Interleukin-1 as a therapeutic target in systemic-onset juvenile idiopathic arthritis

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Systemic-onset juvenile idiopathic arthritis (SoJIA) represents up to 20% of chronic inflammatory arthritis cases in childhood. The clinical manifestations of this disease are unique compared with other forms of juvenile idiopathic arthritis, and many SoJIA patients do not respond to available therapies, including antitumor necrosis factor agents. It has recently been demonstrated that the serum of SoJIA patients contains an interleukin (IL)-1-inducing factor, and an excess of IL-1β is secreted upon activation of SoJIA leukocytes *in vitro*, suggesting that IL-1 might represent a potential therapeutic target in this disease. Indeed, administration of an IL-1 receptor antagonist induced clinical remission and corrected the laboratory abnormalities in a group of patients who had been refractory to conventional therapies, supporting the idea that IL-1 is an important mediator of the disease.

The term juvenile idiopathic arthritis (JIA) encompasses a heterogeneous group of diseases that are classified according to seven major types of presentation: systemic-onset JIA (SoJIA), polyarticular rheumatoid factor (RF)-negative arthritis, polyarticular RF-positive arthritis, oligoarticular arthritis, psoriatic arthritis, enthesitis-related arthritis and undifferentiated arthritis [1]. SoJIA is unique in terms of clinical manifestations, prognosis and response to available therapies, suggesting that it also has a different pathogenesis.

SoJIA shares many clinical features with periodic fever syndromes, which are spontaneous attacks of systemic inflammation without apparent infectious or other environmental triggers, and have therefore recently been classified as autoinflammatory diseases [2]. Most autoinflammatory diseases are inherited as autosomal mendelian traits, cause fever that follows an intermittent or periodic pattern and involve the skin and joints. The triad of fever, rash and arthritis represents the diagnostic hallmark of SoJIA, but the daily spiking fever and/or the rash may be present in some patients long before the onset of arthritis. Although the symptoms of SoJIA are characteristically more persistent than those of periodic fever syndromes, many SoJIA patients experience an intermittent or polycyclic course with flares and remissions [3]. Similarly to patients with autoinflammatory diseases, SoJIA patients usually lack autoantibodies and autoreactive T cells.

In the past 10 years, the genes responsible for at least nine familial autoinflammatory diseases have been described. These include familial Mediterranean fever (FMF), tumor necrosis factor (TNF)-associated periodic fever syndrome, hyperimmunoglobulin (Ig)D-syndrome, familial cold urticaria (FCU), Muckle–Wells syndrome (MWS), chronic inflammatory neurologic and articular syndrome (CINCA), pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome, familial granulomatous disease (Blau syndrome) and familial Crohn's disease and chronic recurrent multifocal osteomyelitis [4,5]. However, many patients fulfilling diagnostic criteria for some of these diseases do not display mutations in the corresponding genes. For example, no mutations have been identified in up to 50% of patients with clinically diagnosed FCU, MWS or CINCA [6,7].

Strikingly, most of the genes mutated in patients with familial autoinflammatory diseases are related to the inflammasome (pyrin in FMF, cryopyrin/*NALP3* in FCU, MWS and CINCA, and *PSTPIP1* in PAPA) [8]. Mutations in other inflammasome-related genes, such as *NALP1*, are associated with autoimmune diseases that cluster with vitiligo [9], and activation of the inflammasome with contact sensitizers or uric acid crystals appears to trigger the inflammatory cascade underlying contact hypersensitivity and gout/pseudogout, respectively [10,11]. In agreement with the notion that the inflammasome ultimately regulates the secretion of interleukin (IL)-1, blocking this cytokine has emerged as a successful form of therapy for many of these disorders [12–16].

Interleukin-1

Interleukin-1 family

The IL-1 family plays an important role in inflammation and host defense. Up to 11 members of this family have been identified to date (Table 1) [17]. Of those, only five have been

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Table 1. Interleukin-1 family.

Name	Former name	Property	Receptor
IL-1F1	IL-1α	Agonist	IL-1R1, -1R2 and -1RAcP
IL-1F2	IL-1β	Agonist	IL-1R1, -1R2 and -1RAcP
IL-1F3	IL-1Ra	Antagonist	IL-1R1, -1R2 and -1RAcP
IL-1F4	IL-18	Agonist	IL-1R5 and -1R7
IL-1F5	IL-1δ	Unknown	IL-1R6
IL-1F6	IL-1ε	Unknown	IL-1R6
IL-1F7	FIL-1λ and IL-1H4	Unknown	IL-1R5 and -1R7
IL-1F8	FIL-1H and IL-1H2	Unknown	IL-1R6
IL-1F9	IL-1H1 and IL-1RP2	Unknown	IL-1R6
IL-1F10	IL-1Hy2 and FKSG75	Unknown	IL-1R1
IL-1F11	IL-33	Agonist	IL-1R4 (ST2)

IL: Interleukin; RAcP: Receptor accessory protein.

thoroughly studied: IL-1α, -1β, -18, -1Ra and the recently reported -33. The remaining six (IL-1F5, -1F6, -1F7, -1F8, -1F9 and -1F10) have been demonstrated to be expressed in various cell types or tissues, but their functions remain to be determined.

IL-1α and -1β are proinflammatory cytokines. Both are synthesized as precursor molecules (pro-IL1α and pro-IL1β) by many different cell types. Pro-IL1α is biologically active and needs to be cleaved by calpain to generate the smaller mature protein. By contrast, pro-IL1β is biologically inactive and requires enzymatic cleavage by caspase-1 in order to become active. IL-1α is primarily bound to the membrane whereas IL-1β is secreted and thus represents the predominant extracellular form of IL-1 [18,19].

There are two transmembrane IL-1 receptors, types I and II. IL-1RI binds IL-1β and this complex recruits the IL-1-receptor accessory protein (IL-1RAcP), leading to the initiation of the signal. IL-1RII is a decoy receptor. Thus, binding of IL-1β to IL-1RII results in its neutralization. All three receptor molecules, IL-1RI, -1RII and -1RAcP, can be shed from the cell membrane and therefore exist in soluble (s) forms (sIL-1RI, -RII and -1RAcP). sIL-1RII and -1RAcP both function as inhibitors of IL-1-mediated signal transduction by sequestering pro-IL-1β and IL-1R1, respectively. IL-1β bound to IL-1RII may also lead to recruitment of IL-1RAcP, therefore depriving the type 1 receptor of IL-1RAcP [18–20].

IL-1Ra is an endogenous receptor antagonist. It exists as three intracellular (ic) isoforms (icIL-1Ra1, -1Ra2 and -1Ra3) and a secreted isoform (sIL-1Ra). IL-1Ra is predominantly produced by activated monocytes and macrophages. sIL-1Ra binds both type I and type II IL-1 receptors, thereby preventing binding and signal transduction by IL-1α and -1β. The functions of icIL-1Ra remain unclear [18,19].

IL-33 has been recently described as a new member of the IL-1 family. It is produced as a propeptide that requires cleavage by caspase-1 and binds to IL-1R4 (ST2). IL-33 has been shown to stimulate T helper (Th)2 responses [21].

Regulation of IL-1 production & activity

The production and biological activity of IL-1 are regulated at multiple levels, including transcription, translation, cleavage and cellular release.

IL-1α and -1β transcription is induced by a wide array of stimuli, including bacterial and viral products, cytokines and so on. The activation of caspase 1 is mediated by a multiprotein complex known as the inflammasome [22,23]. Two types of inflammasome have been described to date – the NALP1 inflammasome, composed of NALP1, the adaptor protein ASC and caspases-1 and -5, and the NALP2/3 inflammasome that contains NALP2 or -3 (also known as CIAS1 or cryopyrin), as well as the caspase recruitment domain-containing protein cardinal, ASC and caspase-1 [8]. Until recently, the mechanism(s) of activation of this complex remained unknown. CIAS$^{-/-}$ mice have revealed, however, that the NALP3 inflammasome can be directly activated by bacteria (*Listeria monocytogenes* and *Staphylococcus aureus*), the purine analogs R848 and R837, bacterial mRNA, double-stranded/viral RNA and uric acid crystals [10,24–26]. Inflammasome activation leads to the conversion of pro-caspase-1 into caspase-1 and

subsequent cleavage of pro-IL-1β into mature IL-1β [19]. Release of mature IL-1β depends on a second signal provided by the nucleotide P2X7 receptor [27], which can be activated by the human cathelicidin-derived peptide LL37 or ATP, leading to an efflux of potassium from the cell [28]. Potassium efflux is responsible for phosphatidylcholine-specific phospholipase C induction, which in turn allows the rise in intracellular free calcium concentration required for activation of phospholipase A_2. This activation is ultimately responsible for lysosome exocytosis and IL-1β secretion [28,29].

As described above, once IL-1β is released there is a tight regulation of its biological effects by a series of inhibitory molecules, including IL-1Ra, sIL-1RI, -1RII and -1RAcP. Dysregulation of any of these steps might lead to increased IL-1β bioavailability and IL-1-mediated inflammation.

Cytokine dysregulation in SoJIA

From the early 1990s, several proinflammatory cytokines, especially IL-6 and TNF-α, have been postulated to play a role in SoJIA based on the detection of elevated levels in the serum or synovial fluid of these patients [30–38].

IL-6 levels have been shown to be elevated in SoJIA serum and to correlate with disease activity, including the severity of joint involvement, platelet counts, C-reactive protein (CRP) and fever spikes [30,36–38]. Synovial fluid levels of IL-6 are markedly elevated in SoJIA and significantly higher than in patients with oligoarticular JIA or adult rheumatoid arthritis [31].

TNF-α levels have been reported to be increased in all subtypes of JIA. In patients with active SoJIA, circulating levels of TNF-α, sTNFR1 and -2 are significantly higher than in controls [32]. The levels of sTNFR1 and -2, but not those of TNF-α, are associated with the persistence and severity of systemic symptoms [31,32,36,37].

There are controversial reports regarding serum levels of IL-1α and -β in SoJIA patients [33,36–38]. IL-1β, however, may be difficult to detect in the serum as significant amounts of pro-IL-lβ remain inside the cell. Additionally, serum IL-1β binds to large proteins such as β-2-macroglobulin, complement and,the soluble type II IL-1 receptor [18], making its detection difficult. The presence of an IL-1 inhibitor in the sera from febrile SoJIA patients was first reported in 1987 and later identified as IL-1Ra [35]. Indeed, IL-1Ra levels are not only markedly increased in these patients, but significantly correlate with the persistence of systemic features, the extent and severity of joint involvement, and CRP and IL-6 concentrations [33,34,36,37].

An IL-1-inducing factor is present in SoJIA serum

In recent years, blood microarray analysis has proven useful in the identification of pathogenic factors and therapeutic targets in human rheumatic diseases [39,40]. Among its uses, this technique can compare gene expression profiles from patient blood with those induced in healthy blood by the addition of cytokines, patient serum and so on.

Indeed, when healthy blood mononuclear cells are incubated with the serum from active SoJIA patients, IL-1 transcription is upregulated. As expected, IL-1 secretion is also induced in a disease-activity-dependent manner [41]. Thus, sera from patients with systemic symptoms induce more IL-1β secretion than sera from patients in whom the systemic symptoms have subsided. These effects of SoJIA serum on healthy peripheral blood mononuclear cells (PBMCs) are recapitulated *in vivo*, as IL-1β and IL-1RII transcription is also upregulated in the mononuclear cells from the patients during the systemic phase of the disease. Genes induced by IL-1β (i.e., pentraxin 3), or potentially involved in IL-1β secretion (i.e., *KCNJ15* or ATP-sensitive inward rectifier potassium channel 15) are also upregulated in the majority of patients. Furthermore, the mononuclear cells from active SoJIA patients secrete an excess of IL-1β protein upon activation. In the same cultures, IL-6 and TNF production is not significantly different from controls, suggesting a SoJIA-specific dysregulation of the IL-1 pathway [41].

IL-1 dysregulation explains many features of SoJIA

Myeloid cells (neutrophils, monocytes and tissue macrophages) are the main source of IL-1β in response to inflammatory and/or infectious insults. IL-1β induces fever through its direct effect on the hypothalamus. IL-1β can also induce IL-6 secretion, which in turn induces fever. IL-1β and IL-6 affect the bone marrow neutrophil pool and result in a rapid increase of circulating granulocytes, explaining the neutrophilia observed in SoJIA patients. IL-1-induced IL-6 gives rise to acute-phase protein production by the liver, thus explaining the high CRP, serum amyloid A and

ferritin observed in SoJIA patients. IL-1 also acts on the endothelium, possibly explaining the presence of rashes in many IL-1-mediated diseases. Finally, IL-1 plays a role in joint destruction by [18,19,42]:

- Enhancing the proliferation of fibroblasts, leading to pannus formation;
- Activating chondrocytes, leading to cartilage destruction;
- Activating osteoclasts, leading to bone resorption.

Although most manifestations of SoJIA can be explained based on dysregulation of IL-1 production, the origin of such dysregulation remains unknown. Several hypothetical scenarios could be envisioned. First, in SoJIA patients, an unusual microorganism could target an otherwise normal innate immune system, resulting in IL-1 overproduction. The presence of a SoJIA serum factor that induces IL-1 production in healthy PBMCs supports this possibility [41]. There is no epidemiological evidence, however, for clustering of SoJIA cases, which would be expected if an infectious agent was indeed the cause of the disease. Second, SoJIA patients could have alterations in their innate immune system, leading to excessive production of IL-1 in response to common infectious agents. Indeed, polymorphisms in genes associated with pattern-recognition receptors and/or controlling IL-1 production could give rise to such a scenario. In favor of this possibility, nonspecific activation of SoJIA PBMCs *in vitro* results in excessive IL-1β secretion [41]. IL-1β can upregulate its own production and could also, therefore, be responsible for the serum effects described above.

Blocking IL-1 is an effective therapy for SoJIA

As opposed to patients with other types of JIA, many SoJIA patients do not respond to conventional arthritis treatments. For example, only a minority of SoJIA patients respond to nonsteroidal anti-inflammatory drugs (NSAIDs) and some patients also fail to respond to high doses of steroids [43] and/or methotrexate, which are used to control systemic manifestations and arthritis, respectively [44]. In addition, steroids do not alter the long-term prognosis of the disease and have severe side effects. High-dose intravenous Ig has failed to prove effective in a controlled trial [45]. The experience with cyclophosphamide, azathioprine and cyclosporine is anecdotal. Anti-TNF therapy has been demonstrated to be effective in most other types of JIA [46,47], with more than 60% of patients sustaining clinical improvement after 5 years of follow-up. However, children with SoJIA do not respond equally well. No randomized, controlled trials have been performed in SoJIA patients, but in at least three studies that included patients with different types of JIA, the highest rate of treatment failure was observed in SoJIA [48–50]. Even if the interpretation of those studies remains difficult owing to a lack of validated response criteria in SoJIA, it appears that anti-TNF therapies have been less effective in patients with this form of juvenile arthritis.

Based on the observation that the serum of SoJIA patients induces IL-1β production, nine SoJIA patients who had failed conventional therapies were treated with anakinra [41], an available recombinant soluble nonglycosylated homolog of human IL-1Ra that competitively inhibits binding of IL-1α and IL-1β to the receptor type I [20]. Anakinra had been used in large clinical trials of adults and children with rheumatoid arthritis and JIA, respectively, and had proven to be less efficacious than anti-TNF drugs [51]. This drug, however, resulted in improvement and/or resolution of clinical manifestations, hematological and biochemical changes in patients with inherited chronic inflammatory diseases affecting IL-1 production, such as MWS [13], familial cold autoinflammatory syndrome [14], PAPA syndrome [12] and neonatal-onset multisystem inflammatory disease/CINCA [15,52,53]. When administered to SoJIA patients, anakinra treatment resulted indeed in remarkable clinical and hematological responses in seven of the nine SoJIA patients included in the study, and it was accompanied by a steroid-sparing effect [41]. Resolution of clinical symptoms, including fever, marked leukocytosis, thrombocytosis anemia, elevated erythrocyte sedimentation rate and arthritis were rapid and sustained [41]. Two other reports have described an immediate and sustained resolution of symptoms in three SoJIA patients treated with this medication [54,55]. Rapid responses to anakinra have also been described in patients with refractory adult-onset Still's disease [56].

Blockade of other proinflammatory cytokines such as IL-6, which may be downstream of IL-1, is also producing promising results [57–59]. Randomized, placebo-controlled studies in large numbers of patients will help elucidate the value of these novel therapeutic agents in controlling disease manifestations. A summary of all therapeutic options available to SoJIA patients is displayed in Table 2.

Table 2. New therapeutic options for systemic-onset juvenile idiopathic arthritis.

Treatment	Strategy	Results of studies	Ref.
Etanercept®	Neutralization of TNF-α	Limited effectiveness, flares and progressive loss of effectiveness, significant number of nonresponders	[48–50,60]
Infliximab®	Neutralization of TNF-α	Transient control of the systemic features, no improvement of arthritis, significant number of nonresponders	[61–63]
Adalimumab®	Neutralization of TNF-α	Anecdotal reports	
MRA®	Neutralization of IL-6	≥50% Improvement of clinical manifestations and laboratory parameters (anemia, CRP, ESR and leukocytosis) in 18 of 29 patients.	[57,59]
Anakinra	Neutralization of IL-1 receptor	Rapid and sustained resolution of clinical symptoms (fever and arthritis) and laboratory parameters (leucocytosis, thrombocytosis anemia and elevated ESR) in 11 of 13 pediatric patients	[41,54,55]
Thalidomide®	Downregulation of TNF-α, IL-6, IL-1 and nuclear factor-κB	Decrease in disease activity, improvement of laboratory parameters (ESR and anemia), corticosteroid sparing agent; ≥50% juvenile idiopathic arthritis improvement scores were obtained in ten of 13 children	[64]
Atorvastin®	Downregulation of TNF-α, IL-6, IL-8 and MHC class II	One case with dramatic improvement of functional status, clinical and laboratory manifestations; safety profile unknown	[65]

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL: Interleukin; MHC: Major histocompatibility complex; TNF: Tumor necrosis factor.

Conclusion & future perspective

SoJIA shares many clinical and laboratory features described in familial autoinflammatory diseases. IL-1β dysregulation, a cardinal feature of several of these diseases, can be traced to mutations in genes encoding proteins within or interacting with the inflammasome. Similar to what is observed in SoJIA, high levels of IL-1β are not, however, present in the serum of patients with autoinflammatory diseases, and *in vitro* activation of innate immune cells from the patients is required in order to detect the excessive production of IL-1β. Patients with autoinflammatory diseases respond clinically to anakinra treatment [12–15] and their serum IL-6 levels subsequently fall [14]. The ability of anakinra to improve the clinical manifestations and laboratory changes of SoJIA patients supports that IL-1 plays a central role in this disease as well.

Even if anakinra has shown remarkable clinical and hematological responses in SoJIA patients, it remains a suboptimal IL-1 inhibitor. Indeed, this drug has a short half-life and necessitates daily injections. Other IL-1 inhibitors, such as IL-1 Trap (an inhibitor of IL-1 consisting of the Fc portion of human IgG1 and the extracellular domains of IL-1R1 and IL-1RAcP), are being tested in clinical trials, and neutralizing human monoclonal antibodies to IL-1β are also being developed.

An important remaining challenge is to determine what causes IL-1 dysregulation in SoJIA. Another important question is whether excessive IL-1 production explains the disease in all versus a subset of SoJIA patients. Indeed,

Executive summary

- Systemic-onset juvenile idiopathic arthritis (SoJIA) represents approximately 20% of juvenile idiopathic arthritis.
- The disease is unique in terms of clinical manifestations and severity of joint involvement.
- Serum interleukin (IL)-6, tumor necrosis factor-α and IL-1Ra levels have been shown to be elevated in SoJIA and to correlate with disease activity whereas IL-1 levels remain controversial.
- Serum of SoJIA patients up-regulates the expression of IL-1α, IL-1β and other innate immunity genes in healthy peripheral blood mononuclear cells (PBMCs).
- The PBMCs from SoJIA patients produce an excess of IL-1β upon activation.
- Anakinra has shown remarkable clinical and hematological responses in SoJIA patients, supporting that IL-1 plays a central role in SoJIA pathogenesis.

patients with similar clinical symptoms may have distinct underlying immune alterations and only large multicentric clinical trials with IL-1 blockers will help elucidate the heterogeneity of the disease. Finally, even if new efficient therapies are becoming available, an important remaining challenge is the development of a specific diagnostic test. Availability of such a test would permit the prompt initiation of effective treatment as soon as the first symptoms of inflammation appear. This might be the best way to prevent the development of arthritis and long-term disabilities.

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