pathogenesis has facilitated the development of targeted therapeutic strategies aimed at selectively interrupting specific inflammatory pathways. Biologic agents directed against IL-1 (e.g., anakinra), IL-6 (e.g., tocilizumab), and TNF-α (e.g., infliximab) have markedly improved disease control and long-term outcomes across a range of autoinflammatory and autoimmune disorders. Furthermore, the introduction of small-molecule therapies, particularly JAK inhibitors, has expanded treatment options by simultaneously modulating multiple cytokine-dependent signaling cascades. Collectively, these advances underscore the dual role of cytokines as both central drivers of immune-mediated pathology and valuable targets for precision-based therapeutic interventions [3, 8, 11–14].

3.2 Rare (autoimmune) diseases and cytokine-targeted therapies

Rare autoimmune diseases arise from disturbances in adaptive immune regulation that result in the breakdown of immunological self-tolerance and subsequent tissue injury. Cytokines are fundamental mediators in these processes, orchestrating immune cell activation, differentiation, and effector functions. Consequently, dysregulated cytokine signaling contributes significantly to disease initiation and progression, making cytokine pathways attractive targets for therapeutic intervention (see **Table 3**).

Developments in immunology have led to the advancement of targeted biologic therapies that specifically inhibit cytokines or their receptors. Antibodies used as therapeutic agents counteract the pathogenic processes that occur by selectively targeting pro-inflammatory cytokines or their receptors, thereby overcoming abnormal immune activation. These therapies have transformed the management of many autoimmune diseases, including rare conditions. Monoclonal antibodies targeting IL-6 signaling, such as tocilizumab, have demonstrated efficacy in diseases with elevated IL-6 activity. Similarly, TNF inhibitors (e.g., infliximab, adalimumab) have been widely used to reduce inflammation and improve clinical outcomes in various autoimmune disorders [13, 14].

Targeting the IL-17 pathway has shown efficacy in Th17-driven diseases, while therapies targeting type I IFNs have demonstrated promise in SLE and interferonopathies. Additionally, small-molecule inhibitors targeting intracellular signaling pathways, particularly JAK inhibitors (e.g., tofacitinib), provide broader immunomodulatory effects by interfering with multiple cytokine signals simultaneously. Until now, the FDA has approved more than 30 cytokine-targeting biologics for clinical use, while more than a 1,000 candidate therapies targeting cytokines or their receptors are in various stages of clinical development globally (see **Table 3**). Dysregulation of cytokine networks, particularly type I IFNs, IL-6, TNF-α, IL-17, and B-cell activating factor (BAFF), is present in SLE. The "interferon signature" observed in SLE patients reflects chronic activation of IFN-stimulated genes and correlates with disease severity and organ involvement. Plasmacytoid dendritic cells represent a major source of IFN-α following activation by nucleic acid-

Drug	Target	Mechanism of action/disease	Reference
Canakinumab	IL-1	IL-1β antibody; Cryopyrin-associated periodic syndromes (CAPS) Familial Mediterranean fever (FMF) Systemic juvenile idiopathic arthritis (sJIA)	[15–22]
Anakinra	IL-1	IL-1 R antagonist; Cryopyrin-associated periodic syndromes (CAPS) Familial Mediterranean fever (FMF) Systemic juvenile idiopathic arthritis (sJIA)	[15–18, 20, 21]
Rilonacept	IL-1	IL-1β antibody; Cryopyrin-associated periodic syndromes (CAPS) Familial Mediterranean fever (FMF) Systemic juvenile idiopathic arthritis (sJIA)	[16–18, 20, 23]
Tocilizumab	IL-6	Blocks IL-6-mediated inflammatory signaling pathways; IL-6 receptor antibody; reduces inflammation; Castleman disease, Takayasu arteritis	[24–29]
Neumega/ Oprelvekin	IL-11	Recombinant protein	
Ustekinumab	IL-12	Humanized antibody targeting the subunit of p40	[16–18]
Apilimod	IL-12	Oral small-molecule inhibitor of IL-12/IL-23 production	[16–18]
Secukinumab	IL-17	Humanized anti-IL-17 antibody; pustular psoriasis, spondyloarthropathies	[16–18, 30]
Fezakinumab	IL-22	Humanized anti-IL-22 antibody	[16–18]
Infliximab	TNF-α	Chimeric TNF-α antibody; binds to TNF-α with high affinity, blocks receptor binding, and induces apoptosis of TNF-α-producing cells; Behçet's disease, sarcoidosis	[22, 31]
Adalimumab	TNF-α	Humanized TNF-α antibody; Behçet's disease, sarcoidosis	[22, 31]
Certolizumab	TNF-α	Humanized TNF-α antibody, PEGylated; neutralizes TNF-α activity; Behçet's disease, sarcoidosis	[22]
Etanercept	TNF-α	TNF receptor p75 fusion protein; Behçet's disease, sarcoidosis	[22, 31]
Golimumab	TNF-α	Humanized TNF-α antibody binds to TNF-α and blocks its interaction with receptors, inhibiting TNF-α-mediated inflammation; Behçet's disease, sarcoidosis	[16–18, 20]
Ozoralimumab	TNF-α	TNF-α nanobody; Behçet's disease, sarcoidosis	[21]
Tofacitinib	Janus kinase inhibitor	Polyarticular course juvenile idiopathic arthritis	[32]

Table 3.
Presentation of available therapies and targeted cytokines.

containing ICs through Toll-like receptor signaling pathways. The therapeutic landscape of SLE has evolved considerably with the introduction of cytokine-directed treatments. Among these, anifrolumab, a fully human monoclonal antibody that blocks signaling through the type I IFN receptor, has demonstrated significant clinical benefits, including reduced disease activity and decreased reliance on corticosteroids in patients with moderate-to-severe SLE [9]. Similarly, belimumab, which inhibits BAFF, limits the survival and maturation of autoreactive B cells and

has become an established component of contemporary SLE management. A group of rare monogenic disorders collectively known as interferonopathies, including Aicardi–Goutières syndrome (AGS) and STING-associated vasculopathy with onset in infancy (SAVI), are characterized by persistent activation of type I IFN pathways. Excessive IFN signaling is considered a key driver of the inflammatory manifestations observed in these conditions. Consequently, therapeutic strategies aimed at interrupting downstream signaling have gained considerable interest. In this context, JAK inhibitors such as baricitinib and ruxolitinib have shown encouraging clinical efficacy by attenuating IFN-mediated immune activation and reducing disease severity.

Behçet's disease and several forms of systemic vasculitis exhibit substantial cytokine dysregulation involving TNF-α, IL-6, IL-17, and IFN-γ. Elevated TNF-α levels contribute to endothelial activation, neutrophil recruitment, and vascular inflammation. Cytokine-targeted therapies have, therefore, emerged as effective treatment strategies in refractory disease. TNF inhibitors, such as infliximab and adalimumab, have demonstrated efficacy in Behçet's disease, particularly in severe ocular, neurological, and vascular manifestations. Tocilizumab has also shown benefit in large vessel vasculitis and refractory Behçet's disease by suppressing IL-6-mediated inflammation.

Anakinra has enhanced the management of sJIA over recent years. JIA is a polygenic systemic autoimmune disease with a strong genetic and immunological background, characterized by chronic inflammation of the joints and, in some subtypes, systemic involvement affecting organs such as the heart, liver, lungs, and kidneys [33]. JIA represents the most common chronic rheumatic disease in children and encompasses a heterogeneous group of disorders with onset before the age of 16 years and persistence of symptoms for at least six weeks. The incidence of JIA ranges from 1 to 22 cases per 100,000 children annually, while prevalence estimates vary between 7 and 150 cases per 100,000 children, depending on geographic region and classification criteria [33–35].

The pathogenesis of JIA involves multifaceted interactions between genetic predisposition, environmental triggers, innate immune activation, and adaptive immune dysregulation [34]. Some cytokines play crucial roles in disease initiation and progression, particularly interleukin (IL)-1β, IL-6, IL-18, TNF-α, and IFN-γ [34]. Among these mediators, IL-1β and IL-6 are considered central drivers of systemic inflammation, especially in sJIA, where features of autoinflammation predominate over classical autoimmunity [35]. Elevated levels of IL-18 are also associated with macrophage activation syndrome (MAS), a severe and potentially life-threatening complication of sJIA characterized by excessive cytokine release and immune hyperactivation [36].

IL-6 contributes significantly to fever, anemia, thrombocytosis, growth impairment, and chronic synovial inflammation by promoting acute-phase protein synthesis and differentiation of Th17 lymphocytes [37]. TNF-α further amplifies inflammatory cascades through the activation of macrophages, endothelial cells, and synovial fibroblasts, ultimately leading to cartilage destruction and bone erosion [38]. Additionally, dysregulation of the JAK/STAT signaling pathway has been implicated in persistent inflammatory responses and disease chronicity [16, 38].

Advances in cytokine-targeted therapies have substantially improved clinical outcomes in JIA. IL-1 inhibitors, such as anakinra and canakinumab, demonstrate remarkable efficacy in systemic forms of the disease by suppressing excessive innate

immune activation and reducing systemic inflammation, fever, and the risk of MAS [15–17]. Tocilizumab, a monoclonal antibody targeting the IL-6 receptor, has shown significant benefit in reducing systemic symptoms and improving joint inflammation in refractory sJIA, stressing the central pathogenic role of IL-6 in disease progression [18, 24, 25, 39]. TNF inhibitors, including etanercept, adalimumab, and infliximab, are widely used in polyarticular forms of JIA and effectively reduce disease activity, synovial inflammation, and radiographic progression through the suppression of TNF-α-mediated inflammatory cascades [16, 17]. More recently, JAK inhibitors, such as tofacitinib, have emerged as promising therapeutic options for patients with refractory disease due to their ability to modulate multiple cytokine signaling pathways simultaneously, particularly those mediated through JAK/STAT signaling [16–18, 22, 26, 27, 31, 40–43].

Despite major therapeutic advances, challenges remain regarding early diagnosis, prediction of therapeutic response, prevention of long-term disability, and management of severe complications such as MAS [16–18]. Future precision medicine approaches incorporating cytokine profiling, genetic biomarkers, transcriptomic analysis, and molecular phenotyping may improve patient stratification and facilitate individualized therapeutic strategies in JIA [22, 27, 31, 43].

Castleman disease (CD) comprises a diverse group of lymphoproliferative conditions associated with dysregulated immune activation, excessive cytokine production, and characteristic histopathological lymph node alterations [28, 29, 44–48]. The disease is classified into unicentric CD (UCD), involving a single lymph node region, and multicentric CD (MCD), which presents with generalized lymphadenopathy, systemic inflammation, constitutional symptoms, cytopenias, and multiorgan dysfunction resulting from cytokine storm syndromes [47, 48]. IL-6 plays a central pathogenic role in most forms of this disease and is considered one of the major drivers of disease progression and systemic inflammatory manifestations [28, 29, 48]. Excessive IL-6 production stimulates hepatic acute-phase protein synthesis, B-cell proliferation, plasma cell differentiation, angiogenesis, and constitutional inflammatory symptoms such as fever, fatigue, cachexia, anemia, and hypergammaglobulinemia [22, 31, 40, 41].

Human herpesvirus-8 (HHV-8)-associated MCD is characterized by viral IL-6 production and severe immune activation, particularly in immunocompromised patients and individuals with HIV infection [22]. In contrast, idiopathic MCD (iMCD) lacks HHV-8 infection but demonstrates marked cytokine dysregulation involving IL-6, VEGF, IL-1β, TNF-α, CXCL13, and IFN signaling pathways [22, 31, 40]. Elevated vascular endothelial growth factor (VEGF) contributes to vascular proliferation, endothelial dysfunction, and capillary leak syndrome, which are frequently observed in severe disease manifestations [29, 49–53].

Targeted cytokine therapy has dramatically improved outcomes in CD. Siltuximab, a chimeric monoclonal antibody directly targeting IL-6, is currently considered first-line therapy for iMCD and has demonstrated substantial efficacy in reducing systemic inflammation, improving laboratory abnormalities, controlling lymphadenopathy, and prolonging survival [51]. Tocilizumab, which is an IL-6 receptor antagonist, has also shown significant advantages in controlling inflammatory manifestations, reducing corticosteroid dependence, and improving constitutional symptoms [16–18, 24, 25, 39, 48]. In refractory or severe cases, combination approaches involving rituximab, corticosteroids, immunosuppressive

agents, antiviral therapy, and chemotherapy may be required to suppress hyperactivated immune responses and control cytokine storm syndromes [28, 48].

Recent transcriptomic and cytokine profiling studies suggest that iMCD may represent a spectrum of hyperinflammatory disorders characterized by dysregulated innate immune activation, abnormal mTOR signaling, and aberrant cytokine network activation [54–56]. Emerging therapeutic approaches include JAK inhibitors, mTOR inhibitors such as sirolimus, and therapies targeting IL-1 and IFN pathways [41–43]. These findings further support the concept that cytokine dysregulation is central to disease pathogenesis and that precision medicine approaches based on cytokine signatures and molecular profiling may improve future therapeutic strategies in CD [29, 50].

4. Future perspectives and precision medicine

Progress in systems immunology, single-cell technologies, proteomic and metabolomic profiling, and computational biology has substantially expanded current knowledge regarding cytokine-driven disease mechanisms and has accelerated the transition toward precision medicine approaches in autoimmune and autoinflammatory diseases [54, 55]. Precision medicine aims to individualize therapeutic strategies according to patient-specific molecular signatures, cytokine expression profiles, genetic predisposition, and biomarker patterns. Such approaches are particularly important in rare immune-mediated diseases characterized by substantial clinical heterogeneity and variable therapeutic responses [54–60]. High-throughput technologies have enabled the identification of disease-specific cytokine signatures and inflammatory pathways associated with disease severity, progression, and treatment response [28, 59–61]. Single-cell RNA sequencing has provided novel insights into immune cell heterogeneity and cytokine-producing cellular populations in diseases such as SLE, RA, and inflammatory bowel disease [16, 26, 38]. Furthermore, advances in bioinformatics and systems biology allow the integration of genomic, transcriptomic, and proteomic datasets to identify novel therapeutic targets and predictive biomarkers [55, 56]. The development of next-generation cytokine-targeted therapies continues to expand rapidly. In addition to monoclonal antibodies targeting IL-1, IL-6, TNF-α, and IL-17 pathways, novel therapeutic strategies include bispecific antibodies, engineered cytokines, cytokine traps, nanobody-based therapeutics, and selective intracellular signaling inhibitors [28]. JAK inhibitors and TYK2 inhibitors are particularly promising because they simultaneously modulate multiple cytokine signaling pathways implicated in autoimmune and autoinflammatory diseases [57–60]. Selective TYK2 inhibitors may provide improved safety profiles compared with broader JAK inhibition while maintaining therapeutic efficacy [59, 60]. Briefly, TYK2 inhibitors have recently emerged as promising targeted therapies for autoimmune and inflammatory diseases due to their ability to selectively modulate cytokine signaling pathways involved in chronic inflammation while potentially reducing some of the adverse effects associated with broader JAK inhibition. TYK2 is a member of the JAK family and plays a pivotal role in intracellular signaling mediated by cytokines such as IL-12, IL-23, and type I IFNs, which are critically involved in the pathogenesis of autoimmune and autoinflammatory disorders. Several TYK2 inhibitors have demonstrated significant therapeutic potential, including deucravacitinib (BMS-

986165), brepocitinib, ropsacitinib (PF-06826647), NDI-034858, SAR-20347, and TAK-279. Among these, deucravacitinib has already been approved for the treatment of moderate-to-severe plaque psoriasis, while other compounds remain under clinical investigation for conditions such as psoriatic arthritis, inflammatory bowel disease, SLE, and other immune-mediated diseases. By selectively targeting TYK2-dependent JAK/STAT signaling, these inhibitors can suppress the production of pro-inflammatory cytokines and immune cell activation. In addition, increasing evidence suggests that modulation of TYK2 signaling may indirectly affect NF-κB and MAPK pathway activation through cytokine cross-talk and interconnected intracellular signaling networks, thereby contributing to broader immunomodulatory and anti-inflammatory effects [58–66]. Emerging cellular therapies also represent an important area of investigation. Regulatory T-cell (Treg) therapies and chimeric antigen receptor T-cell (CAR-T) therapies are being explored for severe refractory autoimmune diseases with encouraging preliminary results [59, 67, 68]. Additionally, mesenchymal stem cell therapies may exert immunomodulatory effects through suppression of pro-inflammatory cytokines and enhancement of anti-inflammatory cytokine production [44]. Advances in mRNA technology and gene-editing approaches such as CRISPR/Cas9 further offer future possibilities for correcting cytokine dysregulation at the molecular level [45, 59]. Artificial intelligence and machine learning algorithms are increasingly used to predict therapeutic responses, identify optimal cytokine-targeted treatment combinations, and stratify patients according to molecular disease phenotypes [45, 55, 58, 59]. Integration of digital health technologies and biomarker-guided monitoring may further optimize disease management and facilitate early therapeutic intervention. Despite these advances, important challenges remain, including high treatment costs, immunogenicity, infection risk, long-term safety concerns, and limited access to biologic therapies in low-resource settings [58–60]. Future research should therefore focus on identifying reliable biomarkers for treatment stratification, understanding mechanisms of therapeutic resistance, and developing safer and more effective immunomodulatory approaches. Continued progress in cytokine biology and precision immunology is expected to substantially improve outcomes and quality of life for patients with rare autoimmune and autoinflammatory diseases [58, 59].

5. Conclusion(s)

Cytokines are central to the pathogenesis of both autoinflammatory and autoimmune diseases, acting as critical mediators of immune dysregulation. The interplay between innate and adaptive immune responses, mediated through complex cytokine networks, underscores the continuum between these disease categories. Continued research into cytokine biology will further enhance our understanding of rare immune-mediated diseases, facilitate the development of more precise and effective therapeutic strategies, and implement precision medicine approaches.

Cytokines are central to the pathogenesis and treatment of rare diseases. Advances in cytokine biology have enabled the development of targeted therapies that significantly improve outcomes.

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Conflict of Interest

The authors declare no conflict of interest.

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