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Review

The History of Cytokines in Rheumatic Disease: An Evolutionary Perspective on Mediators, Inhibitors, and Therapeutics

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Running title: The History of Cytokines in Rheumatic Disease

Abstract

Cytokines are small, secreted proteins that serve as the principal mediators of the immune system, orchestrating the complex interplay of cells involved in inflammation, immunity, and tissue homeostasis. Their dysregulation is a central feature in the pathophysiology of chronic inflammatory conditions, particularly autoimmune rheumatic diseases such as rheumatoid arthritis. This report provides a comprehensive, structured analysis of the history of cytokines, tracing their evolution from vaguely understood biological activities to precisely defined molecular targets for revolutionary therapies. To provide a conceptual foundation, fundamental definitions and classifications of cytokines are established, with a specific focus on how the core properties of pleiotropy, redundancy, and network complexity have profoundly influenced their study and therapeutic manipulation. The narrative subsequently details landmark discoveries of key pathogenic cytokines in rheumatology—including the TNF-α, IL-1, and IL-6 families—while detailing the paradigm shift prompted by the identification of the IL-23/Th17 axis. Parallel to these discoveries, the

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evolution of therapeutic agents is mapped from first-generation biologic disease-modifying anti-rheumatic drugs (bDMARDs), such as TNF inhibitors, to the oral revolution of targeted synthetic DMARDs like Janus kinase inhibitors, and onward to next-generation strategies including bispecific antibodies and engineered cytokines. In the final sections, the current state of the field is synthesized through a critical examination of unresolved questions and knowledge gaps, such as the mechanisms of treatment non-response, the challenge of cytokine redundancy, and the optimal management of systemic comorbidities. Prospective future directions are outlined, emphasizing an increasing focus on biomarker-driven patient stratification, multi-target combination strategies, and the ultimate pursuit of immune tolerance and curative therapies. Together, these developments represent a clear evolutionary trajectory toward the realization of precision medicine in rheumatology.

Keywords: cytokines, rheumatic disease, DMARDs, monoclonal antibodies

1. Introduction

Cytokines are a diverse category of small, soluble proteins or glycoproteins, typically ranging from 5 to 70 kDa, that serve as the primary regulators of the immune system [1]. Secreted by a wide array of nucleated cells - including immune cells such as macrophages and T lymphocytes, as well as non-immune cells like endothelial cells and fibroblasts - they function as essential intercellular signaling molecules [2]. Historically, their nomenclature reflected specific cellular origins or perceived functions, giving rise to terms such as lymphokines, monokines, and interleukins, though these have since been integrated under the broader "cytokine" umbrella [2,3]. These molecules exert their influence by binding to high-affinity receptors via autocrine, paracrine, or endocrine signaling, thereby directing the maturation, differentiation, and activity of the immune network [2,4].

The biological impact of cytokines is governed by a set of core properties that render their network behavior exceptionally complex. These include pleiotropy, where a single cytokine like Tumor Necrosis Factor-alpha (TNF-α) exerts multiple effects across different cell types, and redundancy, where distinct cytokines perform overlapping functions [1,2,5]. Furthermore, the immune response is fine-tuned through synergy, antagonism, and cascade induction, where the secretion of one cytokine triggers a self-perpetuating

loop of secondary mediators [2,6]. This inherent complexity has historically complicated therapeutic efforts; for example, redundancy can lead to treatment resistance when a single cytokine is blocked, while pleiotropy may result in unintended side effects [5,6]. Such challenges have driven the evolution of the field from simple monoclonal antibodies toward more sophisticated strategies, including Janus kinase (JAK) inhibitors and engineered bispecific molecules designed to navigate these intricate pathways.

To fully understand their clinical relevance, cytokines must be situated within the broader context of inflammatory mediators and biologically active molecules. Inflammatory mediators comprise a heterogeneous group of chemical factors - including vasoactive amines, lipids, and complement proteins - that orchestrate the physiological signs of inflammation [7,8]. More broadly, cytokines are classified as biologically active molecules, a term encompassing all proteins, hormones, and growth factors that elicit specific biological responses to maintain homeostasis [9]. In the field of rheumatology, the dysregulation of these mediators is the cornerstone of disease, as their persistent activity drives the chronic inflammation and joint destruction characteristic of various rheumatic pathologies [8].

The aim of this study is to provide a comprehensive overview of the history of cytokines and the evolution of molecular knowledge surrounding them to define a trajectory for future research in rheumatology. By examining the transition from early phenomenological observations to the current era of precision medicine, we seek to elucidate the role of cytokine involvement in the pathogenesis of rheumatic diseases. Ultimately, this perspective aims to facilitate the development of novel diagnostic biomarkers and next-generation therapeutic strategies centered on the precise modulation of the cytokine network.

2. Classification of Cytokines, Mediators, and Biologically Active Molecules

The expansive diversity of the cytokine network necessitates a multifaceted classification system to organize these molecules into coherent groups. Rather than a single universal standard, cytokines are categorized through several parallel frameworks based on their primary biological function, three-dimensional protein structure, genetic homology, or the specific receptor superfamilies they utilize. Each of these classification schemes provides a distinct perspective essential for understanding cytokine biology

and the subsequent development of targeted rheumatological interventions.

2.1 Functional Classification and Context-Dependent Plasticity

From a clinical perspective, cytokines are most intuitively classified by their principal effect on the inflammatory process, established as a functional dichotomy between pro-inflammatory and anti-inflammatory mediators. Pro-inflammatory cytokines, such as TNF-α, Interleukin-1 (IL-1), and IL-6, are the primary drivers of pathogenesis in rheumatic diseases; they are responsible for leukocyte recruitment to the synovium, activation of destructive enzymatic processes, and the perpetuation of chronic tissue damage [1,10]. More recently, the IL-17 and IL-23 families have emerged as critical mediators in this group, specifically in the differentiation of pathogenic Th17 cells [11]. Conversely, anti-inflammatory cytokines, including IL-10, Transforming Growth Factor-beta (TGF-β), and IL-37, serve as regulatory brakes that suppress inflammatory cell activity and promote tissue repair [1,12]. However, this classification is notably context-dependent. The biological outcome of cytokine signaling is dictated by the cellular milieu and timing; for example, while IL-6 is a hallmark pro-inflammatory driver of the acute-phase response, it can also exhibit anti-inflammatory properties by inducing specific inhibitors [5]. Similarly, TGF-β acts as a potent immunosuppressant but can promote highly pathogenic Th17 differentiation in the presence of IL-6 [13].

2.2 Structural and Familial Categorization

Cytokines are also grouped by their tertiary protein structures, which often reflect shared evolutionary origins and mechanisms of receptor engagement. The three primary structural classes include the four-α-helix bundle cytokines (e.g., IL-2, IL-4, IL-6, and GM-CSF), the β-sheet cytokines - characterized by antiparallel beta-strands as seen in the IL-1 and TNF superfamilies - and the cysteine knot cytokines, such as the TGF-β superfamily, which possess an interlocked disulfide bond topology that confers high protein stability [5]. These structural motifs correspond closely with the division of cytokines into major families. The IL family represents the largest and most heterogeneous group, mediating complex communication between leukocytes and various non-immune cells [14]. The Interferon (IFN) family (Types I, II, and III) remains central to antiviral and immunomodulatory responses, while the TNF superfamily molecules are typically synthesized as transmembrane proteins critical for apoptosis and lymphoid organogenesis. Additionally, the chemokine family consists of small proteins (8–10 kDa) defined by their role in leukocyte chemotaxis

[2,14], and Colony-Stimulating Factors (CSFs) primarily regulate the proliferation and survival of hematopoietic progenitor cells [15].

2.3 Receptor Superfamilies and the Molecular Basis of Redundancy

The classification of cytokines by their receptor superfamilies offers the most profound insight into their signaling mechanisms and the molecular basis of functional redundancy. Type I cytokine receptors (the hematopoietin family) represent the largest group and are characterized by shared signal-transducing subunits [16]. This is exemplified by the common γ chain (γc) used by IL-2 and IL-15, the common β chain (βc) shared by IL-3 and GM-CSF, and the gp130 subunit utilized by the IL-6 family. Type II receptors include those for interferons and the IL-10 family, while the TNF receptor (TNFR) superfamily is distinguished by repeating cysteine-rich extracellular domains [5]. In contrast, chemokine receptors are seven-transmembrane G protein-coupled receptors (GPCRs) [17,18], and the TGF-β receptor family possesses unique intrinsic serine/threonine kinase activity.

The discovery of shared signaling chains within these receptor families was a watershed moment in immunology, explaining why diverse cytokines often elicit overlapping biological effects. This understanding shifted the therapeutic paradigm in rheumatology: rather than targeting single cytokines, researchers recognized that inhibiting shared intracellular hubs could provide broader control over poly-cytokine-driven inflammation. This logic directly informed the development of JAK inhibitors [19]. Because the JAK-STAT pathway is the primary signaling conduit for Type I and Type II receptors, small-molecule JAK inhibition effectively dampens the signals of multiple pathogenic cytokines simultaneously, offering a potent therapeutic strategy for complex diseases like rheumatoid arthritis (RA) [20].

3. Discovery of Pathogenic Cytokines and Inhibitors in Rheumatic Diseases

The historical progression of our comprehension of RA is intrinsically intertwined with the elucidation of cytokines. This narrative unfolds as a scientific investigative endeavor, progressing from macroscopic biological observations to the precise identification of specific molecular effectors, culminating in the principled development of therapeutic interventions designed to neutralize their activity. Such seminal discoveries that established TNF-α, IL-1, IL-6, and the IL-23/Th17 axis are pivotal constituents within the pathogenesis of rheumatic diseases.

3.1 The Pre-Cytokine Era: From "Endogenous Pyrogen" to "Lymphokines"

Before the advent of molecular biology and recombinant DNA technology, scientists could only characterize the *activities* of soluble factors, not the factors themselves. In the mid-20th century, research into fever led to the concept of an "endogenous pyrogen" (EP) - a substance produced by the host's own cells, rather than by bacteria, that could induce a febrile response [21]. This was a crucial conceptual leap, suggesting the body produced its own inflammatory mediators. Later work would reveal EP to be primarily IL-1 [22].

Simultaneously, in the field of immunology, researchers studying lymphocyte cultures in the late 1960s and 1970s observed that activated lymphocytes released soluble factors that could influence the behavior of other immune cells. These functionally defined substances were given names reflecting their origins: "lymphokines" if they came from lymphocytes and "monokines" if they came from monocytes [2]. The first such lymphokines were isolated from in vitro cultures in 1969 [23]. These terms were placeholders for what was essentially a "black box" of biological activity. The field began to unify in 1979 at the Second International Lymphokine Workshop, where the term "Interleukin" was proposed to describe these molecules that acted as signals *between leukocytes*, marking a transition toward a more unified nomenclature [22,24].

3.2 The TNF-α Revolution: Unifying "Cachectin" and "Tumor Necrosis Factor" and Targeting the Lynchpin of RA

The story of TNF is a classic example of scientific convergence, where two disparate lines of inquiry led to the same molecule, revolutionizing both oncology and immunology.

In 1975, researchers at Memorial Sloan-Kettering, studying the anti-cancer effects of bacterial toxins first noted by William Coley in the 1890s, identified a factor in the serum of endotoxin-treated mice that caused hemorrhagic necrosis of tumors. They named it "Tumor Necrosis Factor" [6,25]. In a parallel field, immunoparasitologist Anthony Cerami and his group at Rockefeller University were investigating the cause of cachexia, the profound wasting syndrome seen in chronic diseases like cancer and tuberculosis. They identified a macrophage-secreted factor that suppressed lipoprotein lipase and induced this wasting state, which they named "cachectin" [26].

The pivotal moment came in 1985 when Cerami's group, including a young postdoctoral fellow named Bruce Beutler, purified cachectin and sequenced it. They made the stunning discovery that it was the same molecule as TNF [27]. This unified the fields of cancer biology and immunology. More importantly, Beutler and Cerami performed a seminal experiment: they generated antibodies against TNF and showed that passively immunizing mice with these antibodies protected them from the lethal effects of endotoxin shock [28]. This was groundbreaking, as it proved that TNF was not just a correlative marker of disease but a causative mediator of inflammation and pathology. The therapeutic paradigm shifted from using TNF to kill tumors to blocking TNF to treat inflammation.

The focus then turned to autoimmune disease. In the UK, Marc Feldmann and Ravinder Maini were developing a new hypothesis about the pathogenesis of RA, suggesting that cytokine interactions within the synovial tissue were key [29]. In 1989, their group made the critical finding that TNF-α was produced at high levels in synovial cell cultures from RA patients and appeared to be at the apex of the pro-inflammatory cytokine cascade, driving the production of other cytokines like IL-1 and IL-6 [30]. Subsequent work confirmed that TNF and its receptors were abundantly expressed in the rheumatoid joint [31]. This laboratory finding was rapidly translated into animal models, where anti-TNF antibodies were shown to be highly effective at ameliorating collagen-induced arthritis [32]. This provided the direct rationale for human trials. In 1992, Feldmann and Maini initiated the first open-label clinical trial of a chimeric anti-TNF antibody, infliximab, in patients with severe RA [33,34]. The results were remarkably positive, with rapid and dramatic improvements in clinical signs and symptoms, heralding the dawn of the biologic therapy era in rheumatology.

3.3 The Interleukin-1 Axis: A Parallel Pathway of Inflammation and Tissue Destruction

Running parallel to the TNF story was the elucidation of the IL-1 pathway, another critical mediator of inflammation and, particularly, tissue destruction in RA. As mentioned, the story of IL-1 began with research on endogenous pyrogen (EP) in the early 1970s [21]. Charles Dinarello was a key figure in purifying and characterizing EP from human leukocytes [22]. At the same time, in the context of rheumatology, Jean-Michel Dayer and Stephen Krane's group at Harvard made a seminal observation. They found that a factor produced by monocytes, which they termed "mononuclear cell factor" (MCF), could stimulate synovial fibroblasts from RA patients to produce large quantities of collagenase (now known as MMP-1) and

prostaglandins - key mediators of cartilage and bone destruction [35]. In 1979, at the same meeting where "Interleukin" was coined, it was recognized that EP, MCF, and another factor called "lymphocyte activating factor" (LAF) were likely the same entity, which was unified under the name Interleukin-1 [21,24].

The molecular identity of IL-1 was definitively established in 1984-1985 with the cloning of the cDNAs for two distinct but related forms, IL-1α and IL-1β, by several groups, including those led by Dinarello and Peter Lomedico [36–38]. The availability of recombinant IL-1 protein confirmed that this single cytokine was indeed responsible for the vast array of biological activities previously attributed to different "factors," from fever to joint destruction.

A unique and critical chapter in the IL-1 story was the discovery of its own natural inhibitor. In 1984, Dayer's group reported that a factor present in the urine of febrile patients could specifically block the activity of IL-1 on synovial cells without affecting TNF [39,40]. This was the first description of a naturally occurring, specific cytokine receptor antagonist. This molecule, named IL-1 receptor antagonist (IL-1Ra), was purified and cloned in 1990 [21,41]. The existence of a dedicated natural inhibitor highlighted the potent and dangerous potential of unchecked IL-1 signaling, and it provided a ready-made template for a therapeutic agent (anakinra) [42].

3.4 The Rise of Interleukin-6: A Pleiotropic Mediator of Systemic Inflammation and the Acute Phase Response

While TNF-α and IL-1 are potent drivers of local joint inflammation, IL-6 emerged as a key mediator of the systemic features of RA. In the early 1980s, Tadamitsu Kishimoto's group in Japan was investigating the soluble factors that drive the final differentiation of B cells into antibody-producing plasma cells. They identified one such factor and named it B-cell stimulatory factor-2 (BSF-2) [43].

In 1986, Kishimoto's team successfully cloned the cDNA for BSF-2. In a remarkable coincidence of scientific discovery, other research groups independently cloned genes for factors with entirely different biological activities: "interferon-beta2" (a protein with antiviral activity), "hybridoma/plasmacytoma growth factor," and "hepatocyte-stimulating factor" (a factor that induced acute-phase protein production in liver cells) [43,44]. Upon sequence comparison, all of these molecules were found to be identical. This pleiotropy was so fundamental to its nature that when the

molecule was officially named Interleukin-6 in 1988, it was already understood to have a wide range of functions [45].

In RA, IL-6 was found to be produced at high levels in the synovium, often induced by TNF-α and IL-1 [46]. Its unique role, however, lies in its systemic effects. IL-6 is the principal driver of the hepatic acute-phase response, leading to the elevated levels of C-reactive protein (CRP) and fibrinogen seen in active RA [47]. It also contributes to the anemia of chronic disease by inducing hepcidin production, and to the thrombocytosis by acting on megakaryocytes [45]. This central role in systemic inflammation made the IL-6 receptor an attractive therapeutic target, culminating in the development of the monoclonal antibody tocilizumab [43,48].

3.5 The Discovery of the IL-23/Th17 Axis and its Redefinition of T-Cell-Mediated Autoimmunity

For many years, the "Th1/Th2 paradigm" dominated immunology, proposing that autoimmune diseases like RA were primarily driven by a T helper 1 (Th1) cell response, characterized by the cytokine IFN-γ [10]. However, the modest success of therapies targeting Th1 pathways suggested this model was incomplete. The breakthrough came from work distinguishing the functions of IL-12 and a newly discovered cytokine, IL-23. These two cytokines are related; they share a common protein subunit called p40, but are paired with distinct second subunits (p35 for IL-12, and p19 for IL-23) [11]. Using gene knockout mice in models of autoimmunity, a team at DNAX research institute led by Daniel Cua made a pivotal discovery. Mice lacking the IL-12-specific p35 subunit still developed severe autoimmune inflammation, but mice lacking the IL-23-specific p19 subunit were completely protected. This seminal finding, published in *Nature* in 2003, demonstrated that IL-23, not IL-12, was the critical cytokine for driving T-cell-mediated autoimmunity [49].

The immediate question was: what is the cellular target of IL-23? It was known that IL-23 could stimulate T cells to produce IL-17, a pro-inflammatory cytokine that had been cloned back in 1993-1995 but whose cellular source and significance were unclear [50,51]. In 2005, landmark papers from several independent groups, including those led by Casey Weaver [52] and Chen Dong [53], described a novel subset of CD4+ T helper cells. These cells were distinct from Th1 and Th2 cells and were characterized by their signature production of IL-17, leading to their designation as "Th17" cells [54]. They found that the differentiation of these cells was driven by a combination of TGF-β and IL-6, and that IL-23 was not

required for their initial differentiation but was essential for their expansion, stabilization, and pathogenic function *in vivo*.

With the discovery of this new pathogenic T cell lineage, the role of IL-17 in RA was rapidly clarified. IL-17 was found in high concentrations in the RA synovium, where it acts as a potent pro-inflammatory mediator [10]. It synergizes with TNF-α and IL-1 to drive the production of other inflammatory molecules, is a powerful recruiter of neutrophils into the joint, and directly contributes to bone erosion by promoting osteoclastogenesis [50]. The discovery of the IL-23/Th17 axis revealed an entirely new arm of the immune response driving autoimmunity and provided the clear scientific rationale for developing a new class of biologics targeting IL-23 or IL-17 [11]. Table 1 provides a condensed summary of these landmark discoveries.

Table 1. Summary of the discoveries of key cytokines (TNF-α, IL-1, IL-1Ra, IL-6, IL-23/Th17 axis).

Cytokine/ Pathway	Key Discoverer(s)/ Group	Approx. Year	Seminal Finding/ Publication	Pathogenic Mechanism in RA
TNF-α	Carswell, Cerami/Beutler, Feldmann/Maini	1975-1992	Identification as tumor necrosis factor and cachectin; protection from endotoxin shock with anti-TNF Ab; identification as a pivotal cytokine in RA synovium [25-34]	Apex of the inflammatory cascade; induces other cytokines (IL-1, IL-6); promotes cell adhesion and recruitment; activates osteoclasts
IL-1	Beeson, Dinarello, Dayer/Krane	1940s-1985	Identification as endogenous pyrogen (EP) and mononuclear cell factor (MCF); cloning of IL-1α and IL-1β cDNA [21-24, 36-38],	Potent pro-inflammatory mediator; induces fever and systemic symptoms; stimulates production of matrix metalloproteinases (MMPs) leading to cartilage degradation
IL-1Ra	Dayer, Seckinger	1984-1990	Discovery of a specific, natural IL-1 inhibitor in human urine; cloning of the IL-1 Receptor Antagonist (IL-1Ra) [21, 39-42]	Natural brake on IL-1 signaling; its therapeutic form (anakinra) competitively inhibits IL-1 binding to its receptor

IL-6	Kishimoto	1980s-1988	Identification as B-cell stimulatory factor-2 (BSF-2); cloning and unification with other factors (IFN-β2, HSF) to become IL-6 [43-48]	Key driver of systemic inflammation; induces hepatic acute-phase response (e.g., CRP); contributes to anemia, fatigue, and thrombocytosis
IL-23/Th17 Axis	Cua, Weaver, Dong	2003-2005	Discovery that IL-23 (not IL-12) is critical for T-cell mediated autoimmunity; identification of the Th17 cell subset as the source of IL-17 [10,11, 49-52]	IL-17 recruits neutrophils; promotes inflammation; synergizes with TNF/IL-1; drives osteoclastogenesis and bone erosion

APC: Antigen-presenting cell, BSF-2: B-cell Stimulatory Factor-2, DMARD: Biologic disease-modifying antirheumatic drug, CD20: Cluster of differentiation 20, CTLA4-Ig: Cytotoxic T-lymphocyte-associated protein 4-immunoglobulin fusion protein, EP: Endogenous pyrogen, EU: European Union, Fab': Fragment antigen-binding, HSF: Hepatocyte Stimulating Factor, IFN: Interferon, IL: Interleukin IL-1Ra: Interleukin-1 receptor antagonist, JAK: Janus kinase, MCF: Macrophage Chemotactic Factor, RA: Rheumatoid arthritis, Th17: T helper 17 cells, TNF-α: Tumor necrosis factor-alpha TYK2: Tyrosine kinase 2, US: United States

4. The Development of Cytokine-based Targeted Therapy in Rheumatology

The elucidation of the cytokine network in RA, as detailed previously, did not remain a purely academic exercise. It directly catalyzed a therapeutic revolution, transforming RA from a progressively disabling condition into a manageable chronic disease for many patients. This section details the evolution of these therapies, tracing a clear trajectory from the first targeted injectable biologics to orally available small molecules and onward to the innovative strategies of the future. This progression represents a continuous effort to improve efficacy, enhance safety, broaden the base of responsive patients, and address the fundamental challenges of cytokine biology.

4.1 First-Generation Biologics: The Era of Monoclonal Antibodies and Fusion Proteins

The late 1990s and early 2000s marked the dawn of targeted therapy in rheumatology. For the first time, drugs were not broad-spectrum

immunosuppressants but were rationally designed, genetically engineered proteins aimed at neutralizing a single, specific pathogenic molecule.

4.1.1 TNF-α Blockers

Building directly on the foundational work of Feldmann, Maini, Beutler, and Cerami, TNF-α inhibitors were the first class of biologic disease-modifying antirheumatic drugs (bDMARDs) to be developed and approved [55]. Their dramatic success established the "cytokine blockade" principle and set the standard for all subsequent biologics. The first approved agents utilized different molecular strategies to achieve the same goal. Infliximab, first approved for Crohn's disease in 1998, is a chimeric monoclonal antibody, meaning it combines mouse variable regions (for antigen binding) with a human constant region (to reduce immunogenicity) [55]. Adalimumab and golimumab are fully human monoclonal antibodies, further reducing the potential for the patient's immune system to recognize the drug as foreign and develop anti-drug antibodies [56]. Etanercept, also approved in 1998, uses a different design. It is a fusion protein that links two extracellular domains of the human p75 TNF receptor to the Fc portion of human IgG1 [57]. It acts as a "decoy receptor," binding to and neutralizing soluble TNF-α before it can engage with cellular receptors. Certolizumab pegol, a PEGylated Fab' fragment of a humanized monoclonal antibody, lacks the Fc region present in other agents and therefore does not mediate cell-killing mechanisms such as apoptosis, complement-dependent cytotoxicity, or antibody-dependent cell-mediated cytotoxicity. To compensate for the poor in vivo pharmacokinetics of the Fab' fragment, a 40 kDa polyethylene glycol moiety is attached to increase its half-life to a level comparable with whole antibody products [58].

The introduction of TNF blockers transformed RA management. However, their limitations quickly became apparent. A significant proportion of patients exhibit a primary non-response, and others lose response over time [59]. Furthermore, as potent immunosuppressants, they carry an increased risk of serious infections and other side effects, and being injectable proteins, they can be inconvenient for patients [60]. These limitations created a clear unmet need for alternative therapeutic mechanisms.

4.1.2 IL-1 and IL-6 Receptor Blockade

The success of TNF blockade validated the cytokine-targeting approach and spurred the development of drugs aimed at other key pathways identified in the synovium, providing crucial options for patients who failed or were intolerant to TNF inhibitors.

Anakinra is a recombinant form of the naturally occurring IL-1 receptor antagonist (IL-1Ra) [61]. It competitively inhibits the binding of both IL-1α and IL-1β to the IL-1 receptor. While effective, its clinical efficacy in RA was generally found to be more modest than that of TNF inhibitors, and its short half-life requires daily injections, which has limited its use in this indication. However, it proved highly effective in a group of rare autoinflammatory conditions such as cryopyrin-associated periodic syndromes (CAPS), where IL-1β is the central pathogenic driver [21].

Tocilizumab is a humanized monoclonal antibody that targets the IL-6 receptor (both soluble and membrane-bound forms), preventing IL-6 from signaling [62]. Approved for RA in 2009, it proved to be a highly effective therapy, not only for joint inflammation but particularly for the systemic features of RA, such as fatigue, anemia, and the acute phase response, which are strongly driven by IL-6 [43]. Its success provided a valuable alternative for TNF-inadequate responders (TNF-IR).

4.2 The Second Wave of Biologics: Targeting the Th17 Pathway

The discovery of the IL-23/Th17 axis as a new, independent pathway of autoimmunity provided a fresh set of targets for drug development, leading to a second wave of biologics.

Secukinumab and ixekizumab are monoclonal antibodies that directly neutralize IL-17A [63,64]. Bimekizumab represents a further evolution in this class; unlike secukinumab and ixekizumab, which selectively target IL-17A, bimekizumab is a humanized IgG1 antibody that dual-neutralizes both IL-17A and IL-17F. This dual inhibition is hypothesized to provide superior efficacy, as both isoforms are overexpressed in inflammatory tissues and synergistically drive synovial inflammation and joint damage [65]. Ustekinumab takes a different approach, targeting the shared p40 subunit of IL-12 and IL-23, thereby blocking both the Th1 and Th17 pathways [66]. Expanding on this, more selective inhibitors have been developed to target the p19 subunit of IL-23 specifically [67,68]. Risankizumab is a high-affinity humanized monoclonal antibody that binds the IL-23 p19 subunit, effectively inhibiting IL-23 signaling without affecting IL-12, which shares the p40 subunit [67]. Similarly, guselkumab is a selective IL-23 inhibitor that has demonstrated significant efficacy in reducing disease activity in both peripheral and axial forms of psoriatic arthritis by suppressing the IL-23/Th17 axis [68].

These drugs have demonstrated outstanding efficacy in psoriasis, psoriatic arthritis (PsA), and ankylosing spondylitis (AS), where the IL-17/23 axis is

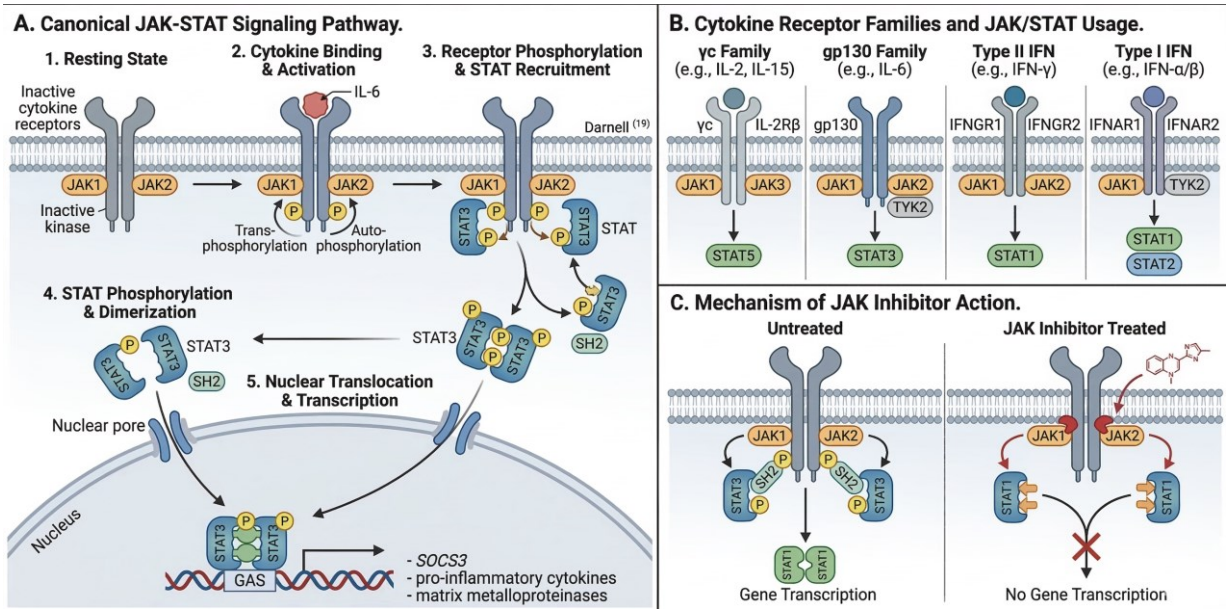
a dominant pathogenic driver [69,70]. However, their performance in RA clinical trials has been surprisingly modest [71]. This discrepancy between diseases has become a key area of debate and research. It strongly suggests that while the IL-17 pathway is present in the RA synovium, it may not be as central or as indispensable to the disease process as the TNF and IL-6 pathways, or that its role is confined to a specific subset of RA patients [72,73]. This highlights the critical concept of a "cytokine hierarchy" that differs between autoimmune diseases, even those that appear clinically similar [74].

4.3 The Oral Revolution: Targeted Synthetic DMARDs

A major paradigm shift in RA therapy occurred with the development of targeted synthetic DMARDs (tsDMARDs) [75]. This marked a move away from large, injectable protein-based biologics to orally available small molecules that could penetrate the cell membrane and inhibit key intracellular signaling pathways.

4.3.1 Discovery and Mechanism of the JAK-STAT Pathway

The JAKs are a family of four intracellular tyrosine kinases (JAK1, JAK2, JAK3, and TYK2) that are essential for transducing signals from Type I and Type II cytokine receptors [19]. When a cytokine binds to its receptor, it brings the associated JAKs into close proximity, allowing them to phosphorylate and activate each other. The activated JAKs then phosphorylate the receptor itself, creating docking sites for Signal Transducer and Activator of Transcription (STAT) proteins (Figure 1). The JAKs then phosphorylate the STATs, which dimerize, translocate to the nucleus, and act as transcription factors to alter gene expression [76]. This



JAK-STAT pathway, elucidated in the early 1990s by researchers including James Darnell, was identified as a critical signaling hub for a multitude of pro-inflammatory cytokines implicated in RA, including IL-2, IL-6, IL-7, IL-15, and interferons [19]. This made the JAK family an exceptionally attractive therapeutic target. A single small molecule inhibitor could, in theory, block the downstream effects of numerous pathogenic cytokines simultaneously, offering a broader mechanism of action than a monoclonal antibody targeting a single cytokine.

Figure 1. The JAK-STAT Signalling Pathway: Mechanism, Diversity, and Therapeutic Targeting in Rheumatoid Arthritis.

4.3.2 Clinical Development of Pan-JAK and Selective JAK Inhibitors

Tofacitinib, the first-in-class “jakinib”, began development in the mid-1990s through a collaboration between the NIH and Pfizer and was approved for RA by the FDA in 2012 [77]. Tofacitinib is considered a "pan-JAK" inhibitor, though it shows greater selectivity for JAK1 and JAK3 over JAK2 and TYK2 [78].

Following the success of tofacitinib, a new generation of more selective JAK inhibitors was developed. The rationale was that by targeting specific JAKs more precisely, one might be able to retain the therapeutic efficacy while minimizing off-target effects associated with inhibiting other JAKs (e.g., effects on hematopoiesis linked to JAK2 inhibition). This led to the development and approval of baricitinib [79], a selective JAK1/2 inhibitor, and upadacitinib, a highly selective JAK1 inhibitor [80]. Filgotinib further exemplifies this trend as a potent, once-daily oral highly selective JAK1 inhibitor that has demonstrated rapid, sustained clinical responses and a favorable safety profile in patients with RA who have had an inadequate response to methotrexate [81]. These oral agents have demonstrated efficacy comparable to, and in some cases superior to, injectable biologics, representing a major advance in the RA treatment armamentarium [82].

4.4 The Next Frontier: Innovative and Future Therapeutic Strategies

The field continues to evolve, driven by the need to treat the remaining population of patients with refractory disease, improve safety, and move toward the ultimate goal of consistent remission or cure. Current research is focused on several innovative frontiers.

4.4.1 Engineered Cytokines and Biosimilars

To address the limitations of natural cytokines (which have short half-lives and high toxicity when used therapeutically), protein engineering techniques are being used to create "smarter" cytokines. Strategies like

pegylation (attaching polyethylene glycol) can extend a drug's half-life, reducing dosing frequency [58]. Fusion proteins can be designed to target cytokines to specific tissues, enhancing local efficacy while minimizing systemic side effects [83,84]. In parallel, as patents for the original blockbuster biologics expire, the market for biosimilars - highly similar, officially approved copies of the original drug - is expanding rapidly. Biosimilars for infliximab, etanercept, and adalimumab are now widely available, offering the potential for significant cost savings and increased patient access to these life-changing therapies [57,85].

4.4.2 Bispecific Antibodies and Multi-Target Approaches

In a direct response to the challenge of cytokine redundancy, bispecific antibodies (BsAbs) are being developed. These engineered molecules have two different antigen-binding sites, allowing them to engage two distinct targets simultaneously [86]. This approach essentially builds combination therapy into a single molecule. In rheumatology, several strategies are being explored in clinical trials, including BsAbs that can neutralize two different cytokines at once or that can bridge two different cells together (e.g., binding to the CD20 marker on a pathogenic B cell and the CD3 marker on a cytotoxic T cell, bringing the killer cell directly to its target) [87]. This represents a logical and sophisticated evolution in therapeutic design, aiming to overcome the therapeutic ceiling seen with single-target agents.

4.4.3 Emerging Modalities

Looking further ahead, several cutting-edge technologies are being explored that could fundamentally change how autoimmune diseases are treated.

MicroRNAs (miRNAs) are small non-coding RNAs that can regulate gene expression post-transcriptionally [88]. Specific miRNAs have been shown to control the production of pro-inflammatory cytokines like TNF-α. Developing drugs that can mimic or inhibit these miRNAs could offer a novel way to fine-tune the inflammatory response at a genetic level [89].

Perhaps the most revolutionary approach is the use of engineered cell therapies. Chimeric Antigen Receptor (CAR) T-cell therapy, which has transformed the treatment of certain blood cancers, involves taking a patient's own T cells, genetically engineering them to recognize a specific target (e.g., the CD19 marker on B cells), and re-infusing them to eliminate the target cell population [90]. Stunningly successful reports of using CD19 CAR-T to induce drug-free remission in patients with severe, refractory systemic lupus erythematosus and systemic sclerosis have ignited immense

excitement about its potential for other B-cell-mediated rheumatic diseases [91,92].

5. Discussion

The journey of cytokine research in rheumatology is a remarkable story of scientific progress, illustrating a clear evolutionary path from observing broad inflammation to designing precision-targeted therapeutics. This journey has fundamentally altered the natural history of rheumatic diseases for millions of people. However, the completion of this journey is not yet in sight. The very successes of the past have illuminated the remaining complexities of the immune system, revealing significant knowledge gaps and unresolved questions. The future of the field lies in addressing these challenges, moving beyond simple immunosuppression toward the ambitious goals of personalized medicine, durable remission, and ultimately, a cure.

5.1 Synthesis of the Evolutionary Trajectory: From Broad Inflammation to Precision Targets

The narrative arc of cytokines' history traces a clear and logical progression. It begins with the earliest immunological studies, which could only describe biological phenomena like fever or inflammation as the work of ill-defined "factors" [21]. The advent of protein biochemistry and molecular biology in the latter half of the 20th century allowed for the identification of the specific molecular culprits, namely cytokines like TNF-α, IL-1, and IL-6 [93]. This knowledge directly enabled the first therapeutic revolution: the development of biologic drugs, such as monoclonal antibodies, that could neutralize these specific targets with high precision [55].

The clinical limitations of these first-generation biologics - namely, non-response in a substantial subset of patients and the inconvenience of injections - drove the next evolutionary step. Scientists looked downstream of the cytokine-receptor interaction to the intracellular signaling hubs, leading to the development of orally available small molecule JAK inhibitors that could block the pathways of multiple cytokines at once [77]. Now, facing the persistent challenges of treatment resistance and the deep-seated complexity of the cytokine network, the field is entering a third era. This new frontier is characterized by even more sophisticated strategies, such as bispecific antibodies designed to overcome redundancy and cellular therapies aimed at resetting the immune system entirely [87,91]. This trajectory is a testament to iterative innovation, where each generation of

therapy is born from the scientific questions raised by the limitations of the last (Figure 2).

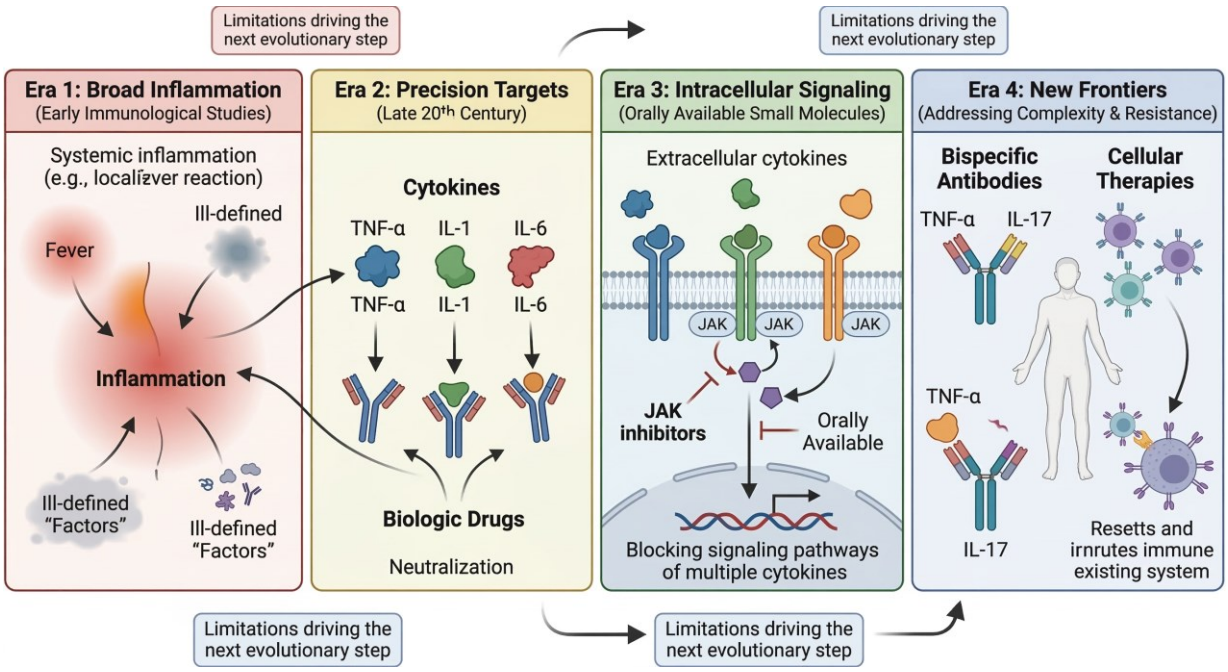


Figure 2. The evolutionary trajectory of cytokine-targeted therapeutics, illustrating the progression from early observations of broad inflammation to the development of precision biologics, intracellular signaling inhibitors, and next-generation cellular and bispecific therapies.

5.2 Current Knowledge Gaps and Unresolved Debates

Despite the powerful therapeutic armamentarium now available, several fundamental questions remain unanswered. These knowledge gaps represent the most active and important areas of current research in rheumatology.

A significant challenge remains: why do 30-40% of patients diagnosed with RA fail to achieve a satisfactory therapeutic response to initial biologic agents, such as TNF inhibitors? [59]. The mechanisms underlying this primary and secondary non-response are poorly understood. It may be due to the dominance of alternative, non-targeted cytokine pathways in those individuals, the influence of genetic background, environmental factors, the development of anti-drug antibodies, or other unknown biological variables [94]. Elucidating these mechanisms is paramount to moving beyond the current "trial-and-error" approach to prescribing.

Our understanding of the cytokine network, with its intricate web of synergistic, antagonistic, and feedback-regulated interactions, remains incomplete [1]. While we can block one or two nodes in this network

effectively, we have yet to fully grasp how to modulate the entire system back to a state of healthy homeostasis. The inherent redundancy of the system means that blocking one pathway may simply lead to compensatory upregulation of another. Developing therapeutic strategies that can account for and overcome this network-level complexity is a major future challenge.

RA is a systemic disease, and chronic inflammation is a known driver of serious comorbidities, most notably accelerating cardiovascular disease (CVD) [95]. A major unresolved debate in clinical practice is how best to manage this excess risk. Should the focus be on aggressively managing traditional CVD risk factors like lipids and hypertension, or should it be on achieving the deepest possible suppression of systemic inflammation through cytokine blockade? While evidence suggests both are important, the optimal strategy and the relative contribution of each approach are still under active investigation and debate [96,97].

The striking difference in the efficacy of IL-17 inhibitors in psoriasis versus RA is a powerful lesson in disease-specific immunology [50]. It demonstrates that even in clinically related autoimmune diseases, the hierarchy and relative importance of pathogenic cytokine pathways can differ profoundly. Understanding the molecular basis for these differences is a key knowledge gap that, if filled, could lead to more rational drug development and application across the spectrum of autoimmune conditions.

5.3 Future Perspectives: Towards Personalized Medicine and Curative Strategies

The future of cytokine-based therapy is shifting from the development of broadly applicable drugs to the creation of intelligent, personalized therapeutic strategies designed to address the specific needs of individual patients and achieve more ambitious outcomes.

The paramount objective within the field of rheumatology is the transition from treatment algorithms based on population-level data to individualized therapeutic approaches [98]. The future lies in the discovery and validation of biomarkers - which could be genetic, proteomic (e.g., serum cytokine profiles), or cellular - that can predict a patient's response to a specific therapy before it is initiated [99]. This would allow clinicians to stratify patients and select the most effective treatment from the outset, maximizing efficacy, minimizing toxicity, and avoiding costly and time-consuming cycles of failed therapies.

Given the complexity and redundancy of the cytokine network, it is likely that combination therapy will be key to treating the most refractory patients. This can be achieved by combining existing drugs with different mechanisms of action or through the development of novel multi-targeting agents like bispecific antibodies [86,100]. The goal is to break through the "therapeutic ceiling" that limits the efficacy of monotherapy and induce deeper, more durable levels of remission.

The ultimate ambition of the field is to move beyond chronic suppression of the immune system and toward the re-establishment of immune tolerance, potentially leading to drug-free remission or a functional cure. This represents the most challenging frontier, but promising strategies are emerging. These include therapies designed to selectively boost the function of regulatory T cells (Tregs), for example with low-dose IL-2, to restore the body's natural control over inflammation [101]. Even more revolutionary are the cellular therapies, such as CAR-T, which have shown the potential to completely eliminate pathogenic B cell populations and "reset" the autoimmune response [90]. While still in their infancy for rheumatic diseases, these strategies represent the most ambitious and potentially transformative future direction in the long and evolving history of cytokine-targeted therapy.

6. Conclusions

The journey of cytokine research in rheumatology is a remarkable story of scientific progress, illustrating a clear evolutionary path from observing broad inflammation to designing precision-targeted therapeutics. This journey has fundamentally altered the natural history of rheumatic diseases for millions of people. However, the completion of this journey is not yet in sight. The very successes of the past have illuminated the remaining complexities of the immune system, revealing significant knowledge gaps and unresolved questions. The future of the field lies in addressing these challenges, moving beyond simple immunosuppression toward the ambitious goals of personalized medicine, durable remission, and ultimately, a cure.

Author Contributions

Conceptualization: S.D & Z.K; Methodology: S.D.; Formal analysis: S.D & S.B; Investigation: S.D, S.B and Z.K; Writing—original draft: S.D, S.B and Z.K; Writing—review & editing: S.D, S.B and Z.K.

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The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflicts of interest.

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История на цитокините при ревматичните заболявания: Еволюционна перспектива върху медиаторите, инхибиторите и терапевтичните средства

Резюме

Цитокините са малки, секретирани протеини, които служат като основни медиатори на имунната система, координирайки сложните взаимодействия между клетките, участващи във възпалението, имунитета и тъканната хомеостаза. Тяхната дисрегулация е централна характеристика в патофизиологията на хроничните възпалителни състояния, особено при автоимунните ревматични заболявания като ревматоидния артрит. Настоящият доклад представя цялостен, структуриран анализ на историята на цитокините, проследявайки тяхната еволюция от неясно дефинирани биологични активности до прецизно определени молекулярни мишени за революционни терапии. За осигуряване на концептуална основа са установени фундаментални дефиниции и класификации на цитокините, с особен акцент върху това как основните им свойства - плеиотропност, редундантност и мрежова сложност - са оказали дълбоко влияние върху тяхното изследване и терапевтична манипулация. Изложението впоследствие детайлизира ключови открития на патогенни цитокини в ревматологията - включително фамилиите на TNF-α, IL-1 и IL-6 - като същевременно описва промяната в парадигмата, предизвикана от идентифицирането на оста IL-23/Th17. Паралелно с тези открития е проследена еволюцията на терапевтичните агенти - от първото поколение биологични болест-модифициращи антиревматични лекарства (bDMARDs), като TNF инхибиторите, до „оралната революция“ на таргетните синтетични DMARDs, като Janus киназните инхибитори (JAK-инхибитори), и по-нататък към стратегиите от следващо поколение, включващи биспецифични антитела и инженерно модифицирани цитокини. В заключителните раздели съвременното състояние на областта е синтезирано чрез критичен анализ на нерешените въпроси и пропуските в познанията, като механизмите на терапевтична резистентност (липса на отговор), предизвикателството на цитокинната редундантност и оптималното управление на системните придружаващи заболявания. Очертани са перспективни бъдещи насоки, акцентиращи върху нарастващия фокус върху стратификацията на пациентите чрез биомаркери, комбинираните стратегии с множество мишени и крайния стремеж към постигане на

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имунен толеранс и куративни терапии. В своята съвкупност тези разработки представляват ясна еволюционна траектория към реализирането на прецизната медицина в ревматологията.

Ключови думи: цитокини, ревматични заболявания, DMARDs (БПАРС), моноклонални антитела