

The Emerging Role of Interleukin-1 β in Autoinflammatory Diseases

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Abstract The autoinflammatory syndromes are a group of multisystem disorders characterized by recurrent episodes of fever and systemic inflammation affecting the eyes, joints, skin, and serosal surfaces in the absence of an immune reaction. Recent advances have revealed the importance of interleukin-1 β , not only in the pathogenesis of many of these rare inherited diseases, but also in acquired diseases. The development and availability of anti-interleukin-1 β therapeutics have introduced the possibility of proof-of-concept studies, which are likely to further widen this field.

Keywords Interleukin-1 · Inflammasome · Autoinflammatory diseases · Caspase-1 · Cryopyrin · NLRP3 · CAPS · Anakinra · Rilonacept · Canakinumab

Introduction

The autoinflammatory syndromes are a group of multisystem disorders characterized by recurrent episodes of fever and systemic inflammation affecting the eyes, joints, skin, and serosal surfaces in the absence of an immune (high-titer autoantibodies or antigen-specific T cells) reaction [1]. The mammalian immune system is composed of two arms: the acquired or adaptive immune system, and the innate immune system. Innate immunity is a genetically encoded, hardwired system that provides a rapid response to danger signals [2].

The systemic autoinflammatory syndromes are recognized as disorders of innate immunity and are entirely distinct from the classical autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, which are diseases rooted primarily in adaptive immunity [3•]. There is no doubt, however, that the two immune systems are intertwined and that the range of self-reactive immunologic disease represents a continuum between the two [4]. Interleukin (IL)-1 has long been acknowledged as a potent mediator of host responses to infection and inflammation [5, 6], and more recently, IL-1 β has emerged as a key player in the mediation of inflammation in general and in the autoinflammatory diseases (AIDs) in particular [7•]. This article reviews the emerging body of evidence concerning the role of IL-1 β in AIDs.

The Innate Immune System and Interleukin-1 β

Two major classes of receptors involved in innate immunity are the Toll-like receptors, which are membrane bound, and the nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), which are cytosolic. Both receptor classes recognize pathogen-associated molecular patterns (PAMPs), and the NLRs in particular appear to sense endogenous signals, the so-called danger-associated molecular patterns (DAMPs). More than 20 NLR-encoding genes have been identified in humans. Most proteins appear to have a leucine-rich repeat domain at the C-terminal (this is thought to be the ligand-binding motif), a NOD that is central to the formation of multimeric complexes, and an N-terminal effector domain. These regulate activation of caspases (a group of intracellular cysteine proteases), which in turn activate a variety of cellular responses, including apoptosis pathways, transcription of nuclear factor- κ B (NF κ B), and cytokine activation [8].

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Cryopyrin is the most studied and best understood member of the NLR family and is the key component of the NLRP3 inflammasome. The inflammasome is a multimeric cytosolic platform consisting of cryopyrin, the adaptor protein ASC (apoptosis-associated speck protein with a caspase activation and recruitment domain), procaspase-1, and in some cases CARDINAL [9]. Once activated by PAMPs or DAMPs [10], cryopyrin interacts with the other protein components of the inflammasome. This oligomerization results in cleavage of procaspase-1 to caspase-1, which in turn cleaves inactive pro-IL-1 β to the mature active IL-1 β .

IL-1 β is a key proinflammatory cytokine with pleiotropic effects [7•]. Binding of IL-1 β to its receptor induces intracellular signaling and transcription of other proinflammatory genes, hence, dysregulation of IL-1 β production has serious pathological consequences. Its transcription, activation, and release are tightly regulated, and the activity of IL-1 β after release is further regulated by IL-1Ra, an endogenous antagonist of IL-1 α and IL-1 β [11]. Once released, circulating IL-1 β binds to the IL-1 receptor [11]. The binding of IL-1 β to its receptor type I (IL-1RI) and to the IL-1 receptor accessory protein (IL-1RAcP) stimulates intracellular signaling and transcription of other proinflammatory cytokines. The primary role of the NLRP3 or caspase-1 inflammasome is to tightly regulate activation of IL-1 β . Once released into the extracellular environment, the activity of both IL-1 β and IL-1 α is further regulated by IL-1Ra, which antagonizes their binding to IL-1RI [12, 13]. Pivotal to the recent developments in our understanding of the role of IL-1 β in AIDs has been the success of agents that block IL-1 in these disorders. Anakinra (a recombinant IL-1 receptor antagonist), rilonacept (an IL-1 Trap), and canakinumab (a fully human anti-IL-1 β monoclonal antibody) are the three anti-IL-1 agents that have been widely studied and used in the clinical arena, and there are phase 2 clinical trials under way with another anti-IL-1 β antibody, XOMA 052 (XOMA, Berkeley, CA).

Therapeutic Anti-Interleukin-1 Agents

Anakinra is a recombinant, humanized form of the endogenous IL-1Ra. It acts by blocking the binding of IL-1 β to the IL-1RAcP [7•]. Anakinra must be given by daily subcutaneous injection and has a half-life of 4 to 6 hours. Initially developed for use in sepsis and licensed for use in patients with rheumatoid arthritis [14], it was the first anti-IL-1 agent to be used successfully in the AIDs. Anakinra has been shown to be efficacious in several AIDs, as discussed later, and has to date appeared safe and reasonably well-tolerated. The main factor discouraging use of this drug has been painful injection site reactions, particularly shortly after initiation of treatment.

Rilonacept is a dimeric fusion protein made up of the extracellular domains of the IL-1RI and the IL-1RAcP attached to the constant region of a human IgG molecule. As it contains both components of the IL-1 binding site, rilonacept has picomolar affinity for IL-1 [15]. Rilonacept has been licensed in the European Union and the United States for use in adults and children older than 12 years of age with two of the forms of cryopyrinopathy (discussed below). It has a half-life of 8.6 days and is administered once weekly by subcutaneous injection, making it an attractive option compared with daily injections of anakinra. Adverse events associated with rilonacept include injection site reactions and an apparent increased risk of infection.

Two anti-IL-1 β monoclonal antibodies have been developed. The first of these, canakinumab, is a fully humanized IgG₁ anti-IL-1 β antibody that neutralizes the bioactivity of IL-1 β by preventing binding to its receptor [16]. Canakinumab has a half-life of 21 to 28 days, and in the European Union and the United States, a license has been granted for eight weekly subcutaneous injections for treatment of the cryopyrinopathies in adults and children 4 years of age and older. Like the other anti-IL-1 agents, canakinumab has a favorable adverse event profile to date, with only a minor increase in infections compared with placebo.

XOMA 052 is an engineered monoclonal antibody with 97% human sequence and high affinity for IL-1 β . It is reported to inhibit the binding of IL-1 β to IL-1RI but has little effect on its affinity for IL-1RII and the soluble inhibitory receptors sRI, sRII, and sRAcP. XOMA 052 has shown efficacy in reducing inflammation in murine models of acute gout and diet-induced obesity [17]. Results of clinical studies have not yet been reported.

Human Diseases Associated with Interleukin-1 β

Cryopyrin-Associated Periodic Syndrome

Developments in the understanding of the pathogenesis of cryopyrin-associated periodic syndrome (CAPS), a rare AID, have been instrumental in the advances in our knowledge of the role of IL-1 β in AIDs in general. Also known as the cryopyrinopathies, CAPS is an inherited inflammatory disorder that presents with variable severity. Historically, the disease spectrum was described as the following separate syndromes in increasing severity: familial cold autoinflammatory syndrome (FCAS); Muckle-Wells syndrome (MWS); and chronic infantile neurologic cutaneous and articular (CINCA) syndrome, which is also known as neonatal-onset multisystem inflammatory disorder (NOMID). It is now clear that these are not discrete

disease entities, as there is often substantial overlap between them. Symptoms include episodes of self-terminating fever, urticarial rash, arthralgia, myalgia and red eyes due to a combination of uveitis, episcleritis, and/or scleritis associated with an elevated acute-phase response [18]. At the milder end of the spectrum, FCAS is associated with a cold-induced urticarial rash, along with fever, chills, joint pain, headache, and red/sore eyes; episodes typically resolve within a few hours [19]. MWS presents similarly, except that the symptoms, rather than appearing on cold stimulus, typically occur every day, usually late in the afternoon. MWS is also associated with a degree of chronic central nervous system inflammation causing meningitic headaches, visual problems, and progressive sensorineural deafness in approximately 40% of affected individuals [20]. AA amyloidosis and renal failure are serious complications in 25% of patients [18]. The most severe form of CAPS is CINCA syndrome, which in addition to the above is characterized by progressive, chronic, aseptic meningitis; deafness; visual loss due to a combination of recurrent uveitis and band keratopathy and optic nerve atrophy accompanying chronic papilledema;

developmental delay; and severe cartilage hypertrophy resulting in physical disability [21].

Linkage studies by three separate groups in 2001 to 2002 identified that the mutated gene in all three syndromes was *NLRP3*, the gene encoding cryopyrin [22–24]. These gain-of-function mutations disrupt the closed (inactive) configuration of cryopyrin, thus promoting inflammasome assembly (Fig. 1) [25]. It must be noted, however, that approximately one third of individuals with CINCA/NOMID are mutation negative [21], although some of these may be mosaics, and in our practice and that of others, there appear to be increasing numbers of patients presenting with less severe CAPS-like disease who are responsive to anti-IL-1 β therapy but who are without an identifiable mutation in *NLRP3*.

Blockade of IL-1 β in CAPS has been extremely successful. Several studies of anakinra therapy in CAPS have been published. In an open-label study of four FCAS patients subjected to an experimental cold challenge, anakinra prevented the development of all signs and symptoms of cold exposure [26]. Another study of eight patients with FCAS showed that all signs and symptoms

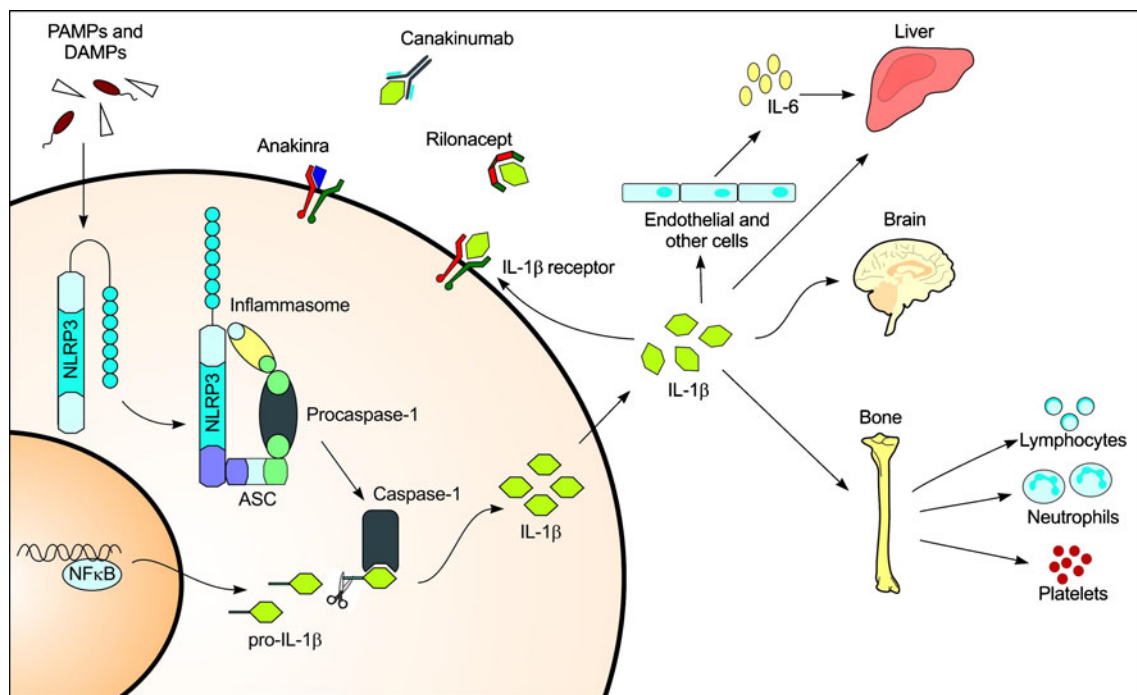


Fig. 1 Activation of the NLRP3 inflammasome leads to the release of interleukin (IL)-1 β , which stimulates widespread inflammatory responses. Pathogen-associated and danger-associated molecular patterns (PAMPs and DAMPs) within monocytes and macrophages are recognized by pattern-recognition receptors such as NLRP3. The resulting activation of NLRP3 leads to its interaction with the other components of the NLRP3 inflammasome (apoptosis-associated speck protein with a caspase activation and recruitment domain [ASC] and procaspase-1). The NLRP3 inflammasome results in polymerization of procaspase-1 to produce the caspase-1. Caspase-1 in turn cleaves pro-IL-1 β to yield the active cytokine, IL-1 β . IL-1 β is released from the

cell and induces an inflammatory response: the production and release of the acute-phase proteins is stimulated by direct action on the liver or indirectly via IL-6 released from endothelial and other cells. IL-1 β acts centrally on the hypothalamus to induce fever. IL-1 β stimulates bone to induce bone resorption and breakdown of cartilage, and production and enhanced activation of lymphocytes, neutrophils, and platelets. The anti-IL-1 therapies anakinra, rilonacept, and canakinumab act by blocking binding to the IL-1 receptor, trapping the IL-1 β molecule, or binding to it, respectively. Stimulation of nuclear factor- κ B (NF κ B) signalling pathways leads to upregulated IL-1 β mRNA transcription and increased pro-IL-1 β production

resolved within 24 hours of dose administration, and this remission lasted 36 hours [27]. Similar symptomatic remission has been reported in CINCA/NOMID patients, together with significant response of acute-phase markers serum amyloid A and C-reactive protein [21, 28], although this may not necessarily halt the development of irreversible bone changes [29]. More recently, a single-center observational study of 12 patients with MWS treated with anakinra for a median of 11 months and followed up for the same median time period showed significantly reduced disease activity and improvements in patient-derived health measures in all patients, and improved hearing in 1 patient [30]. Injection site reactions appear to be the most commonly reported side effect with use of anakinra, with upper respiratory tract infections and urinary tract infections also frequently reported.

More than 150 patients with FCAS and MWS have now been treated with rilonacept within 3 clinical trials. The first was an open-label study in which five patients with FCAS were retreated at time of flare and then weekly [31]. The second was a randomized, double-blind, placebo-controlled study, including a withdrawal phase, of weekly rilonacept therapy for 24 weeks in 47 FCAS and MWS patients [32], and the third was an open-label extension of this study with the addition of 55 more patients [33]. In all studies, patients experienced significant reductions in serum amyloid A and C-reactive protein in response to rilonacept therapy. The adverse event profile showed increased risk of infection, with 80%, 48%, and 33% of patients experiencing infections in the first, second, and third studies, respectively. In the randomized study, 43% of patients developed anti-rilonacept antibodies, and in the open-label extension, 41%. In the same two studies, injection site reactions were significant: 48% and 61%, respectively.

Results of studies of canakinumab in adults and children with CAPS exhibiting disease across the severity spectrum have been overwhelmingly positive. Lachmann et al. [34, 35] have reported complete clinical remission within 8 days that lasted a median of 100 to 185 days.

Familial Mediterranean Fever

Familial Mediterranean fever (FMF) is an autosomal recessive AID characterized by lifelong, recurrent, self-terminating episodes of fever and systemic inflammation that usually manifests as serositis, peritonitis, arthritis, myalgia, and sometimes pleurisy and pericarditis [36]. FMF is associated with mutations in *MEFV*, the gene encoding the protein pyrin, which was previously known as marenostin. The function of the mutated pyrin is not yet entirely clear; however, it is a member of the death domain superfamily and known to be associated with IL-1 production. Wild-type pyrin binds to ASC, thereby inhibit-

ing assembly of the NLRP3 inflammasome; it also binds directly to caspase-1, disrupting its ability to cleave pro-IL-1 β to the bioactive conformation [37]. Although colchicine remains the drug of choice in the treatment of FMF by virtue of its well-documented efficacy [38], there have been several reports of the successful use of IL-1 blockade in FMF, mainly in patients with incomplete colchicine response [39, 40] or complete colchicine resistance [41, 42].

Tumor Necrosis Factor Receptor–Associated Periodic Syndrome

Tumor necrosis factor receptor–associated periodic syndrome (TRAPS) is an autosomally dominant, inherited disorder characterized by self-limiting episodes of fever accompanied by localized and systemic inflammation presenting as abdominal pain, pleurisy, myalgia, and a migratory rash. TRAPS is associated with mutations in tumor necrosis factor receptor superfamily 1A (*TNFRSF1A*), a 10-exon gene located on chromosome 12p13. The mechanisms by which heterozygous mutations cause systemic inflammation remain unclear and may well be mutation specific. Under normal circumstances, tumor necrosis factor (TNF) signaling is terminated by metalloproteinase-dependent cleavage of the extracellular domain; this also results in release of soluble TNF receptor 1 (TNFR1), which competes with the cell surface receptor in binding circulating TNF. While some TNFR1 variants do demonstrate impaired cleavage and a “shedding defect,” this is not the case in other TRAPS-causing mutations, which must exert their pathogenic effect by different means. It is thought that mutant misfolded receptors may give rise to enhanced or prolonged signaling, possibly through retention within the endoplasmic reticulum [43–47]. Anti-TNF drugs are now being replaced by anti-IL-1 drugs as the treatment of choice for TRAPS because the former have been associated with an unfavorable adverse event profile and often only transient or limited efficacy [48–50]. The success of anti-IL-1 therapy in this disease has suggested the pivotal role of this cytokine. Sustained remission of disease activity with anakinra has been reported [48, 51], and a clinical trial of canakinumab in TRAPS is currently under way (<http://www.clinicaltrials.gov> identifier NCT01242813).

Mevalonate Kinase Deficiency

Previously known as the hyperimmunoglobulin D and periodic fever syndrome, mevalonate kinase deficiency (MKD) is a rare autosomal recessively inherited AID resulting from mutations in *MVK*, the gene encoding mevalonate kinase [52]. The disease manifests as recurrent episodes of fever in association with lymphadenopathy, malaise, abdominal pain, diarrhea, vomiting, rash, and arthralgia [52, 53]. Mevalonate kinase is involved in the

cholesterol, farnesyl, and isoprenoid biosynthesis pathway, and until recently, its role in the activation of inflammation had been unclear. It is now thought that isoprenoid deficiency may affect signaling pathways involving enzymes such as Rac1, phosphatidylinositol 3-kinase, and PKB, which could activate caspase-1 and thus IL-1 and the inflammasome. Support for this has come from the finding that mononuclear cells from patients with MKD release elevated levels of IL-1 β [54] and, importantly, from the fact that success has been reported with anakinra therapy [55, 56]. There are no reports of the use of rilonacept or canakinumab in this disease.

Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne

Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) is an exceptionally rare syndrome characterized by joint inflammation, cystic acne, and cutaneous ulcers and is the result of autosomal dominantly inherited mutations in the *PSTPIP1* gene [57]. The *PSTPIP1* protein is known to interact with pyrin, and the postulated mechanism of activation of inflammation is that mutated *PSTPIP1* may impair the ability of pyrin to bind to ASC, thus promoting inflammasome assembly [3•]. As in MKD, mononuclear cells from patients with PAPA release elevated levels of IL-1 β , and the use of anakinra has been successful in one reported case [58, 59].

Deficiency of the Interleukin-1 Receptor Antagonist

Deficiency of the IL-1 receptor antagonist (DIRA), a rare AID, is the result of recessive mutations in *IL1RN*, the gene encoding the endogenous IL-1 receptor antagonist [58, 60]. DIRA is associated with skin manifestations ranging from small, localized areas of pustules to generalized pustulosis and bony abnormalities such as rib widening and multifocal osteolytic lesions; as one would predict, treatment with anakinra resulted in clinical improvement in the skin and bone manifestations, as well as rapid and sustained decline in serologic acute-phase reactants [60].

Systemic-Onset Juvenile Idiopathic Arthritis and Adult-Onset Still's Disease

Systemic-onset juvenile idiopathic arthritis (SoJIA) and adult-onset Still's disease are diseases of unknown molecular etiology that share similar features of fever, rash, myalgia, arthritis and arthralgia, serositis, and lymphadenopathy [61]. Although the precise pathophysiology remains unknown, a great deal of evidence implicates the involvement of IL-1 β . Following a 6-h incubation period, serum from patients with SoJIA (but not the healthy controls) induced IL-1 β transcription in healthy mononu-

clear cells, and transcription of other genes known to be involved in IL-1 induction was also upregulated [62]. Several reports—a combination of retrospective chart reviews [63], open-label studies [61, 64], and placebo-controlled studies [65]—show the efficacy of anakinra in SoJIA, although injection site reactions in this patient group proved to be a limiting factor. Studies of rilonacept in SoJIA have shown similar efficacy [66, 67], although there were six serious adverse events, and 29% of patients experienced injection site reactions. A trial of canakinumab showed good responses in 59% of the 23 patients [68].

Schnitzler Syndrome

Schnitzler syndrome is characterized by fever, arthralgia, bone pain, urticaria-like rash, and lymphadenopathy together with an IgM monoclonal gammopathy [69]. Although the etiology of this disease is unknown, disease response to anakinra has been overwhelming, with 100% efficacy reported [70].

Gout

Gout and pseudogout are inflammatory conditions associated with the accumulation of monosodium urate or calcium pyrophosphate dihydrate crystals in joints and periarticular tissues, respectively; these crystals are known to be direct activators of the NLRP3 inflammasome [10]. The involvement of IL-1 has been proven clinically by the successful treatment of patients with anakinra [71] and canakinumab [72].

Type 2 Diabetes Mellitus

Increasing evidence suggests that type 2 diabetes mellitus is a disease of chronic inflammation. Overnutrition is the main cause of type 2 diabetes mellitus, with the associated chronic hyperglycemia playing a fundamental role in upstream and downstream pathways, leading to inflammation and insulin resistance. Chronic exposure of pancreatic islet cells to a hyperglycemic environment is thought to trigger the generation of reactive oxygen species (ROS) [73•], and the increased glycolysis associated with hyperglycemia is known to result in mitochondrial oxidative stress, which drives ROS generation [74]; ROS are a known activator of the NLRP3 inflammasome. Although it was previously believed that only cells of the immune system expressed IL-1 β , it is now known that cells outside the immune system, including pancreatic B cells, can express IL-1 β ; expression of IL-1 β mRNA is upregulated in response to prolonged hyperglycemic conditions [75]. This localized increase in IL-1 β secretion contributes to B-cell apoptosis and thus increased insulin resistance—a vicious

cycle [73]. Studies have shown that IL-1 blockade using anakinra not only reduced levels of inflammatory markers but also improved B-cell function and glycemic control [76], and that this response is sustained for at least 36 weeks [77].

Conclusions

The work over the past decade on AIDs and IL-1 has been a remarkable demonstration of the power of bed-to-bench, reverse translational, and translation medical research. The identification of the genetic mutations underlying CAPS, an exceptionally rare disease, and the subsequent demonstration that these patients could be restored to normal health with IL-1 blockade were in themselves remarkable. The studies from Tschopp's group describing the IL-1 inflammasome and the effect of *NLRP3* mutations in causing constitutive overproduction of active IL-1 β provided an elegant molecular explanation of a rare disease and provided insights into the regulation of IL-1 in general.

The recent accumulation of data indicating that IL-1 β is a key proinflammatory cytokine involved in the pathogenesis not only of the rare inherited AIDs, but also of more prevalent acquired diseases has been accompanied by the development and availability of a variety of therapeutic agents targeting IL-1. We are now entering a period of basic and clinical research evaluating the role of the innate immune response, and IL-1 in particular, in diseases such as gout, diabetes, and ischemic heart disease, and exploring the benefits of IL-1 blockade in acquired complex diseases.

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