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Reclassification of Cytokine-Based Immune-Mediated Inflammatory Diseases: Mechanisms and Therapeutic Advances of IL-1-Driven Inflammatory Diseases

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Abstract: Immune-mediated inflammatory diseases (IMIDs) represent a heterogeneous group of disorders driven by immune dysregulation, involving multiple organ systems and characterized by substantial clinical diversity. Traditional classification based on affected organs fails to capture shared pathogenic mechanisms and impedes the development of unified therapeutic strategies. In recent years, reclassification of IMIDs according to the dominance of key cytokine hubs has emerged as a focus of research. Interleukin-1 (IL-1), crucial in triggering and maintaining innate immune reactions, is key to the onset and continuation of inflammation. Aberrant activation of the IL-1 axis serves as a pathogenic driver in several prototypical auto-inflammatory diseases (AIDs) and plays a role in the development of inflammatory diseases like gout, hidradenitis suppurativa, recurrent pericarditis, and chronic recurrent multifocal osteomyelitis (CRMO), demonstrating a high degree of mechanistic convergence. Therapeutic strategies targeting IL-1 have shown favorable efficacy and safety in multiple clinical studies, with several agents approved for corresponding indications. As molecular mechanisms are further elucidated and biologic therapies continue to evolve, the IL-1 axis is increasingly recognized as a common inflammatory nexus within IMIDs. The reclassification framework centered on IL-1 provides a conceptual basis for the implementation of shared-treatment strategies across distinct diseases and establishes a theoretical and practical foundation for precision-targeted interventions.

Keywords: Interleukin-1; Immune-Mediated Inflammatory Diseases; Autoinflammatory Diseases; Targeted Therapy

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1. Introduction

Cytokines play a crucial role in immune-mediated inflammatory diseases (IMIDs). Among the various cytokines, interleukin-1 (IL-1) has received widespread attention in recent years as a key molecule driving inflammatory diseases. The IL-1 axis plays a pivotal role in the initiation and maintenance of inflammation, especially in conditions like adult-onset Still's disease, systemic juvenile idiopathic arthritis, and gout, where its pathological effects and significance as a therapeutic target are prominent [1]. This review will focus on IL-1-driven IMIDs, explore its central position in pathological mechanisms, and summarize the latest progress and future prospects of IL-1-based therapeutic strategies.

2. Complex biological effects of IL-1

IL-1 is one of the key cytokines in IMIDs, and its biological effects are complex and involve multi-level regulatory mechanisms. The primary IL-1 family members, IL-1β, IL-1α, and IL-1 receptor antagonist (IL-1RA), are crucial for the start and upkeep of innate immune responses.

2.1. Generation and regulatory mechanisms of IL-1β

IL-1β is primarily produced by myeloid cells, and its production is tightly regulated through various mechanisms [2,3]. Caspase-1-mediated cleavage is triggered by the inflammasome, a multiprotein complex composed of sensor proteins and the adaptor protein ASC, which can oligomerize to create a platform for caspase-1 cleavage. Caspase-1 also triggers the activation of gasdermin D, forming membrane pores for releasing IL-1β and inducing pyroptosis.

2.2. Multifunctional characteristics of IL-1α

IL-1α, unlike IL-1β, is persistently produced in a state of activity in all cells, and its function is significantly site-specific [1]. IL-1α not only regulates the expression of downstream cytokines in the nucleus as a transcription factor but also regulates the function of the NLRP3 inflammasome by interacting with mitochondrial cardiolipin [4]. IL-1α appears to be released mostly through lytic cell death, making it an "alarmin" that which leads to local inflammation in sterile inflammation, like ischemia.

2.3 . Anti-inflammatory effects of IL-1RA

In the IL-1 family, IL-1RA is another important member with potent anti-inflammatory properties, which competitively adheres to IL-1R1 and blocks signal transmission by IL-1α and IL-1β, thereby inhibiting inflammatory responses. However, IL-1RA exists in multiple isoforms and may have additional functions.

3. IL-1 and IMIDs

Based on the biological characteristics of IL-1, its central role in IMIDs is further reflected in the pathological mechanisms of specific disease subgroups, especially in monogenic autoinflammatory diseases (AIDs) highly correlated with the IL-1 axis and some IMIDs with complex mechanisms. This section will focus on IL-1-driven IMIDs, explore the etiology and mechanism of IL-1 in monogenic autoinflammatory diseases, and analyze its connection with other IMIDs, providing a theoretical basis for the exploration of precision treatment strategies.

3.1. IL-1-driven monogenic AIDs

From the perspective of pathological mechanisms, mAIDs can be divided into the following three categories.

(1) Diseases caused by mutations in inflammasome-related genes, which directly lead to excessive release of IL-1 and inflammatory responses due to continuous activation of the inflammasome.
(2) Diseases that activate IL-1 through mechanisms outside the inflammasome, involving the accumulation of intracellular stress triggers or abnormalities in immune signaling pathways.
(3) Diseases caused by defects in IL-1 signaling regulation, resulting from uncontrolled inhibition of IL-1 signaling.

3.1.1. Inflammasome-related gene mutations

The inflammasome is a multi-protein assembly formed in the cytoplasm with the participation of pattern recognition receptors. Mutations in inflammasome-related genes can trigger the generation of caspase-1, mediate the generation of active forms of IL-1β and IL-18, and fulfill an essential function in AIDs. Cryopyrin-associated periodic syndromes (CAPS) constitute a series of disorders resulting from mutations in the NLRP3 gene that encodes the cryopyrin protein, leading to enhanced caspase-1 enzyme activity, thereby increasing the synthesis of IL-1β and activating downstream proinflammatory cytokines.

The condition is typified by recurrent fever, urticarial rash with neutrophil infiltration, headache, arthralgia, conjunctivitis, and systemic inflammatory response. Familial Mediterranean fever (FMF) is the primary AID due to mutations in the MEFV gene, which can lead to a reduction in the quantity or altered function of pyrin, resulting in overactivation of the NALP3 inflammasome and thus triggering an inflammatory response. The common symptoms of this autosomal recessive genetic disease include recurrent intermittent fever, synovitis, serositis, and rash. The pathogenesis of NLRP1-related autoinflammatory syndrome is similar to the NLRP3 inflammasome pathway. NLRP1, ASC, caspase-1, and caspase-5 make up the NLRP1 inflammasome and NLRP1 gene mutations increase the activity of caspase-1 enzyme, thereby resulting in the production of IL-1β. The clinical manifestations of NLRP1-related autoinflammatory syndrome include skin hyperkeratosis, arthritis, recurrent fever, elevated CRP, and vitamin A deficiency.

3.1.2. Regulatory gene mutations that activate the inflammasome exogenously

These genes encode the proteins that regulate inflammasome activation through exogenous mechanisms. Variations in the MVK-encoding gene cause mevalonate kinase deficiency, a rare autosomal recessive genetic disease that results in abnormalities of the mevalonate metabolic pathway and decreased MVK activity. Clinical manifestations include periodic fever, joint swelling and pain, abdominal pain. Heterozygous variations in tumor necrosis factor receptor superfamily member 1A on chromosome 12 contribute to the autosomal dominant genetic disease known as tumor necrosis factor receptor-associated periodic syndrome.

In TRAPS, mutated TNFR1 protein accumulates in the endoplasmic reticulum, and abnormal autophagy leads to the production of IL-1β [5]. All clinical symptoms of TRAPS patients were completely relieved, and inflammatory markers returned to normal after receiving canakinumab treatment [6]. While etanercept is beneficial for more than 80% of TRAPS patients, only 30% achieve complete remission [7]. Majeed syndrome is a rare autosomal recessive genetic disease caused by mutations in the gene encoding phosphatidic acid phosphatase Lipin-2 on chromosome 18p11. by modifying the activation of the P2X7 receptor, the Mg^{2+} dependent phosphatidic acid phosphatase (PAP), a gene product of LPIN2, or lipin-2 protein, may modulate the activation of the NLRP3

inflammasome.

3.1.3. Diseases with defects in IL-1 signaling regulation

The core mechanism of this category of diseases is the uncontrolled inhibition or abnormal modulation of IL-1 signaling, causing overactivation or improper suppression of the IL-1 signaling pathway. DIRA is an uncommon autosomal recessive genetic AID that primarily arises from autosomal recessive missense mutations or large deletions in the IL1RN gene, resulting in the IL-1 receptor antagonist (IL-1Ra) to be absent or cease to function [8–11]. IL-1Ra plays a crucial role in preventing IL-1α and IL-1β from attaching to the IL-1 receptor. Its deficiency induces uncontrolled IL-1 signaling, ultimately triggering severe systemic inflammatory responses. Recombinant IL-1 receptor antagonist (anakinra) is currently proven to be an etiologically efficient treatment, and the FDA officially approved its application for treating IL-1 receptor antagonist deficiency in December 2020.

3.2. Polygenic-related IMIDs

Although monogenic autoinflammatory diseases (mAIDs) (as in **Table 1**) provide a clear genetic basis for studying the contribution the IL-1 axis to inflammatory diseases.

Table 1. Autoinflammatory diseases: Genes, symptoms, and treatment targets

Disease	Genes	Clinical Manifestations	Therapeutic Targets
Gout	ABCG2, ADRB3, ALC16A9, ALDH16A1, GCKR, LRRC16A, MTHFR, PDZK1, R3HDM2, RREB1, SLC17A1, SLC17A3, SLC22A11, SLC22A12, SLC2A9, SLC2A12 [12], MAF175[13], URAT1 [14]	Recurrent inflammatory arthritis, tophi, uric acid kidney stones	IL-1
Still's Disease	Class II HLA locus, HDAC9 [15], LACC1/ FAMIN[16]	Fever, arthritis, arthralgia, rash	IL-1, IL-6, TNF, IL-18, IFN-γ
Chronic Recurrent Multifocal Osteomyelitis (CRMO)	IL1RN, FBLIM1[17], Pstpip2[18,19], LPIN2[20]	Recurrent fever, arthritis, multifocal bone inflammation	IL-1, TNF
Hidradenitis Suppurativa	PSENEN, NCSTN, PSEN1[21]	Inflammatory nodules, sinus tracts, open comedones	IL-1, IL-36, IL-17, JAK, TNF
Recurrent Pericarditis	MEFV177[22], HLA-B14, DRB1*01, DQB1*0202[23]	Pleuritic chest pain, pericardial friction rub, ECG changes, pericardial effusion	IL-1

The etiology of IMIDs is often more complex, involving the interaction of multiple genes and multi-level immune regulation. These polygenic-related IMIDs not only exhibit heterogeneity in genetic backgrounds but also show broader clinical features and diverse tissue involvement patterns. Based on this, further research on the involvement of IL-1 signaling pathway underlying polygenic-related IMIDs can deepen the understanding of their pathological mechanisms and provide important directions for exploring precision treatment strategies.

3.2.1. Gout

Gout, an inflammatory disorder, is marked by the accumulation of monosodium urate (MSU) crystals in joints or soft tissues. Common clinical manifestations include arthritis and tophus deposition. The IL-1 pathway is key

to the development and progression of gout. In clinical practice, IL-1 antagonists are recommended in domestic and international guidelines as second-line therapy for gout patients who are intolerance or unresponsive to conventional medications. Among them, in June 2025, Firsekibart (formerly known as Genakumab, a fully human anti-IL-1â monoclonal antibody) was approved in China by the National Medical Products Administration (NMPA) for the treatment of acute gout. Its phase III trial demonstrated that, in patients with acute gout flares, Firsekibart was non-inferior to compound betamethasone in pain relief, with a favorable safety profile. Furthermore, the risk of recurrence was reduced by 90% and 87% at 12 and 24 weeks, respectively[24]. Another study showed that Firsekibart provided superior efficacy compared with etoricoxib in terms of pain relief within 72 hours of acute gout flare, onset of action, recurrence frequency, and time to recurrence[25]. During the intercritical period of gout, Firsekibart has also been shown to significantly reduce the incidence of acute flares in the early stage of urate-lowering therapy, with recurrence rates markedly lower than those observed with colchicine[26]. Anakinra, rilonacept, and canakinumab also achieved satisfactory results in relieving pain during the acute phase of gout and preventing recurrence during the intermittent phase [27]. Notably, canakinumab gained FDA approval for acute gout in August 2023.

3.2.2. Still's disease (AOSD and sJIA)

The systemic inflammation known as Still's disease is typified by fever, rash, and arthritis, which is classified into systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD) based on the age of onset. Although the mechanism of IL-1 in Still's disease is still being explored, IL-1 antagonistic therapy has achieved satisfactory results. For example, anakinra can induce complete remission in 58% of AOSD patients and 40–45% of sJIA patients [28–30]. Additionally, rilonacept and canakinumab are also widely used to treat Still's disease [31–34]. It is recommended in the latest 2024 EULAR guidelines to initiate anti-IL-1 therapy as soon as possible after diagnosis of Still's disease [35]. Canakinumab was approved by the FDA in May 2013 and June 2020 for the treatment of sJIAandAOSD, respectively. Notably, a multicenter phase 2 study presented at the 2025 EULAR Congress showed that Firsekibart demonstrated comparable efficacy to tocilizumab with a favorable safety profile in patients with active sJIA [36].

3.2.3. Chronic recurrent multifocal osteomyelitis (CRMO)

The main feature of CRMO is chronic recurrent aseptic osteomyelitis, and the knee, ankle, or wrist joints are the most frequently impacted. Mutations in LPIN2, Pstpip2, IL1RN, and FBLIM1 may be associated with the occurrence of CRMO. Research has demonstrated that when the classic NLRP3 inflammasome is activated, Lipin2 decreases ATP-promoted potassium efflux, which encourages the synthesis of downstream IL-1β and the development of P2X7R pores [37].

Meanwhile, children with active CRMO have peripheral blood cells that exhibit increased expression of IL-1β messenger RNA (mRNA) [38]. Anakinra and canakinumab have been reported to be utilized to treat CRMO in clinical practice [39]. Besides IL-1 monoclonal antibodies, anti-TNF agents are also common therapeutic targets [40].

3.2.4. Hidradenitis suppurativa

The chronic inflammatory disease known as hidradenitis suppurativa predominantly impacts the skin of the axilla, groin, and perianal region. It can produce inflammatory nodules, abscesses, and fistulas, secreting foul-smelling

purulent secretions. Research indicates that the IL-1β expression in skin lesions of hidradenitis suppurativa is 130 times higher than that of healthy individuals [41]. IL-1β can recruit neutrophils, T cells, and monocytes to the skin by stimulating endothelial cells and enhance the expression of chemokines as CXCL1, CXCL6, CXCL8, CXCL11, CCL20, and CCL22 [42]. Simultaneously, IL-1β can upregulate the expression of matrix metalloproteinases, which subsequently accelerates skin damage and the formation of sinuses. Twenty individuals with moderate to severe hidradenitis suppurativa was administered with anakinra, exhibiting an effective rate of 78% that was significantly better than the placebo group, and no serious adverse reactions were observed [43].

3.2.5. Recurrent pericarditis

Recurrent pericarditis refers to the recurrence of pericarditis following an initial attack, with an interval of 4–6 weeks. Studies have indicated that neutrophils and monocytes in patients with recurrent pericarditis produce large amounts of IL-1 through inflammasome activation [44]. During pericardial tissue damage, IL-1α initiates sterile inflammation by triggering damage-associated molecular patterns (DAMPs). The inflammasome processes and releases IL-1β, causing pericardial congestion, edema, and sensory hyperactivity, and amplifies the inflammatory cascade reaction [45]. In clinical practice, anakinra and rilonacept can significantly reduce the risk of pericarditis recurrence, and there are also a few case reports of treatment with canakinumab [46–49]. Among these three medications, rilonacept gained FDA approval in March 2021 for managing recurrent pericarditis.

3.2.6. Rheumatoid arthritis

Rheumatoid arthritis is a chronic inflammatory, multifactorial, autoimmune disease that typically manifests by symmetrical involvement of multiple peripheral joints, articular pain and swelling, and morning stiffness. Additionally, rheumatoid arthritis often presents with non-articular manifestations such as serositis, vasculitis, Felty's syndrome, peripheral neuropathy, and pulmonary involvement in later stages of the disease [50]. Studies have shown that the expression of IL-1 is significantly elevated in the synovial fluid of patients with rheumatoid arthritis, widely participating in the inflammatory response in synovial tissue [51]. Anakinra has undergone multiple clinical studies in the field of rheumatoid arthritis and received FDA approval for related indications in November 2001. The combination of anakinra with methotrexate or other disease-modifying antirheumatic drugs (DMARDs) not only performed more effectively than placebo plus methotrexate in a 24-week efficacy observation period [52–54], but also benefits patients with rheumatoid arthritis in the long run [55]. Furthermore, an increased dosage of anakinra contributed to ACR20 response for more patients [55]. In another Phase II clinical study of canakinumab, the drug demonstrated significant superiority in ACR50 evaluation over the placebo within 12 weeks [56]. Besides IL-1, IL-6, JAK, CD20, and TNFα are also important therapeutic targets [57].

4. Conclusion and prospects

Significant progress has been made in research on inflammatory diseases driven by IL-1 over the past few decades. From the discovery of inflammasomes to the precise regulation of the IL-1 axis, these advancements have revolutionized the treatment of autoinflammatory diseases and other IMIDs. Although IL-1 inhibitors have demonstrated remarkable efficacy in certain diseases, numerous challenges still exist, such as treatment tolerance, long-term safety, and limitations in more complex diseases including polygenic IMIDs. Furthermore, the interaction between IL-1 and other inflammatory pathways remains incompletely understood, providing vast

opportunities for developing combined targeting strategies.

Disclosure statement

The authors declare no conflict of interest.

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