



Review article

Targeting IL-1 β in disease; the expanding role of NLRP3 inflammasome

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ABSTRACT

NLRP3 inflammasome activation and IL-1 β secretion have recently emerged as a central mechanism in the pathogenesis of disease. Genetically defined syndromes like cryopyrin-associated periodic syndromes (CAPS, cryopyrinopathies) and familial Mediterranean fever (FMF) or diseases associated with NLRP3 activation by danger signals like gout, pseudogout, Alzheimer's disease or type 2 diabetes are included in this group of diseases. The contribution of anakinra, a recombinant, nonglycosylated human IL-1 receptor antagonist, in both the identification and treatment of such syndromes was considerable. Recently, rilonacept, a long-acting IL-1 receptor fusion protein, and canakinumab, a fully humanized anti-IL-1 β monoclonal antibody, have been developed, with the intention to further extent IL-1 β inhibition treatment strategies to a broader spectrum of disorders beyond the characterized autoinflammatory syndromes, offering a more favorable administration profile. On the other hand, the developed caspase-1 inhibitors, even though effective in experimental models, were not proven efficient in the treatment of inflammatory diseases.

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1. Introduction

The innate immune system is assigned to recognize and encounter bacterial and viral infections. Recently, nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) have emerged as key players for the proper accomplishment of this process through recognition of pathogen associated molecular patterns or PAMPs [1]. Except from PAMPs, NLRs also sense endogenous stress signals known as damage associated molecular patterns or DAMPs [1,2]. NLR dependent recognition of either exogenous or endogenous danger signals initiates the recruitment of adaptor proteins and the formation of molecular platforms referred to as inflammasomes [1,2]. The subsequent activation of caspase-1 results in the post-transcriptional, proteolytic modulation of the related cytokines interleukin-1 β (IL-1 β), IL-18 and probably IL-33 from their precursor to their active and secreted form, enhancing the inflammatory process. Among several NLRs that form inflammasome platforms, the most studied are NALP1, NALP3 (NLRP3) and IPAF [1,2].

2. NLRP3 inflammasome and IL-1 β in disease

The identification of the critical role of NLRP3 inflammasome in the maturation of the above mentioned cytokines, motivated the study of its role in the pathogenesis of several syndromes. The term IL-1 β

dependent autoinflammatory syndromes has been adopted for such syndromes. This group of diseases is characterized by defective regulation of innate immune response and the absence of autoantibodies or antigen-specific T cells [3].

Dysregulation of NLRP3 inflammasome due to mutations in inflammasome related genes has been implicated in the pathogenesis of cryopyrin-associated periodic syndromes (CAPS, cryopyrinopathies), familial Mediterranean fever (FMF) and the pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA) (Fig. 1) (Table 1). In addition, NLRP3 inflammasome activation by danger signals (Fig. 2) like monosodium urate (MSU), calcium pyrophosphate dihydrate (CPPD), amyloid-beta, glucose or silica and asbestos, either directly or by common intracellular mediators [2], is proposed as a key molecular mechanism in a group of disorders like gout, pseudogout, Alzheimer's disease, pulmonary fibrosis or even type 2 diabetes mellitus (T2DM) (Fig. 1) [3].

2.1. Genetically defined NLRP3 inflammasome related syndromes

CAPS, including familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and neonatal-onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous articular (CINCA) syndrome are disorders with a direct implication of inflammasome in pathogenesis due to identified mutations in the *NLRP3* gene [4–6]. *NLRP3* mutations are gain-of-function mutations that lead to constitutive NLRP3 inflammasome activation and pro-IL-1 β processing [4]. Another autoinflammatory syndrome associated with NLRP3 inflammasome dysregulation is FMF. This disorder is characterized by mutations in the *MEFV* gene, that encodes the protein pyrin [7]. IL-1 β has been implicated in the

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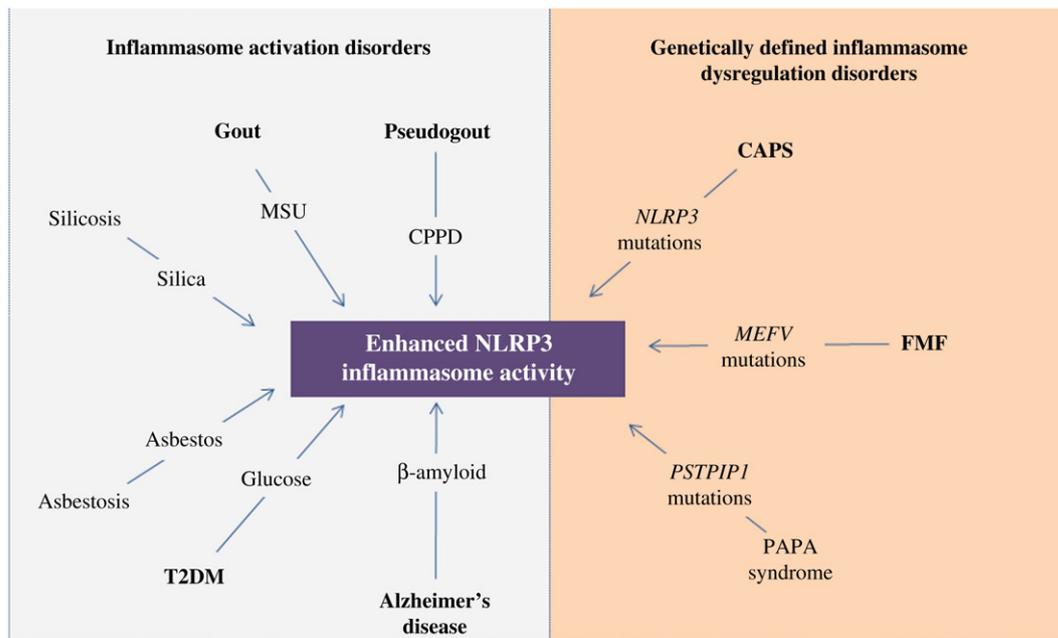


Fig. 1. The spectrum of NLRP3 inflammasome-dependent disorders. NLRP3 inflammasome activation by either endogenous or exogenous danger signals results in increased IL-1 β processing and it is implicated in the pathogenesis of a group of disorders. Moreover, mutations in NLRP3 inflammasome-related genes is suggested to result in NLRP3 inflammasome dysregulation and inflammation that characterizes this group of syndromes.

pathogenesis of the disease, as soon as experimental systems have proposed a central role for pyrin in the regulation of NLRP3 inflammasome, through protein interactions with ASC adaptor protein and caspase-1 (Fig. 2) [8,9]. Moreover, PAPA syndrome is caused by mutated PSTPIP1/CD2BP1 protein. This protein interacts with pyrin. PAPA-associated mutations result in increased binding capacity of PSTPIP1 to pyrin and exert a negative effect in the previously mentioned role of pyrin [10]. In consistence with this observation, peripheral blood monocytes (PBMCs) from a patient with PAPA syndrome and cell lines transfected with such mutations produce higher levels of IL-1 β [10], providing an association between this syndrome and NLRP3 inflammasome.

Table 1
Implication of NLRP3 inflammasome in the pathogenesis of IL-1 β activation syndromes.

Disease	Implication of NLRP3 inflammasome	Pathogenic mechanism related to NLRP3 inflammasome
Cryopyrin-associated periodic syndromes (CAPS)	Direct	<i>NLRP3</i> gene mutations
Familial Mediterranean fever (FMF)	Indirect	<i>MEFV</i> gene mutations
Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA)	Indirect	<i>PSTPIP1</i> gene mutations
Gout/pseudogout	Direct	NLRP3 inflammasome activation by MSU/ CPPD ^a crystals
Hyperimmunoglobulinemia D/periodic fever syndrome (HIDS)	Unknown	<i>MVK</i> ^b gene mutations/IL-1 β overproduction
Systemic juvenile idiopathic arthritis (SoJIA)	Unknown	Unknown
Adult onset Still disease (AoSD)	Unknown	Unknown
Fibrosing disorders	Possible	NLRP3 inflammasome activation by asbestos/silica
Alzheimer's disease	Possible	NLRP3 inflammasome activation by amyloid- β
Deficiency of interleukin-1-receptor antagonist syndrome (DIRA)	None	<i>IL1RN</i> gene mutations

^a Monosodium urate/calcium pyrophosphate dehydrate.

^b Mevalonate kinase.

2.2. Disorders characterized by NLRP3 inflammasome activation

Except from the above genetically defined syndromes, several disorders have been associated with NLRP3 inflammasome activation by host-derived or external danger signals. Experimental models suggest that NLRP3 inflammasome-dependent recognition of MSU and CPPD crystals and subsequent increased pro-IL-1 β maturation in macrophages [11] play a key role in the pathomechanism puzzle of gout and pseudogout. To further provide evidence for the proposed role of IL-1 β in the pathogenesis of gout, mice deficient in IL-1 β receptor and in MyD88, an adaptor molecule that transduces Toll-like receptor (TLR) and IL-1 signaling, were not susceptible to MSU initiated inflammation [12]. Concerning Alzheimer's disease, it has been reported that increased IL-1 β secretion by mouse microglial cells through amyloid-beta-dependent NLRP3 inflammasome activation is important for the inflammation and tissue damage that characterizes this syndrome [13]. NLRP3 inflammasome activation by asbestos or silica has been further associated with the pathogenesis of the pulmonary fibrotic disorders, asbestosis and silicosis [14]. Of interest, there is growing evidence for the implication of NLRP3 inflammasome-dependent IL-1 β secretion in the pathogenesis of T2DM. Experimental data suggest that glucose is able to increase IL-1 β secretion in the insulin-secreting pancreatic islets, resulting in pancreatic β -cell apoptosis and diminished insulin secretion [15]. Glucose-dependent IL-1 β maturation has been recently linked to thioredoxin-interacting protein (TXNIP), a protein associated with insulin resistance and NLRP3 inflammasome activation [15,16]. More specifically, chronic hyperglycemia is proposed to result in reactive oxygen species (ROS) production, while glucose induces TXNIP expression. The enhanced ROS production causes dissociation of TXNIP from thioredoxin and subsequent binding of TXNIP to NLRP3 that results in inflammasome activation [15,16].

2.3. Other IL-1 β associated inflammatory syndromes

Several inflammatory disorders have been suggested to be IL-1 β associated based on reports indicating favorable outcome after IL-1 blockade with anakinra in the disease course. However, the role of NLRP3 inflammasome in the pathogenesis of the above syndromes has not been elucidated yet. Hyperimmunoglobulinemia D/periodic

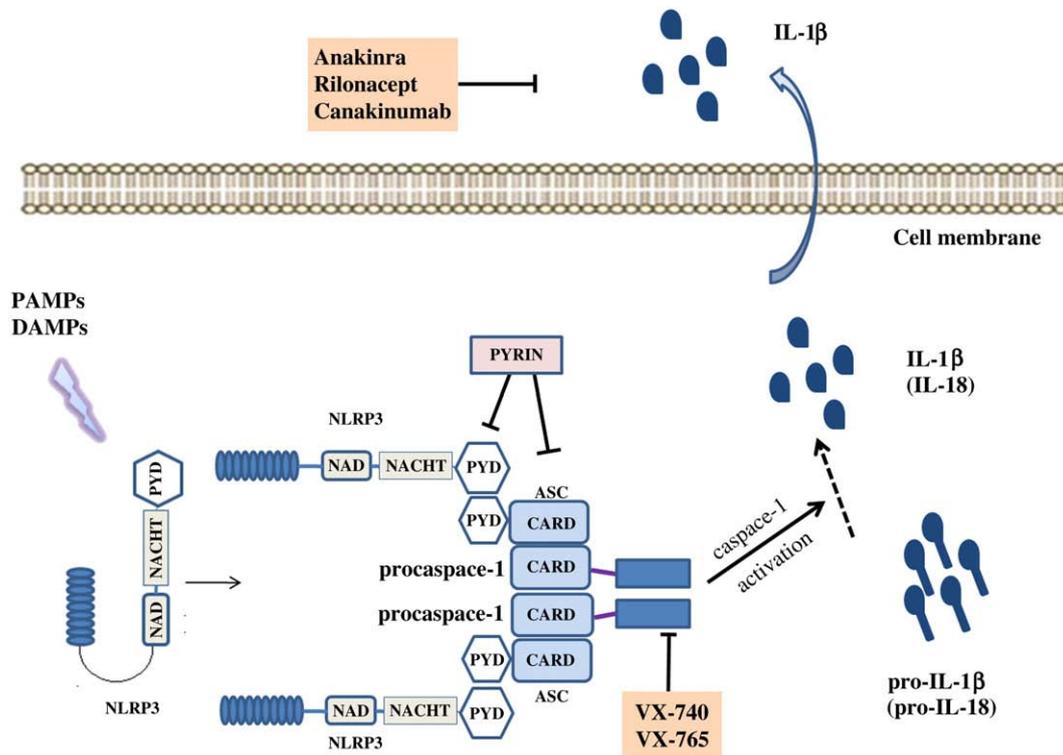


Fig. 2. NLRP3 inflammasome function and developed inhibition strategies. Ligand sensing of PAMPs or DAMPs by NLRP3 results in the recruitment of the adaptor protein ASC and procaspase-1 due to homotypic interactions of the effector domains, pyrin domain (PYD) or caspase recruitment domain (CARD). The subsequent activation of caspase-1 results in increased IL-1 β and IL-18 secretion due to increased proteolytic maturation of pro-IL-1 β and pro-IL-18. Pyrin is suggested to inhibit inflammasome activation through interactions with ASC and caspase-1. Administration of VX-740 and VX-765 inhibits NLRP3 inflammasome function at caspase-1 level, while anakinra, rilonacept and canakinumab act extracellularly by preventing IL-1 receptor activation. (ASC, apoptosis-associated speck-like protein containing a CARD; NACHT, domain present in NAIP, CIITA, HET-E and telomerase-associated protein; NAD, NACHT-associated domain).

fever syndrome (HIDS), Schnitzler syndrome and Behçet's disease are autoinflammatory syndromes that could be included in this group of disorders [3]. The deficiency of interleukin-1-receptor antagonist syndrome (DIRA), caused by mutations in the gene encoding the interleukin-1-receptor antagonist (*IL1RN*), is also directly associated with IL-1 β [17,18], but not with NLRP3 inflammasome.

Except from these IL-1 β -associated autoinflammatory syndromes, IL-1 β has been implicated in the pathogenesis of a variety of diseases like systemic-onset juvenile idiopathic arthritis (SoJIA) [19,20], adult onset Still disease (AoSD) [20], rheumatoid arthritis (RA) [21], Crohn's disease or Blau syndrome [3].

Concerning SoJIA, even though there are controversial experimental data for the ability of PBMCs from patients suffering from this disorder to produce high levels of IL-1 β upon activation [19,20], the efficacy of IL-1 inhibitors suggests an implication of this cytokine in the pathogenesis of the disease.

Concerning RA there is no concluding data for the implication of NLRP3 inflammasome activity in inflammation at rheumatoid synovium [22], even though genetic variations of inflammasome related genes have been correlated with the severity of the disease [23].

Crohn's disease [24] and Blau syndrome [25] are disorders that are characterized by granulomatous inflammation and have been associated with genetic variations in Nod2 that results to enhanced NF κ B activity [26]. Despite the proposed role for NF κ B in the increased expression of IL-1 β gene, neither increased IL-1 β secretion from PBMCs from patients with Blau syndrome after TLR and Nod2 activation was observed [27] nor efficacy of IL-1 inhibition in the treatment of these disorders has been reported. Interestingly, the identification of polymorphisms in the autophagy related *ATG16L1* gene as a risk factor for Crohn's disease [24] possibly links IL-1 β maturation with Nod2, autophagy and NLRP3 inflammasome. More specifically, in experimental models Nod2 has been suggested to

modulate autophagy in a ATG16L1-dependent manner, while cells homozygous for Crohn's disease-related mutations fail to accomplish this role [28,29]. Moreover, ATG16L1 deficiency results in NLRP3 inflammasome-dependent secretion of IL-1 β after stimulation with endotoxin due to impaired induction of autophagy [30]. The pathogenic role of the Nod2/autophagy system in the IL-1 β maturation in Crohn's disease needs further investigation.

The periodic fever with aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome is a relatively common periodic fever syndrome in childhood and its etiology is unknown. Even though it is characterized by elevated IL-1 β , TNF α and IL-6 during attacks [31], a pathogenic role for IL-1 β has not been proven.

3. Strategies for inflammasome targeting in disease

The proposed key pathogenic role for IL-1 β dysregulation in the inflammatory process provided the rationale for inflammasome targeting strategies (Fig. 2). Even though both IL-1 β blockade and caspase-1 inhibition have been suggested in order to inhibit the effect of inflammasome hyperactivity, IL-1 β blockade strategies are used in clinical practice.

4. IL-1 inhibitors

Currently, the developed IL-1 inhibitors are anakinra, a recombinant IL-1Ra; rilonacept, a 'cytokine trap'; and canakinumab, a monoclonal anti-IL-1 β antibody (Table 2).

4.1. Anakinra

Anakinra (KineretTM) is the first IL-1 inhibitor designed and it was approved by the FDA in 2001 for the treatment of patients suffering

Table 2
IL-1 blockade agents in clinical use.

Biologic agent	Pharmacology	Targeted cytokine	Administration	Adverse reactions
Anakinra	Recombinant human IL-1 receptor antagonist (rhIL-1Ra)	IL-1 α IL-1 β	Subcutaneously, 100 mg once daily	Injection site reactions, upper-respiratory tract infections, cases of localized herpes, varicella and leishmaniasis, acute hepatitis (3 cases)
Rilonacept (IL-1 Trap)	Dimeric protein consisting of the extracellular portion of the IL-1 receptor and the Fc portion of human IgG1	IL-1 α IL-1 β	Subcutaneously, 320 mg loading dose followed by 160 mg once weekly	Injection site reactions, upper respiratory tract infections
Canakinumab (ACZ885)	Humanized monoclonal anti-IL-1 β antibody	IL-1 β	Subcutaneously, 150 mg every 8 weeks	Upper respiratory tract infections

from moderate to severe RA, unresponsive to the treatment of at least one disease modifying anti-rheumatic drug (DMARD) therapy. It is the recombinant, nonglycosylated form of human IL-1 receptor antagonist thus acting as a competitive inhibitor of IL-1 α and IL-1 β binding to IL-1 receptor [32]. Anakinra is administered subcutaneously once daily, due to its short half-life. Injection-site reactions and upper respiratory tract infections are the primarily reported adverse events. Localized herpes, varicella and leishmaniasis infections have been also reported in patients receiving anakinra [33]. Recently, anakinra has been implicated in the occurrence of acute hepatitis in three patients with SoJIA [34].

4.2. Rilonacept (IL-Trap)

Rilonacept (IL-1Trap/Arcalyst™) is a dimeric fusion glycoprotein, consisting of the Fc portion of human IgG1 and the human IL-1 receptor (IL-1RI and IL-1 receptor accessory protein) extracellular domains [35,36] that received FDA orphan drugs approval for the treatment of FCAS and MWS in 2008. It binds with high affinity and neutralizes both IL-1 α and IL-1 β . It is also administered subcutaneously once weekly due to the longer half-life of rilonacept compared to anakinra, while presenting a comparable safety profile and being well tolerated [36,37].

4.3. Canakinumab (ACZ885, Ilaris™)

Canakinumab (ACZ885) is a fully humanized monoclonal antibody against IL-1 β , offering high specificity for IL-1 β and relative longer half-life [38]. The latter permits the subcutaneous administration of the drug every 8 weeks in order to achieve suppression of inflammation, as suggested by pharmacokinetic and clinical studies. Canakinumab has been proven well tolerated and safe as it concerns the occurrence of injection site reactions and serious infectious adverse events [39].

5. Clinical trials and experience

5.1. Cryopyrin-associated periodic syndromes

Three distinct but genetically and phenotypically related rare disorders caused by autosomal dominant or de novo mutations of *NLRP3* are included in this group. From mild to severe, the cryopyrinopathies encompass FCAS, a disorder that presents with cold-induced fevers, urticaria-like rash and systemic inflammation; MWS, characterized by unrelated to cold exposure fever, arthritis, rash and sensorineural hearing loss that prior to treatment with IL-1 β inhibitors was leading to amyloidosis in 25% of patients; and NOMID or CINCA that presents with neonatal onset fevers, urticaria-like rash, bone deformities, chronic aseptic meningitis and mental retardation [3].

Several clinical studies indicate the remarkable efficacy of anakinra in CAPS, resulting in clinical remission and improved laboratory inflammatory markers like ESR, CRP and serum amyloid A [40–46]. In addition, stabilization or improvement in hearing in patients with MWS and NOMID/CINCA receiving anakinra has been reported, especially when treatment was initiated early in the disease course [42,43,46]. Reduction

of splenic amyloid deposition, resolution of amyloidosis dependent renal dysfunction and restoration of spermatogenesis in two patients with amyloidosis have been observed [44,45]. The efficacy of IL-1 inhibition with anakinra in CAPS has been further demonstrated by the rapid, within days, regression of clinical findings after withdrawal of treatment and the remission achieved after re-initiation of anakinra [40,42]. Rilonacept has been demonstrated to be effective and well tolerated in phase III clinical studies when administered once weekly in patients suffering from FCAS and MWS (44 and 3 patients respectively) and received as a result FDA 'orphan drug' approval [36,37]. The efficiency of canakinumab in the treatment of CAPS, in every 8 weeks administration, has been recently reported, offering a selective and promising IL-1 β blockade strategy. Treatment with canakinumab resulted in immediate and lasting disease remission, with a median time until disease flare of 100 days, in all 15 patients [39].

5.2. SoJIA and AoSD

SoJIA and AoSD are systemic inflammatory syndromes that share common clinical characteristics like fever, rash, arthritis, serositis and elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and serum ferritin levels. Long-lasting corticosteroid treatment even though effective causes several severe complications like growth retardation and bone demineralization. As a result, corticosteroid sparing strategies using disease-modifying anti-rheumatic drugs (DMARDs) like methotrexate or TNF α inhibitors have been developed without sufficient efficacy [47].

Several groups have reported the effectiveness of anakinra in the majority of patients suffering from AoSD and in a significant proportion of patients with SoJIA, unsuccessfully treated with DMARDs or even anti-TNF α , implicating inflammasome activation in the pathogenesis of these disorders [19,20,33,48–53]. Moreover, Gattorno et al. distinguished two subgroups of SoJIA patients according to anti-IL-1 response; the first subgroup consists of approximately 40% of patients that exhibited dramatic and lasting response to anakinra with no need of adjunctive therapy, while the second subgroup consists of patients that partially responded to IL-1 inhibition and remained steroid or second-line agent dependent and non-responders. This observation may suggest heterogeneity in SoJIA pathogenesis, proposing a central role for inflammasome at least in the first subgroup [20]. In conclusion, IL-1 blockage is an effective and promising treatment strategy for patients with SoJIA and AoSD, minimizing the need for corticosteroid administration and the resultant serious side effects.

5.3. Gout and pseudogout

Gout and pseudogout are common inflammatory diseases characterized by deposition of MSU and CPPD crystals respectively in the joints and periarticular tissue, leading to acute attacks or chronic arthritis. The treatment of choice for acute inflammatory attacks includes non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and colchicine [54]. This type of medication increases the risk of cardiovascular, gastrointestinal or renal complications, especially in

older people, rendering necessary the development of alternative treatment strategies.

Based on the proposed role of NLRP3 inflammasome in MSU recognition, anakinra was administered with favorable results for the treatment of acute gouty attacks, especially in patients without tophaceous arthritis [55–57], while rilonacept is reported to suppress chronic gouty arthritis, further reinforcing the above statement [58]. Concerning pseudogout, prevention of acute attacks by anakinra has been reported in a case of end stage renal patient [59].

5.4. Familial Mediterranean fever

FMF is an autoinflammatory syndrome prevalent in the Mediterranean basin [60], which is characterized by recurrent febrile attacks accompanied by polyserositis which may be complicated by secondary amyloidosis. Even though colchicine is the well-established and effective treatment for FMF, 5–10% of patients are non-responders or do not tolerate this standard treatment.

Several reports suggested that IL-1 inhibition with anakinra is effective in the prevention of FMF attacks [9,61–64], while a single report demonstrated effectiveness in the resolution of disease flares [65], offering an adjunctive to colchicine treatment. Of great interest would be the effect of the treatment with IL-1 inhibitors in preventing the development of AA amyloidosis, as observed in the case of cryopyrinopathies and in a patient with FMF and Behçet's disease [66]. Alternatively, the use of the specific anti-IL-1 β antibody canakinumab in the prevention and resolution of FMF attacks may reinforce the suggested implication of impaired inflammasome regulation in the pathogenesis of the disease, in contradistinction to the non-specific IL-1 inhibition by anakinra. Concluding, even though IL-1 inhibition has no such dramatic results in FMF as in CAPS and colchicine remains an effective, inexpensive and well tolerated drug, IL-1 targeting strategies currently enrich the therapeutic arsenal for the intriguing, resistant to colchicine subgroup of FMF patients.

5.5. Rheumatoid arthritis (RA)

Biologic agents have been recently become the cornerstone in the treatment of RA in patients that inadequately responded to standard DMARDs. Anakinra, originally developed and approved for the treatment of moderate to severe RA, even though promising, was proven moderately effective, especially when compared to other biologic agents like TNF α inhibitors, Tocilizumab or Rituximab [67]. Moreover, co-administration of anakinra with etanercept did not offer any additional advantage compared to etanercept alone, while it increased the risk for serious infections [68]. The modest effectiveness and the daily use of anakinra precluded the widespread introduction of the agent in the treatment for RA. Clinical trials using canakinumab are ongoing, trying to gain a role for IL-1 inhibition in the treatment of this disease, if proven successful, and offer an additional targeted therapy.

5.6. Type 2 diabetes mellitus (T2DM)

Peripheral insulin resistance accompanied by the additional impairment in pancreatic β -cell function participates in the pathogenesis of T2DM. During the time course, pancreatic β -cell apoptosis results in decompensation in insulin secretion, a process that depends at least in part on intra-islet IL-1 β production [15]. A possible preservation of islet function through inhibition of apoptosis would offer a significant delay in disease course. These observations prompted the use of anakinra in a double-blind clinical trial in 70 patients with T2DM, with a concomitant improvement in β -cell secretory function and glycemia after 13 weeks [69]. Recently, the same group reported sustained improvement in β -cell function and inflammatory markers for 39 weeks after treatment withdrawal [70]. Even though the short duration of the study hinders the extraction of definitive conclusions for the efficiency of IL-1 in

controlling serum glucose concentrations and preventing complications of diabetes, this study was the springboard for the evaluation of innate immunity interventions in the treatment of diabetes mellitus. Ongoing clinical trials evaluating the efficacy of canakinumab in the treatment of type 1 diabetes after 12 months of treatment and type 2 diabetes, as an additive to metformin agent, with a trial duration of 24 to 48 after a 4 month dose ranging period, will provide data for the long term effect of IL-1 β inhibition in achieving optimal glucose levels.

5.7. Other autoinflammatory syndromes

The effectiveness of anakinra in several other autoinflammatory disorders has been reported in case-communications. Anakinra controlled both the frequency and severity of febrile attacks when administered to patients suffering from HIDS [71,72]. Administration of this agent to patients suffering from Schnitzler syndrome was successful, raising queries for the classification of this disorder, characterized by monoclonal IgM, urticaria, intermittent fever and arthralgia, in the autoinflammatory diseases group [73–76]. Several cases reported the efficacy of IL-1 inhibition in the treatment of patients with Behçet's disease [66,77] and in the treatment of pyoderma gangrenosum and arthritis flares in patient with PAPA syndrome [78,79]. Even though TNF- α inhibition is the treatment of choice in patients with TRAPS, anakinra has been proven effective in five patients requiring high doses of steroids and in two patients resistant to TNF- α blockade treatment [80,81]. Recently, two separate groups described an autoinflammatory syndrome with neonatal onset skin and bone involvement caused by mutations in the *IL1RN* gene encoding the interleukin-1-receptor antagonist [17,18]. Treatment with anakinra completely resolved the manifestations of the disease. Furthermore, a patient with severe idiopathic cold urticaria who did not carry mutations in NLRP3 was successfully treated with anakinra [82]. This agent was also proven effective in patients suffering from idiopathic recurrent pericarditis, an inflammatory syndrome of undefined origin [83].

6. Caspase-1 inhibitors

In order to limit the biological effect of caspase-1 and the subsequent enhanced IL-1 β and IL-18 maturation, small molecular inhibitors of the active site of caspase-1 have been developed. Several caspase-1 inhibitors have been used in experimental models but clinical trials were only conducted for pralnacasan (VX-740) and VX-765. Clinical trials for the use of pralnacasan in RA, psoriasis and osteoarthritis have been discontinued due to liver abnormalities observed in animal toxicology models in prolonged and high dose medication schedules [84]. Concerning VX-765, a phase II clinical trial for the evaluation of its safety and tolerability in subjects with chronic plaque psoriasis treated for 28 days was completed in 2005, but the study results were never reported [84]. Even though ex vivo inhibition studies using VX-765 in peripheral blood monocytes from patients suffering from CAPS reported blockade of excess IL-1 β and IL-18 production [85], its efficacy in treating patients with this syndrome has not been confirmed. The possible development of such molecular inhibitors with favorable safety profile could offer an alternative in the treatment of inflammatory disorders if proven effective.

7. Concluding remarks

Dysregulation of NLRP3 inflammasome, as demonstrated for cryopyrinopathies and proposed for FMF and PAPA syndrome, or activation by endogenous or exogenous danger signals, as suggested for gout, gains a critical role in the better understanding of disease pathogenesis, offering a target for therapeutic interventions.

IL-1 inhibition consists in a novel strategy for the treatment of an increasing spectrum of diseases. It has been proven a revolutionary

approach for the management of the disease activity in patients with cryopyrinopathies or DIRA, while offering favorable results in several other above mentioned disorders. Except from the family of autoinflammatory syndromes, IL-1 is a key cytokine implicated in the pathogenesis of several disorders. As a result, IL-1 inhibition is currently studied in disorders like idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, osteoarthritis, atherosclerosis, post-infarction remodeling, cardiovascular and chronic kidney disease or even malignant diseases like smoldering or indolent myeloma and metastatic cancer expressing IL-1 gene. The development of the novel members of the IL-1 inhibitors family will offer advantages. The daily subcutaneous injection of anakinra, in addition to frequent injection site reactions that may lead to discontinuation is a disadvantage not existing with the latter developed agents. Furthermore, the specific blockade of IL-1 β by canakinumab breaks new ground for the study of the implication of NLRP3 inflammasome in disease.

8. Learning points

- NLRP3 inflammasome constitutes a high molecular complex that regulates IL-1 β secretion, while it is implicated, directly or indirectly, in a wide group of disorders.
- IL-1 β dependent autoinflammatory syndromes constitute a group of disorders characterized by defects in essential inflammasome proteins or inflammasome regulatory elements.
- IL-1 inhibitors constitute an effective and well tolerated therapeutic approach for the treatment of such syndromes.
- Except from anakinra, a recombinant IL-1 receptor antagonist, canakinumab and rilonacept have been recently developed for the inhibition of IL-1 β .

Conflict of interest

The authors declare no financial or commercial conflict of interest.

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