

Interleukin-1: Ariadne's Thread in Autoinflammatory and Autoimmune Disorders

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ABSTRACT: Autoinflammatory and autoimmune disorders are characterized by chronic activation of the immune system, which leads to systemic self-directed inflammation in genetically predisposed individuals. Mutations in inflammasome-related proteins have been associated with autoinflammatory disorders, and the link between inflammasome and autoimmune disorders is becoming increasingly clear. As researchers learn more about these two areas, other disorders that were once thought to be autoimmune are now being considered autoinflammatory, or as having at least an autoinflammatory component. This review depicts the role of interleukin-1 as "Ariadne's thread" on the path through the labyrinth of autoinflammatory and autoimmune disorders and emphasizes the blurred boundary between innate and adaptive immune systems.

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Interleukin-1 (IL-1), the first cytokine discovered (in the 1980s), is a potent mediator of inflammation. It coordinates systemic host defense responses to pathogens or various injuries, and the whole IL-1 system represents an attractive target for different therapeutic interventions. The identification of a new cytoplasmic complex of proteins, called inflammasomes which sense intracellular danger- or pathogen-associated molecular patterns and regulate IL-1 β activation and secretion, has enhanced our understanding of the role of IL-1 in biology and many disease processes. Dysregulation of the inflammasome is the cause of a family of monogenic autoinflammatory disorders. This dysregulation has also been involved in the pathogenesis of differ-

Dysregulation of the inflammasome is the pivotal cause in the pathogenesis of autoinflammatory disorders and seems also to participate in different systemic autoimmune conditions

ent multifactorial polygenic diseases with an autoinflammatory component, and even in different autoimmune diseases.

Classical autoimmune disorders are associated with the presence of autoantibodies and autoantigen-specific T cells; however, in addition to the classical major histocompatibility complex (MHC) class II-associated diseases, such as systemic lupus erythematosus and rheumatoid arthritis, the autoimmunity paradigm has also been the dominant conceptual framework when considering the pathogenesis of a range of other chronic inflammatory conditions, such as inflammatory bowel disease and systemic onset juvenile idiopathic arthritis.

Several difficulties arise when the autoimmunity concept is evoked to describe the self-directed tissue inflammation encountered in many diseases, such as hereditary periodic fevers, now framed in the context of autoinflammatory disorders, for which autoantibody, autoreactive T cells, and MHC allelic associations are lacking [1].

FROM MONOGENIC TO MULTIFACTORIAL AUTOINFLAMMATORY DISORDERS

Advances in cellular and molecular biology have revealed that impaired control of innate immune system generates the so-called autoinflammatory disorders, a group of heritable diseases characterized by unprovoked attacks of systemic inflammation in

the absence of autoantibodies and autoreactive T cells [2]. Following the discovery of the familial Mediterranean fever (FMF) gene in 1997 and the tumor necrosis factor (TNF) receptor-associated peri-

odic syndrome (TRAPS) gene in 1999, there has been an extraordinary revolution in the understanding of monogenic autoinflammatory disorders, with identification of multiple genes and new clinical entities, all characterized by subverted mechanisms of inflammation. Their unifying pathogenetic mechanism is a dysregulation of the inflammasome, which leads to overproduction of IL-1 β [3]. At a clinical level, autoinflammatory disorders

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Table 1. Clinical trials in progress related to interleukin-1 blockade in the monogenic autoinflammatory disorders

	Phase	Status	Study	Disease	Clinical Trial.gov Identifier
Anakinra	3	Recruiting	Anakinra in adult patients with colchicine-resistant FMF	FMF	NCT01705756
	1	Completed	The use of anakinra in the treatment of familial cold autoinflammatory syndrome	FCAS	NCT00214851
Canakinumab	3	Recruiting	Efficacy, safety and tolerability of ACZ885 in pediatric patients with the following cryopyrin-associated periodic syndromes: familial cold autoinflammatory syndrome, Muckle-Wells syndrome and CINCA syndrome	CAPS	NCT01576367
	3	Completed	The safety and efficacy of canakinumab in patients aged ≥ 4 years diagnosed with cryopyrin-associated periodic syndromes in Canada	CAPS	NCT01105507
	3	Completed	Efficacy and safety study of canakinumab administered for 6 months (24 weeks) in Japanese patients with cryopyrin-associated periodic syndromes followed by an extension phase	CAPS	NCT00991146
	2	Completed	Evaluation of the safety and efficacy of canakinumab in pediatric patients with colchicine-intolerant or colchicine-resistant FMF	FMF	NCT01148797
	2	Completed	Efficacy and safety of canakinumab in patients with colchicine-resistant FMF	FMF	NCT01088880
	3	Active	Efficacy, safety and tolerability of ACZ885 in pediatric patients with the following cryopyrin-associated periodic syndromes: familial cold autoinflammatory syndrome, Muckle-Wells syndrome and CINCA syndrome	CAPS	NCT01302860
	–	Recruiting	Clinical outcomes and safety: a registry study of canakinumab patients (B-confident)	CAPS	NCT01213641
	2	Active	Canakinumab in patients with active hyper-IgD syndrome	MKD	NCT01303380
	2	Completed	Efficacy and safety study of ACZ885 in patients with tumor necrosis factor receptor-associated periodic syndrome	TRAPS	NCT01242813
	3	Recruiting	Efficacy and safety of canakinumab in patients with hereditary periodic fevers	HPFs	NCT02059291

CAPS = cryopyrin-associated periodic syndromes, FMF = familial Mediterranean fever, HPFs = hereditary periodic fever syndromes, MKD = mevalonate kinase deficiency syndrome, TRAPS = tumor necrosis factor receptor-associated periodic syndrome

are defined by recurrent fever attacks with constantly increased acute-phase reactants and several inflammatory phenomena involving skin, joints, serosal membranes, etc., that usually start in childhood and are mostly induced by IL-1 β -directed pro-inflammatory cascade. Therefore, monotherapy with blocking IL-1 agents often leads to a reduction in disease severity in most autoinflammatory disorders [4]. Table 1 presents a list of the most recent clinical trials on this group of diseases.

Recent advances in our knowledge on the pathogenesis of many multifactorial polygenic disorders with a presumed auto-inflammatory component have paved the way for the introduction of novel therapeutic modalities. Type 2 diabetes mellitus (T2DM) is profoundly influenced by inflam-masome activation-dependent IL-1 release: high serum concentrations of glucose lead to increased IL-1 β production in human β cells, which is followed by NF- κ B activation, Fas signaling up-regulation, and β cell apoptosis. Different scientists have found that oligomers of islet amyloid polypeptide, a protein deposited in the pancreas of patients with T2DM, might trigger NLRP3 inflammasome, enhancing mature IL-1 β production and resulting in a progressive decrease in the number of β cells [5]. Several studies have also been performed to prove IL-1 blockade as an effective strategy for β cell function and glycemic control [6]. Other evidence derives from the positive effects of a single dose of canakinumab on HbA1c levels [7]. Clinical trials are in progress to determine whether gevokizumab might improve glycemic control in subjects with T2DM in combination with metformin (ClinicalTrials.gov

Interleukin-1 plays a critical role in the complex pathways linking innate and adaptive immune systems

NCT01144975, NCT01066715, NCT00513214) [8]. However, further results are needed to give anti-IL1 agents a role in the management of T2DM.

Patients with idiopathic recurrent acute pericarditis (IRAP) are usually characterized by absence of autoantibodies or self-reactive T cells, and are brilliant responders to IL-1 inhibition [9]. In addition, IRAP may occur in patients with FMF and TRAPS, disclosing the diagnosis of these two autoinflammatory disorders [10], and may also be the only clinical symptom in patients carrying low-penetrance TRAPS-related mutations [11]. A multicenter study evaluating the incidence of TRAPS

mutations in patients with IRAP has demonstrated that positive family history of pericarditis, failure of treatment with colchicine, and need for immunosuppressive agents are crucial diagnostic clues [12]. Fifteen young patients with IRAP were evaluated after treatment with anakinra, revealing a 95% reduction in recurrences [13]. A phase IV study to prove anakinra efficacy in patients with IRAP is ongoing (ClinicalTrials.gov NCT02219828).

Many pro-inflammatory cytokines have a critical role in orchestrating the body's reaction to monosodium urate (MSU) and calcium pyrophosphate dihydrate crystals: both these crystals activate the NLRP3 inflammasome, resulting in intense production of bioactive IL-1 β [14]. Further evidence for the role of IL-1 β in the pathogenesis of gout is shown by the demonstration that IL-1 β receptor-deficient mice are not susceptible to MSU-induced inflammation. Further proof of the concept that IL-1 is basically involved in patients with gout

and pseudogout derives from the favorable results obtained with anakinra in an open-label study [15]. In line with these findings, Vitale et al. [16] recently reported three patients with chronic tophaceous gout unresponsive to standard therapy, in whom anakinra led to remarkable amelioration of joint symptoms within 24 hours. Interestingly, the patients were also affected by T2DM and, along with reduced joint symptoms, also achieved a marked improvement in glycemic control [16]. Moreover, a large study on crystal-induced arthritis demonstrated the superior therapeutic effect of canakinumab and rilonacept as compared to corticosteroids [17,18]. A phase III study testing canakinumab efficacy in the prevention of gout attack recurrence is now ongoing for patients intolerant or unresponsive to colchicine (ClinicalTrials.gov NCT01362608).

Adult-onset Still's disease (AoSD) is a rare inflammatory disorder of undisclosed etiology, characterized by increased pro-inflammatory cytokines in the serum [19] and substantial risk of macrophage activation syndrome which occurs as a severe complication with a higher mortality rate than in children with systemic onset juvenile idiopathic arthritis, the pediatric counterpart of AoSD. Robust evidence on IL-1 involvement in the pathogenesis of AoSD derives from the beneficial effects observed when treating these patients with IL-1 antagonists. Notably, in an open randomized multicenter study in 22 patients with AoSD, monotherapy with anakinra has been effective in those refractory to conventional treatments such as corticosteroids and methotrexate [20]. Also, canakinumab and rilonacept have proven effective in inhibiting IL-1 in AoSD [21,22].

THE MELTING POT OF AUTOIMMUNE DISORDERS

The pathogenesis of rheumatoid arthritis (RA) has actually been related to multiple pro-inflammatory cytokines, such as TNF α and IL-1 β [23], and understanding RA pathophysiological mechanisms has clarified the role of cytokines as new potential targets for biological therapy. In this regard anakinra, alone or in combination with methotrexate, has been evaluated in several controlled studies of patients with RA, improving the disease course and preventing radiological progression of joint damage [24]. A phase II dose-finding study also evaluated the favorable response of canakinumab in patients with active RA despite ongoing methotrexate therapy [25].

The etiology of chronic uveitis remains uncertain, though this condition is the most frequent extra-articular sign of different systemic autoimmune rheumatologic disorders, such as the oligoarticular variant of juvenile idiopathic arthritis, seronegative spondyloarthritis, and Behçet's disease (BD). The inflammatory process leading to uveitis is mainly driven

by Th-17 cells and directed by many pro-inflammatory cytokines, chiefly TNF α and IL-1 β [26]. In fact, anakinra, canakinumab and gevokizumab might suppress immune mediated ocular inflammation not only in animal models but also in different diseases in which severe uveitis is part of the clinical spectrum, such as Blau syndrome, early-onset sarcoidosis, and BD [27-29]. Three multicenter phase III clinical trials are underway to test the safety and efficacy of gevokizumab in treating active non-infectious uveitis (ClinicalTrials.gov NCT01684345), quiescent non-infectious uveitis (ClinicalTrials.gov NCT01747538), and BD-associated uveitis (ClinicalTrials.gov NCT01965145), whereas a phase II clinical trial with gevokizumab is presently being conducted for patients with scleritis (ClinicalTrials.gov NCT01835132).

The pathogenesis of BD is still unknown, and continuous efforts are in progress to characterize its biologic background where genetic and environmental factors cooperate, suggesting that the disease lies probably at the crossroad between autoimmune and autoinflammatory syndromes. The role of innate immunity in BD has been suggested not only by increased levels

Anti-interleukin-1 agents may represent new weapons for treating autoimmune disorders, displaying, like autoinflammatory conditions, self-directed systemic inflammation in genetically predisposed individuals

of IL-1 in both serum and synovial fluid but also by the relevant effect obtained with IL-1 inhibition [30]. A pilot study is currently testing the clinical efficacy of anakinra (ClinicalTrials.gov NCT01441076). Canakinumab

has also shown positive results [31]. Additional evidence for the role of IL-1 β in BD derives from a trial with gevokizumab that has led to complete resolution of intraocular inflammation in both uveitis and retinal vasculitis [32].

Sjogren's syndrome (SS) is characterized by infiltration of mononuclear cells in the salivary and lacrimal glands, leading to dryness of both mouth and eyes. Although its pathogenesis remains unknown, several studies have hypothesized that subverted cytokine pathways might contribute to the pathological setting of the syndrome. Highly increased concentrations of IL-1 have been found in the salivary fluid and peripheral blood of patients with SS, suggesting this cytokine as the master regulator in the development of SS local and systemic manifestations [33]. In addition, an imbalance between salivary IL-1 and IL-1 receptor antagonist (IL-1Ra) most likely promotes the typical inflammatory lesions in the mouth. Some authors have also hypothesized that IL-1 β might display a proteolytic activity, disrupting acinar and ductal gland structure [34]. Anti-IL-1 agents are now regarded as potential treatment tools, and a randomized double-blind placebo-controlled trial has revealed that IL-1 inhibition with anakinra is able to reduce fatigue in patients with SS [35]. Recent data from a prospective double-blind randomized trial also demonstrate that targeting IL-1 by topical application of anakinra reduces dry eye disease-related symptoms [36].

Chronic diffuse interstitial wall inflammation in the lung is the precondition for progressive pulmonary fibrosis, which characterizes all interstitial lung diseases. Alveolar macrophages are involved in different pulmonary inflammatory processes through IL-1 hypersecretion after a host of exogenous and endogenous stimuli [37]. Several studies have revealed the presence of IL-1 β in the pulmonary fibrous tissue, suggesting a causative link between IL-1 and fibrosis [38]. A genetic variability in the IL1RN gene, encoding the physiological IL-1Ra, may also contribute to the pathogenesis of idiopathic pulmonary fibrosis [39]. NLRP3 inflammasome is probably involved in pneumoconiosis [40], and a phase I/II study is underway to test skin gene expression after administration of the IL-1 inhibitor rilonacept in patients with systemic sclerosis (ClinicalTrials.gov NCT01538719), though further studies are required to explore the exact role of IL-1 in the pathogenesis of pulmonary inflammatory processes in their entirety.

CONCLUSIVE REMARKS

This review has shown how the inflammasome works as an activating platform for the release of bioactive pro-inflammatory IL-1 β . Dysregulation in this cascade may be caused by mutations in the genes coding for inflammasomal components and/or their interaction partners, leading to autoinflammatory scenarios. However, the contribution of deregulated inflammasomes to the field of autoimmune disorders, such as RA and SS, was recently suggested and corroborated by the efficacy of IL-1 blockade in these conditions. New avenues for the therapy of such diseases will be paved in the near future and our way of managing these patients will likely be revolutionized.

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