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Targeting the Inflammasome in Rheumatic Diseases

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Abstract

Activation of the inflammasome, a protein complex responsible for many cellular functions, including the activation of the pro-inflammatory cytokines IL-1β and IL-18, has been identified as a key participant in many rheumatic diseases including autoimmune, inflammatory and autoinflammatory syndromes. This review will discuss the recent advances in understanding the role of this complex in various rheumatic diseases. Further, it will focus on available therapies which directly and indirectly target the inflammasome and its downstream cytokines to quiet inflammation and possibly dampen autoimmune processes.

Introduction

Over the past few decades, the treatment of rheumatic diseases has evolved from blanket suppression of inflammation with medications like glucocorticoids to specific targeting of inflammatory pathways with sophisticated biologic therapies. This therapeutic revolution has dramatically improved a physician's armamentarium and patient outcomes. One inflammatory complex, termed the inflammasome, has been an exciting area of investigation in rheumatic disease. Targeting of this complex and its downstream cytokines has resulted in several FDA approved therapies, and more indications are in the pipeline. This review will summarize the mechanisms by with the inflammasome is involved in rheumatic disease and describe the impact targeting the inflammasome has had on patient care for autoimmune and autoinflammatory diseases.

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The inflammasome

The inflammasome is a signaling platform which, when activated, results in the oligomerization and activation of inflammatory caspases. Caspase-1 is the quintessential inflammatory caspase and is the primary enzyme responsible for cleavage and activation of interleukin-beta (IL-1β) and IL-18, (reviewed in (1)). Various "danger signals," including cellular stress, microbial products and crystalline material can trigger inflammasome activation. Some inflammasome activators, particularly during intracellular infections, may also result in an inflammatory form of cell death, termed pyroptosis(2). The inflammasome platform utilizes a central scaffold, such as NOD-like receptor (NLR) family members to assemble after activation. NLRP3 is the best characterized member of this family and is activated downstream of many physiologically relevant inflammatory triggers. NLRP3 interacts with an adaptor molecule, apoptosis-associated speck-like protein containing a CARD (ASC), which then interacts with the CARD domain on caspase-1, resulting in caspase-1 oligomerization and activation (reviewed in(3), summarized in Figure 1). Other inflammasome scaffolds not related to the NOD-like receptor also serve similar functions in inflammasome assembly but their triggers for activation primarily include cytosolic nucleic acids. These include Absent in Melanoma 2 (AIM2), IFN-γ inducible protein 16 (IFI16) and retinoic acid inducible gene I (RIG-I)(4). Intriguingly, these proteins also contribute to cellular antiviral responses, which may integrate inflammation and chronic interferon production in certain autoimmune diseases (3).

Because of its important inflammatory role, inflammasome activity is tightly regulated at multiple levels. Priming or "signal 1", typically via NFκB activation by toll-like receptor (TLR) ligands, stimulates NLRP3 and IL-1β transcription and prepares the cell for a vigorous response upon activation (5, 6). De-ubiquitination of NLRP3 has also been reported as an important intermediate step for inflammasome priming(7). Subcellular compartmentalization contributes to inflammasome regulation, and anti-inflammatory signals may block inflammasome assembly by preventing co-localization of inflammasome components(8). Other adaptor and signaling molecules, such as caspase 8, also participate in inflammasome regulation (reviewed in(9)). Ultimate assembly and activation of the inflammasome requires ligands specific for different inflammasome scaffolds or cellular metabolic changes. These "signal 2" stimuli are as diverse as bacterial peptidoglycans, crystalline materials, oxidative stress and nucleic acids (10–13).

Targeting Inflammasome Activation *in vivo*

Thus far, medications used to target the inflammasome have primarily focused on inhibition of the pro-inflammatory cytokine IL-1β (see Table 1). IL-18 blockade is feasible, but trials in rheumatic diseases have not yet been undertaken for this target. Current approved medications include anakinra, a soluble receptor antagonist for IL-1R1, rilonacept, a soluble IL-1 receptor with preference for IL-1β>IL-1α, and canakinumab, a neutralizing antibody for IL-1β(14). These medications are approved for use in cryopyrin-associated periodic syndrome (CAPS) patients, and anakinra is also approved for use in rheumatoid arthritis(15). However, as described below, many indications are currently being explored for these medications.

Inhibitors of activation of the inflammasome complex itself are also in development. Small molecule caspase-1 inhibitors have been developed and have shown improvement in inflammation in murine models and small human studies(15, 16). Recently, an orally available small molecule inhibitor of NLRP3 inflammasome activation has shown benefit in murine models of multiple sclerosis and Muckle-Wells Syndrome(17). Inhibitors of ASC oligomerization are also in development(18). This pipeline of inflammasome inhibitors is expanding and will hopefully increase therapeutic options for rheumatic disease patients.

Other medications that were initially developed for non-inflammasome-related indications have been found to have inflammasome inhibiting activity. Glyburide, which is prescribed for type II diabetes, has inhibitory effects on NLRP3 inflammasome activation(19). Omega-3 fatty acids, a component of fish oil, have also been shown to inhibit the NLRP3 inflammasome(20). Caspase-1 is inhibited by thalidomide, a medication used for multiple myeloma and for refractory rheumatic disease such as cutaneous lupus(21, 22). Antimalarial medications, such as hydroxychloroquine and chloroquine, which interferes with toll-like receptor (TLR) 7 and 9 activation in the lysosomal compartment, blocks inflammasome activation and IL-1β release following certain inflammasome activating triggers(13, 23). Colchicine, which inhibits microtubule assembly, is able to block inflammasome activation by preventing co-localization of ASC with NLRP3(24, 25). Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the NLRP3 inflammasome via blockade of Cox-2 effects on this complex(26). Some of these listed medications have been shown to have effects in rheumatic diseases, but further research is needed to determine the extent to which these effects are inflammasome-dependent.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder characterized by elevated type I interferon production(27) and immune complex deposition within the tissues leading to generation of an inflammatory response and subsequent organ damage. Presentations are varied between patients, and affected organs can include diverse areas including brain, bone marrow, skin, kidney and lungs. Also contributing to mortality in SLE is a striking increased risk of cardiovascular disease(28).

Recently, there is accumulating evidence for a role of the inflammasome in SLE pathogenesis. Upregulation of inflammasome components has been noted in lupus nephritis biopsies(29), and overexpression of inflammasome scaffolds such as IFI16 and AIM2 have also been reported in leukocytes from SLE patients(30). Immune complexes containing DNA or RNA antigens, can prime the inflammasome for activation and subsequently trigger assembly of NLRP3 inflammasome complexes (13, 23). The activated complement component, C3a, promotes ATP secretion and thus serves as a trigger for inflammasome activation(31). Neutrophil extracellular traps (NETs), which are increased in SLE patients and likely contribute to pathogenesis(32, 33) stimulate NLRP3 inflammasome activation and promotion of IL-1β and IL-18 activation and release(34). Genetic polymorphisms associated with RIG-I signaling have also been reported to have associations with SLE, but whether this relates to inflammasome activity of RIG-I or other interferon-related signaling has not been determined(35).

Murine studies have also suggested a role for the inflammasome in lupus pathogenesis. Nonspecific inhibitors of NLRP3 have demonstrated protective effects in several murine models of lupus(36–38). Inhibition of a well-described activator of NLRP3 inflammasome assembly, the P2X7 receptor, also benefits lupus nephritis(39). Absence of caspase-1 is also protective from autoantibody generation and lupus nephritis in the pristane model of lupus(40). Blockade of other activators of the NLRP3 inflammasome, such as high-mobility group box 1 protein (HMGB1), abrogates caspase-1 activation and improves lupus nephritis in BXSB mice(41). The role of other inflammasome complexes, such as that driven by AIM2 activation is less clear in SLE. Absence of AIM2 is protective in some models(42), but others have shown that inhibition of AIM2 may promote lupus pathogenesis. (43, 44). Stimulation of RIG-I has been shown to exacerbate lupus nephritis(45). The inflammasome-activated cytokines IL-1β and IL-18 also has an important role in murine lupus. Absence of IL-1β is protective in an anti-double stranded DNA induced lupus model(46) and inhibition of IL-1β downregulated autoantibody production from B cells isolated from mice with active lupus(47). Inhibition of IL-18 in the MRL-Fas^{lpr} model improved nephritis and skin disease(48, 49), and reductions in IL-18 transcripts are associated with improvement in nephritis(50).

Targeting of the inflammasome has not risen to the clinical forefront in SLE, but there are some reports that suggest it may be worthwhile. A very small, non-placebo controlled trial of lupus patients with refractory arthritis suggested that there may be a small benefit to the use of anakinra(24). Antimalarial therapy, a cornerstone of lupus treatment has inhibitory effects on inflammasome activation (13, 23) and has been shown to reduce IL-18 concentrations in SLE serum(51). Consumption of ω-3 FA have shown substantial benefit in murine models of lupus; they reduce inflammatory cytokine production, including lowering levels of IL-1β and IL-18(52, 53). One short-term, placebo controlled trial of ω-3FA did not show significant benefit to disease activity over 12 weeks(54), but the baseline SELENA-SLEDAI disease activity was low in these patients (mean of 1.5). Another placebo-controlled trial of ω-3FA in lupus patients with higher baseline activity (mean SLAM-R 10.2) showed improvement in both BILAG and SLAM-R scores(55). Whether the effects of ω-3FA are related to their inhibition of the inflammasome in this disease remains to be determined. Another way inflammasome inhibition may benefit lupus patients is by ameliorating complications of treatment. Cyclophosphamide-induced bladder inflammation is mediated by the inflammasome and treatment with glyburide improved this side effect in murine models(56).

Rheumatoid Arthritis

Rheumatoid arthritis is a systemic autoimmune disease characterized by symmetric, small joint inflammation that affects approximately 1% of the US population. Patient sera and joint fluids are characterized by increased concentrations of inflammatory cytokines including IL-1β, Il-6, IL-17 and TNFα(57). When left unchecked, progressive inflammation will result in joint destruction, disfigurement and disability(58). Despite major advances in therapy, there is still a great need for additional therapeutic development as many patients are unable to achieve complete remission with the use of current medications.

There are robust data from murine models which argue for a role for inflammasome activation in rheumatoid arthritis. Mutations in *A20/Tnfaip3*, which predispose mice to an RA-like disease, result in enhanced activation of the inflammasome, and disease is ameliorated in the absence of a functional NLRP3 inflammasome(59). In collagen-induced arthritis, another murine model of RA, inhibition of NLRP1 inflammasome activation is protective(60), and a functional ASC molecule is required for disease activity(61). Caspase-1 has also been shown to be required for chronic arthritis development in response to streptococcal cell wall antigens(62).

In human studies, evidence also exists to support a role for the inflammasome in RA. Components of the NLRP3 inflammasome are increased in peripheral blood mononuclear cells (PBMCs) of untreated RA patients(63), and myeloid and endothelial cells are likely sources of production in RA synovium(64). Elevated circulating levels of IL-18 and caspase-1 (although the active form was not determined) were seen in the sera of RA patients(63). Genetic evidence has linked polymorphisms and subsequent overexpression of NLRP1 to risk of RA(65). Presence of minor polymorphisms in both NLRP3 and an inflammasome regulating protein CARD8 were associated with increased disease severity and seropositivity(66). A NLRP3 polymorphism (rs4612666) is associated with poor response to anti-TNF therapy(67). These studies suggest that the inflammasome is upregulated and active in RA.

Evidence also supports a role for the inflammasome-activated cytokine IL-18 in RA. IL-18 polymorphisms have also been associated with RA risk(68). IL-18 promotes inflammation and production of pro-osteoclastogenic cytokines from fibroblast-like synoviocytes(69). Angiogenesis within the arthritic joint is also promoted by IL-18(70). Animal models suggest that IL-18 is required for induction of arthritis in mice by zymosan(71) and for collagen-induced arthritis in rats(72). However, no significant studies evaluating the role of IL-18 blockade in human arthritis have been conducted to date, so the role of IL-18 in human RA remains untested.

One of the first biologic medications to show benefit in rheumatoid arthritis was the IL-1 receptor antagonist, anakinra, and this resulted in FDA approval for this medication in 2001. However, the effectiveness of this medication is not as robust as other biologic therapies, and significant injection site reactions has limited its utility in RA(73). Thus, the use of anakinra has fallen to a second-line therapeutic in this disease. A small trial has shown some efficacy for canakinumab in improving RA disease activity, but this remains experimental(74).

Given that the inflammasome can have roles in addition to facilitating IL-1β activation, it is unknown whether targeted inhibition of the inflammasome itself would have more impact on arthritis activity in this disease. Some indirect evidence stems from recent studies which demonstrated that addition of fish oil/ω-3 fatty acids to triple therapy with hydroxychloroquine, sulfasalazine and methotrexate improved remission rates and lowered rates of treatment failure in a cohort of newly diagnosed rheumatoid arthritis patients(75). Further, consumption of one serving of fish per week was associated with a 29% relative risk reduction for RA(76). However, it is unknown whether the effects of fish oil are related

to inflammasome inhibition. A phase II clinical trial was completed in 2002 for the caspase-1 inhibitor, pralnacasan, in rheumatoid arthritis. Abstracts suggested improved clinical activity, but the trial was formally withdrawn secondary to possible fibrosis in the liver(77). No further follow up was reported.

Other types of inflammatory arthropathies have not been well studied with regard to the role of the inflammasome. A small trial did not find evidence for NLRP3 polymorphisms associated with ankylosing spondylitis(78). However, another small trial suggested that thalidomide may have some benefit in ankylosing spondylitis(79), but whether this was related to thalidomide's effects on caspase-1 was not explored.

Systemic-Onset Juvenile Idiopathic Arthritis and Adult-Onset Stills Disease

Systemic onset juvenile idiopathic arthritis (s-JIA) has been defined by the International League of Associations for Rheumatology (ILAR) as: "arthritis in one or more joints with or preceded by fever of at least two weeks duration which is documented to be quotidian for at least three days, accompanied by one or more of the following: evanescent erythematous rash; lymphadenopathy, hepatomegaly, and/or splenomegaly; and serositis" (80). The disease accounts for ~5–9% of JIA cases (81). Onset of symptoms typically occurs between 1 and 5 years of age, with a peak incidence at 2 years (82). Historically, s-JIA was a disease associated with significant morbidity, with ~30% of patients developing destructive polyarthritis (83). Patients with s-JIA are additionally at increased risk for macrophage activation syndrome (MAS), a form of secondary hemophagocytic lymphohistiocytosis manifested by fever, hepatosplenomegaly, lymphadenopathy, cytopenias, coagulopathies, and CNS inflammation. Morbidity and mortality is quite high with this complication, with one study citing mortality rates as high as 22% (84). Adult-Onset Stills Disease (AOSD) is often considered part of the spectrum of s-JIA, with later age onset (85). It too is manifested by spiking fevers, polyarthritis, evanescent rash, lymphadenopathy and pharyngitis, and can be complicated by MAS.

Polymorphims in NLRP3 may be associated with s-JIA(86), but study of the inflammasome itself has been limited in s-JIA and AOSD. However, the downstream cytokines IL-1β and IL-18 have been well characterized. IL-1β plays a key role in the pathogenesis of s-JIA and AOSD. IL-1β production is significantly increased in activated peripheral blood mononuclear cells isolated from patients with s-JIA (87) and in patients with untreated AOSD (88, 89). Serum from s-JIA patients can induce transcription of the IL-1 locus in PBMCs from healthy controls (87). The exact cellular source of IL-1β in s-JIA and AOSD has yet to be definitively identified, but clinical response to IL-1 blocking agents highlights the key role of the cytokine in disease pathogenesis. IL-18 levels also appear to correlate with disease activity in s-JIA (90). IL-18 induces IFN-γ, IL-17, and TNF-α, and likely plays a crucial role in macrophage activation. IL-18 levels are elevated in children with active JIA regardless of type; however, levels are markedly higher in children with s-JIA (91). IL-18 levels measured in serum and synovial fluid from s-JIA patients have been shown to increase with CRP level, IL-6 level, IL-1 level, number of active joints, and radiological score. It has additionally been shown that children in which IL-18 levels predominate over IL-6 levels are more likely to develop MAS(92).

Advances in understanding the role of the inflammasome, and particularly the role of IL-1β, in the pathogenesis of s-JIA and AOSD, have revolutionized therapy for affected patients. The IL-1 inhibitor, anakinra, was the first biologic agent to demonstrate significant efficacy, and has become a cornerstone in the treatment of s-JIA. Effectiveness in treating s-JIA was first reported in 2004, when anakinra produced a prompt and full response in two patients with refractory disease (93). Two larger and more comprehensive trials evaluating the efficacy of anakinra were released in 2011. The first of these was a multicenter, double-blind, placebo-controlled trial which included 24 patients. Treatment and control groups each had 12 patients and were given one month of anakinra vs. placebo. Primary outcome was defined as a 30% improvement in criteria of American College of Rheumatology for pediatric response (ACR Pedi 30), resolution of symptoms, and at least 50% decrease in CRP and ESR. After one month, 67% of anakinra-treated patients achieved primary endpoint compared with 8% of patients in the placebo group (94). The second study was a multicenter, international, observational trial looking at 46 s-JIA patients undergoing treatment with anakinra. 90% of study participants experienced resolution of systemic symptoms and refractory arthritis. Additionally, at two months, the majority of patients no longer required corticosteroids (95). These studies demonstrate the effectiveness of IL-1 antagonism with anakinra in treatment of s-JIA. Similar dramatic response to treatment with anakinra has additionally been demonstrated in AOSD, and the drug has been proposed as a treatment of choice for patients with refractory disease, but is not yet FDA approved for this indication (96).

Two phase III trials demonstrating efficacy of canakinumab for treatment of s-JIA were described in 2012. The first study was a double-blind, placebo-controlled trial with a primary outcome measure of adapted JIA ACR 30 response and resolution of fever within 15 days of starting treatment. 84% of patients in the treatment group achieved ACR 30 response, compared with 10% in the placebo group. The second study was a two-phase trial, in which all subjects received canakinumab as part of an open-label first phase. Forty five percent of patients were able to taper glucocorticoids during this phase, and 33% of patients were able to discontinue them. The second phase consisted of a double-blind, placebo-controlled withdrawal study in which the primary outcome was time to flare. 75% of patients in the placebo group experienced a flare of their disease, compared with 25% of patients in the canakinumab group, a statistically significant difference(97). Successful treatment of AOSD has additionally been reported with canakinumab, even in patients with disease refractory to treatment with anakinra(98). More recently, several studies have demonstrated good response in both AOSD and sJIA to treatment with rilonacept (99, 100).

Autoinflammatory Disorders

Abnormalities in the NLRP3-inflammasome appear to be responsible for many monogenic autoinflammatory diseases. Mutations in NLRC4 have also been identified to contribute to autoinflammatory disorders(101, 102). These diseases are the results of defects either in the inflammasome itself, pathways leading to its activation, or downstream steps in the activation of IL-1. Autoinflammatory disorders have been classified as IL-1-mediated (cryopyrin associated periodic syndromes (CAPS) and deficiency of interleukin 1 receptor agonist (DIRA)), partially IL-1 mediated (familial Mediterranean fever (FMF),

hyperimmunoglobulinemia D syndrome (HIDS), pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA)), and mediated by other pathways (Blau-Syndrome, cherubism, IL-10 receptor deficiency, Majeed's Syndrome, TRAPS)(103).

CAPS comprises a clinical spectrum of three diseases: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells Syndrome (MWS) and neonatal-onset multisystem inflammatory disease (NOMID). These diseases are all caused by an autosomal dominant mutation in NLRP3(104). Clinical presentation includes fever, urticarial rash, arthritis, conjunctivitis, and significantly elevated inflammatory markers (105). Severity of the disease ranges from episodes that are triggered by cold exposure and resolve within hours in FCAS, to continuous fever, permanent organ damage and death in untreated NOMID (106, 107).

DIRA is caused by autosomal recessive loss of function mutations in the IL1RN gene, which encodes the IL-1 receptor antagonist (IL-1Ra). These patients typically present with multifocal osteomyelitis and periostitis, pustular dermatitis, and elevated inflammatory markers. Fever is often low grade or can be absent (107, 108). FMF is an autosomal recessive autoinflammatory condition, the result of largely missense mutations in the MEFV gene (109). This gene encodes a protein known as pyrin, a major regulatory component of the inflammasome (110). The disease typically presents with recurrent febrile episodes marked by large joint arthritis and acute abdominal pain secondary to peritonitis (111, 112). Patients typically have leukocytosis, elevated ESR and CRP during acute flares (113). Type AA secondary amyloidosis, often leading to renal impairment, is the most frequent complication, occurring in ~13% of patients in a 2005 Turkish study (114). The frequency of amyloidosis is impacted by the use of colchicine, however(115).

HIDS is an autosomal recessive disease resulting from mutations in MVK (mevalonate kinase gene) (116). The disease is manifested by recurrent fevers (typically occurring every 4–6 weeks), rashes, abdominal pain, diarrhea, vomiting, tender lymphadenopathy, nonerosive arthritis, and elevated inflammatory markers (8, 117). IgD levels are persistently elevated (118). In most instances, the disease has a benign course and self-resolves in adulthood.

PAPA syndrome is caused by autosomal dominant mutations in the PSTPIP1 gene. Patients present with early-onset, deforming pyogenic arthritis, cutaneous ulcers, and pathergy. ESR and CRP are elevated during flares (119, 120).

TNF receptor-associated periodic syndrome (TRAPS) is an autoinflammatory syndrome resulting from autosomal dominant mutations in the TNFRSF1A gene, which encodes the TNF receptor (TNFR1). It is the second most common autoinflammatory disease (121, 122). Mean age of disease onset is 10 years, although this varies from 1 to 63 years. The disease manifests as recurrent fevers, acute abdominal pain, myalgias, and arthritis. Ocular involvement including conjunctivitis and anterior uveitis is seen in roughly half of patients (123–125).

IL-1 inhibition is currently the most successful targeted therapy in autoinflammatory disorders, and is utilized in the treatment of CAPS, colchicine-resistant FMF, TRAPS,

HIDS, and DIRA (126). IL-1 blockade is now considered standard treatment for patients with CAPS. Treatment with anakinra, canakinumab, and rilonacept has been shown to result in complete resolution of symptoms in most cases (106). Anakinra has been used to treat NOMID for over 10 years and virtually all patients show a rapid response with resolution of fever, rash, and improvement inflammatory markers. However, doses needed to control symptoms in NOMID patients are significantly higher than those needed to treat FCAS patients (106). DIRA patients additionally have a striking response to treatment with anakinra, with rapid resolution of symptoms and normalization of inflammatory markers(107, 108).

Colchicine remains the standard therapy in patients with FMF, in many cases inducing complete remission. Colchicine has additionally been shown to be effective in preventing amyloidosis in many patients (127). Importantly, a role for colchicine in blocking inflammasome activation has recently been noted(25), but whether this is the mechanism by which colchicine works in FMF has yet to be determined. However, a minority of patients are unresponsive to or unable to tolerate colchicine. IL-1 blockade is a promising treatment approach in these patients. Successful treatment with anakinra has been demonstrated (128). Additionally, in a randomized, placebo-controlled trial published in 2012, rilonacept was effective at treating the disease (129). Case reports for the effectiveness of canakinumab are also noted.

Treatment of HIDS is challenging and typical therapies such as NSAIDs, corticosteroids, and colchicine are not effective. Etanercept and anakinra have been used with satisfactory response in some cases, and early treatment of attacks with anakinra may be a successful treatment strategy(130, 131). PAPA syndrome is additionally quite challenging to treat. Corticosteroids, cyclosporine, tacrolimus, IVIG, TNF inhibitors and thalidomide have been used with varying response. Response to IL-1 blockade is currently limited to case reports(132), but in general, IL-1 blockade is more effective at controlling arthritis and anti-TNF therapies are more effective for skin manifestations.

One would expect, based on the genetic defect causing TRAPS, that TNF blockade would be the treatment of choice for these patients. Interestingly, treatment with TNF agents can reduce frequency and severity of flares, but it does not eliminate them and efficacy of these agents often decreases over time(133, 134). More recently, anti-IL-1 therapy with anakinra or canakinumab has been used with promising results, and is becoming the treatment of choice in some centers (135, 136).

Crystal Arthropathies

Gout and pseudogout are characterized clinically by erythema, edema, warmth, and severe pain, reflecting a highly inflammatory response driven by monosodium urate (MSU) or calcium pyrophosphate dehydrate (CPPD) crystals, respectively. The prevalence of gout alone is estimated to occur in up to 3.9 percent of the population of the United States(137) and has a rising incidence(138). Evidence of CPPD is present in 15 - 44 percent of the population, with increasing prevalence with age(139). The inflammasome and subsequent

IL-1β production, is centrally implicated in the pathogenesis of crystal-induced inflammatory arthritis.

Priming of the inflammasome for a gouty attack may occur through toll-like receptor recognition of the crystals themselves or by engagement of TLRs by fatty acids or other microbial patterns(47, 140, 141). MSU may also activate dendritic cells in a receptor-independent mechanism by which MSU electrostatically binds cholesterol-within the lipid rich membrane leading to lipid sorting and activation of an intracellular signaling cascade involving Syk(142). MSU and CPPD crystals are then able to stimulate NLRP3 inflammasome activation resulting in production of activated IL-1β(143). Reactive oxygen species (ROS), potassium efflux, and p62 induced autophagosomal inhibition have all been identified as mechanisms of activation of the inflammasome upon MSU exposure(144–147). Thus, MSU and CPPD act by at least two mechanisms to promote IL-1β activation; 1) priming resulting in induction of NFκB activation and IL-1β transcription and 2) inflammasome activation and cleavage of pro IL-1β to its biologically active form.

Murine models have shown supportive evidence for the role of the inflammasome in crystal-induced inflammation. Mice deficient in ASC, caspase-1 or the IL-1R had attenuated inflammatory response to intraperitoneal injection of MSU crystals(143). Further, lack of caspase-1 led to a moderate reduction of joint inflammation following joint co-injection with long-chain fatty acids(148). Other models have not demonstrated a profound effect of caspase-1 deficiency on the inflammation in MSU-injected joints(143, 149). These findings suggest that there may be additional pathways which contribute to IL-1β activation in gouty arthritis.

CPPD crystals are implicated in the inflammatory arthritis more commonly known as pseudogout. CPPD demonstrates similar activation of inflammatory caspases and subsequent formation of IL-1β as seen with MSU(143). NLRP3 deficient mice demonstrate impaired IL-1β release upon CPPD stimulation, indicating the integral role NLRP3 has on inflammasome activation. Similar to the findings in MSU, CPPD also recruits neutrophils when injected intraperitoneally in mouse models; a finding attenuated in mice deficient in caspase-1 or ASC(74).

Basic calcium phosphate has been studied in murine models and does not appear to have an inflammasome-dependent inflammatory effect(150). The inflammasome's role in cholesterol crystal-driven arthritis has not been studied, however cholesterol crystals do trigger IL-1β in an NLRP3 dependent manner(151).

NSAIDs are a mainstay of therapy for gout and CPPD. NSAIDs impact inflammation through COX-1/COX-2 inhibition. COX-2 activation increases LPS-induced NFκB activation and promotes mitochondrial damage and ROS generation, which contribute to inflammasome activation(26, 152–155). Blockade of these pathways via NSAIDs reduces LPS-driven IL-1β production(29). Thus, NSAIDs may contribute to control of inflammation through inflammasome-modulating effect in addition to their effect on prostaglandin formation(156).

Colchicine, an alkaloid that prevents microtubule organization, is commonly used to treat acute flares of gout. Pre-treatment with colchicine prior to intra-articular MSU injection leads to reduced processing of IL-1β and inflammation(143). Colchicine prevents inflammasome activation by disrupting colocalization of NLRP3 and ASC, which is mediated by microtubules(25). Colchicine has also been found to increase AMPK activity, which thus inhibits NFκB activation and subsequent production of IL-1β(157).

IL-1 inhibition is a novel therapy for treatment of gout and has demonstrated clinical efficacy. Anakinra, a recombinant human IL-1R antagonist, has been utilized in uncontrolled studies of patients with contraindications to or failure of therapy with NSAIDs and colchicine. Although no randomized control trial has been performed, anakinra has been studied in a small open-labeled proof-of-concept study as well as several case reports and retrospective studies(158–160). These reports have demonstrated a favorable clinical response. The American College of Rheumatology recommends anakinra for treatment of a severe flare of gout or for treatment of gout refractory to traditional therapy modalities(161). Rilonacept has also demonstrated preliminary efficacy in gout. A double-blind active-controlled study of 225 patients with gout did not demonstrate improvement in pain relief compared to indomethacin alone(162). However, patients on rilonacept demonstrated a significant reduction in risk of gout attacks in patient initiating allopurinol versus those maintained on placebo alone(163–165). Rilonacept's application for FDA approval for gout was denied in 2012, and the committee requested additional clinical information. Canakinumab has been investigated in several randomized control trials and is approved in Europe for treatment of acute gout flares. Canakinumab performed favorably compared to intramuscular triamcinolone for reduction of pain symptoms as well for reducing the risk of a new gout flare(166–168). Additional randomized control trials have studied canakinumab compared to colchicine for prophylaxis against gout flare in patients who recently started allopurinol. Canakinumab demonstrated lower mean number of flares, greater time to the first new gout flare, and shorter duration of flares than the colchicine group(168).

Treatment of pseudogout with IL-1 inhibition is limited to case reports(169–171). Although European League Against Rheumatism (EULAR) guidelines mention IL-1 inhibition as a possible future therapy, it is currently not recommended as standard therapy by EULAR for treatment of CPPD(172).

Conclusion

The importance of the inflammasome in the pathogenesis of autoimmune and autoinflammatory disease has become apparent over the last decade. Continued investigation in this arena will likely lead to additional indications for anti-IL-1 therapies. Novel usages for medications with effects on the inflammasome, such as ω-3FA, will also expand as our understanding of this complex and its role in disease broadens. Further, novel inflammasome inhibitors are in development and will hopefully have similar beneficial effects on a multitude of rheumatic conditions.

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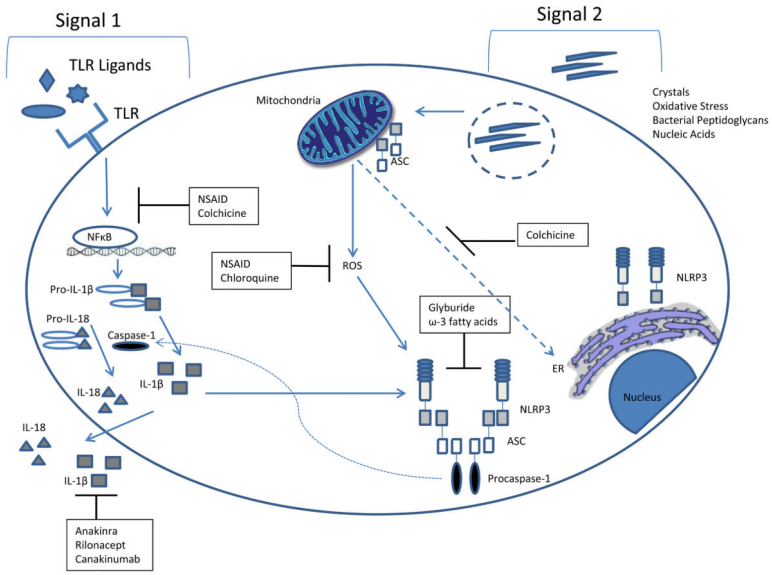

Figure 1. NLRP3 inflammasome activation and targeted therapy

Signal one of inflammasome activation requires priming, often by toll-like receptor ligands. Signal two, which activates the inflammasome, stems from a wide variety of diverse stimuli such as crystals, oxidative stress, bacterial peptidoglycans, and nucleic acids. This cartoon depicts the mode of action of various medications and their impact on the inflammasome.

Abbreviations ASC, apoptosis-related speck-like protein; CARD, caspase recruitment domain; ER, endoplasmic reticulum; NFκB, nucleaer factor kappa B; NSAID, nonsteroidal anti-inflammatory drug.

Table 1

Approved and experimental uses of available medications with inflammasome modulating activities.

Medication	Mechanism	Approved uses	Experimental uses
Anakinra	IL-1R1 antagonist	CAPS, RA	Gout, Pseudogout, sJIA, AOSD, HIDS, TRAPS
Canakinumab	Neutralizing IL-1β antibody	CAPS, sJIA	FMF, Gout, AOSD, HIDS, TRAPS
Rilonacept	Soluble IL-1 receptor	CAPS	FMF, sJIA, AOSD, HIDS, TRAPS
Colchicine	Inhibits microtubule assembly which disrupts inflammasome activation.	Gout	FMF
Fish Oil/ω-FA	Inflammasome inhibition	----	SLE, RA
Hydroxychloroquine	Blockade of immune complex activation of the inflammasome	SLE, RA	
Glyburide	Inhibition of NLRP3	Type II diabetes	SLE
Thalidomide	Inhibition of Caspase-1	Multiple Myeloma	SLE, AS

Abbreviations: AOSD=adult onset Still's disease; AS=ankylosing spondylitis; CAPS=cyropyrin-associated periodic syndrome; FA=fatty acids; FMF=familial Mediterranean fever; HIDS=hyper-IgD syndrome; RA=rheumatoid arthritis; sJIA=systemic juvenile idiopathic arthritis; SLE=systemic lupus erythematosus; TRAPS=tnf-receptor associated periodic syndrome.