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Title: The Clinicopathologic Significance of Inflammasome Activation in Autoimmune Diseases

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Abstract

Autoimmune diseases are characterized by dysregulated immune tolerance to self and inflammatory damage to tissues and organs. The development of inflammation involves multiple innate and adaptive immune pathways. Inflammasomes are multimeric cytosolic protein complexes that form to mediate host immune responses upon recognizing pathogen- or danger-associated molecular patterns via pattern recognition receptors (PRRs). The accelerating pace of inflammasome research has demonstrated important roles for inflammasome activation in many pathologic conditions encompassing infectious, metabolic, autoinflammatory, and autoimmune diseases. The inflammasome is generally comprised of a PRR, pro-caspase-1 and an adaptor molecule connecting the PRR and pro-caspase-1. With inflammasome activation, pro-caspase-1 becomes active caspase-1 that converts pro-IL-1β and pro-IL-18 into mature and active IL-1β and IL-18, respectively. Having multipotent effects on immune and non-immune cells, the cytokines IL-1β and IL-18 induce and promote systemic and local inflammatory responses. Human studies have reported increased levels of these cytokines, altered activation of inflammasome-related molecules, and/or presence of inflammasome activators in rheumatic diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), crystal-induced arthropathies, and Sjögren's syndrome. Such changes are found in the primary target organs like the kidneys, joints and salivary glands as well as in the cardiovascular system. In animal models of rheumatic diseases, inflammation and tissue damage improves upon genetic or pharmacologic targeting of the inflammasome, supporting its pathogenic role. Here, we review the clinicopathologic significance and therapeutic targeting of inflammasome activation in rheumatic diseases and related conditions based on recent findings.

Keywords: inflammasome, autoimmune diseases, IL-1β, IL-18

Introduction

Inflammation plays a critical role in the pathogenesis of rheumatic diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and crystal-induced arthropathies. Multiple innate and

adaptive immune pathways and molecules are involved in the development of inflammation. Germ-line encoded pattern-recognition receptors (PRRs), like Toll-like receptors (TLRs), expressed by innate immune cells recognize pathogen- and danger-associated molecular patterns (PAMPs and DAMPs), which are derived from invading pathogens and stressed host cells, respectively. Upon recognizing these molecules, the innate immune cells produce an array of inflammatory molecules like IL-1β and IL-18 which are regulated by multi-protein complex inflammasomes for their maturation and secretion (1, 2). An increasing body of evidence supports the role of the inflammasome in rheumatic diseases such as SLE, crystal-induced arthropathies, and RA. In this review, we discuss the biological processes, clinical significance and therapeutic targeting of inflammasome activation in rheumatic diseases and related conditions, focusing on recent advances.

Inflammasome types and activation

Inflammasomes are multimeric cytosolic protein complexes that form to mediate host immune responses upon sensing PAMPs or DAMPs (1, 2). Assembly of an inflammasome cleaves pro-caspase-1 into active caspase-1 that converts pro-IL-1β and pro-IL-18 into mature and active IL-1β and IL-18, respectively. Inflammasome activation can lead to pyroptosis, a type of inflammatory cell death, and active caspase-1 enables the non-conventional secretion of numerous cytosolic proteins (3). The inflammasome typically comprises three components: 1) a PRR sensing PAMPs or DAMPs; 2) pro-caspase-1; 3) and an adaptor molecule like ASC (apoptosis-associated speck-like protein containing a caspase activation and recruitment (CARD)) which links the sensor and pro-caspase-1 (1, 2). Based on the types of PRRs present in individual inflammasomes, they can be classified into nucleotide-binding domain–like receptor (NLR), absent in melanoma 2-like receptor (ALR), and pyrin inflammasomes (Figure 1). The NLR inflammasome family members that include NLRP1, NLRP3, and NLRC4 have a central nucleotide-binding domain (NBD), a C-terminal leucine-rich repeat (LRR) and a pyrin or CARD (1, 2). PRRs of individual inflammasomes can sense distinct stimuli (Figure 1). AIM2 recognizes intracytoplasmic DNA whereas NLRP3 can be triggered by PAMPs, DAMPs and even environmental chemicals (e.g. silica) (1, 2). While caspase-1-containing inflammasomes are classified as canonical inflammasomes, non-canonical inflammasomes with caspase-4/5 and -11 are identified in humans and mice, respectively. The CARD motif of caspase-4, -5 and -11 can directly bind with the lipid A moiety of intracellular lipopolysaccharide, leading to the activation of these caspases and subsequent secretion of IL-1β and IL-18 (2, 3).

Among the inflammasomes, the best characterized is the NLRP3 inflammasome (3). While intracellular levels of ASC and pro-caspase-1 are stable, the quantity of NLRP3 present in resting myeloid cells (e.g. human monocytes) is insufficient to allow activation in response to stimuli, suggesting that NLRP3 is a limiting factor regulating NLRP3 inflammasome activation (3-5). NLRP3 that is upregulated by PRRs via active NF-κB can be regulated by post-translational mechanisms including phosphorylation and ubiquitination (3). Reactive oxygen species (ROS), K+ efflux, ATP and lysosomal rupture can mediate the activation of the NLRP3 inflammasome (3). High levels of extracellular ATP also result in K+ efflux by activating the P2X purinoceptor 7 (P2X7R) channel. Many NLRP3 triggers increase mitochondrial ROS production, and NLRP3 inflammasome activation is inhibited by pre-incubation with some antioxidants (3). Never in mitosis gene, a (NIMA)-related protein kinase 7 (NEK7) is essential for formation of the NLRP3 inflammasome in murine macrophages by directly interacting with NLRP3 (6). Bruton tyrosine kinase (BTK), which is involved in B cell receptor and TLR signaling, physically interacts with ASC and NLRP3, and inhibiting BTK suppresses NLRP3 inflammasome activation (7). These findings highlight the fundamental role of the inflammasome in handling attacks and dangers imposed to the host through interacting with multiple cellular and molecular pathways.

Inflammasome and rheumatic diseases

Inflammasomes regulate the maturation and secretion of IL-1β. Having pleiotropic effects on multiple immune and non-immune cells, IL-1β can be accountable for many clinical manifestations in autoimmune and inflammatory diseases (8). As an endogenous pyrogen, IL-1β induces fever which is frequently found in rheumatic diseases. IL-1β serves as an upstream regulator of innate and adaptive immune responses by promoting the production of other inflammatory cytokines like IL-6, TNF-α, and IL-17 (8, 9). Similarly, IL-18 is known to enhance T helper 1 (Th1) cytokine IFN-γ production. Thus, it is natural to consider the potential role of the inflammasome in developing inflammation and tissue damage in rheumatic diseases. A body of evidence supporting this notion has accumulated over a decade through human and animal studies. Several known causative or pathogenic molecules for rheumatic diseases can activate inflammasomes, leading to IL-1β and IL-18 production. These include monosodium urate and calcium pyrophosphate dihydrate (CPPD) crystals responsible for gout and pseudogout, respectively (10), as well as dsDNA and U1-snRNP-containing lupus immune complexes (Figure 2) (11, 12). Also, monocytes and macrophages in patients with rheumatic diseases, especially SLE, have increased expression of inflammasome components and/or enhanced inflammasome

activation (13, 14), suggesting the existence of an intrinsic alteration in the intracellular inflammasome pathways. Of note, some polymorphisms of inflammasome-related genes were reported to be associated with susceptibility, severity and/or treatment response of rheumatic diseases, including SLE and RA (15-20). The improvement of disease activity was observed in murine models of SLE, RA, crystal-induced arthropathies, and Sjögren's syndrome by genetically or chemically targeting inflammasome activation (see details below). In addition to the immune system, dysregulated inflammasome activation in rheumatic diseases likely affects multiple organ systems including the kidneys, lungs, eyes, and cardiovascular system, contributing to morbidity and mortality (21, 22). The links between inflammasomes and individual rheumatic diseases are discussed below.

Inflammasome and SLE

Possible dysregulation of inflammasome activation in lupus was identified as early as 3 decades ago. These studies reported increased *IL1b* gene expression and IL-1β production in the kidneys of lupus-prone mice and from human monocytes, respectively (23, 24). Although the exact mechanism for these findings were not clear at that time, the discovery of inflammasomes and its role in IL-1β secretion revealed new insights into the pathogenesis of lupus. Unique to SLE, autoimmune features, such as immune complexes, can provoke the inflammatory response. Immune complexes containing dsDNA or U1-snRNP (U1-small ribonuclear protein) can activate the NLRP3 inflammasome in human monocytes, leading to IL-1β and IL-18 production (11, 12). Several pathways, including ROS, K+ efflux and TLRs, were involved in this phenomenon as inhibition of ROS production, K+ efflux and TLR activation suppressed cytokine production. IL-1β released from such activated monocytes enhanced Th17 responses, which are increased in lupus, supporting the implication of inflammasome activation in dysregulated adaptive immune responses in lupus (12). Confirming this chronic inflammasome activation, patients with SLE demonstrate increased circulatory levels of IL-1β and IL-18 (22, 25). Neutrophil extracellular traps (NETs) that contain self-DNA and other molecules like the anti-bacterial protein LL-37 play a role in the pathogenesis of lupus. Both NETs and LL-37 activate the inflammasome in human and murine macrophages, leading to the release of IL-1β and IL-18 (Figure 2) (13). The released IL-18 stimulates NETosis in human neutrophils, suggesting a feed-forward inflammatory loop involving NET and inflammasome activation. Inflammasome activation and IL-18 production can be responsible in part for vascular dysfunction in SLE through impairment of vascular repair mechanisms; caspase-1 inhibition and IL-18 neutralization improved dysfunctional SLE endothelial progenitor cell

differentiation (22). Also, patients with SLE had increased AIM2 expression correlating with disease activity, and blocking AIM2 expression in lupus-prone mice reduced disease activity (26). The association of *IL1B, IL18* and *NLRP1* polymorphisms was reported in patients with SLE with different ethnic backgrounds, supporting the possible genetic implication of certain inflammasome-related genes in SLE (15-17).

Monocytes and macrophages of patients with SLE appear to be more prone to inflammasome activation (13, 14). Patients with SLE have enhanced inflammasome activation in monocyte-derived macrophages upon NET and LL-37 stimulation (13). Also, freshly isolated monocytes from patients with SLE demonstrate increased expression of *NLRP3*, *AIM2* and *CASP1* (14). The expression of these genes correlated with IFN scores, and IFN-α enhanced caspase-1 expression via interferon regulatory factor 1 (IRF1) (Figure 2). These findings support the positive interaction of type I IFN and inflammasome in lupus through priming of monocytes for robust inflammasome activation. Indeed, patients with SLE have increased levels of caspase-1 activation in monocytes that correlated with serum levels of IL-1β, anti-dsDNA antibodies, and disease activity (25). Also, ATP-induced IL-1β production was increased in macrophages of patients with SLE (27). Recently, the role of macrophage migration inhibitory factor (MIF) in up-regulating NLRP3 expression was shown in human monocytes stimulated with the U1-snRNP lupus immune complex (4). Upon exposure to the latter, human monocytes produced MIF, and blocking MIF binding to its receptor CD74 suppressed NLRP3 expression and subsequent caspase-1 activation (4). The expression levels of MIF and CD74 correlated at the single cell level, supporting the autocrine and paracrine effects of MIF in regulating NLRP3. Of note, a separate study showed the implication of MIF in activating the NPRP3 inflammasome through its interaction with NLRP3 (5). These findings support a role for MIF in lupus pathogenesis, further substantiated by human and animal studies which showed the relationship of MIF genotypes with SLE and improvement of murine lupus by blocking MIF, respectively (28, 29).

In accordance with human studies, animal studies support a pathogenic role for inflammasomes in lupus. Mice lacking caspase-1 were protected against autoantibody production, type I IFN response and glomerulonephritis upon pristane challenge (30). In the same lupus animal model, the caspase-1 deficiency reduced vascular dysfunction, which is a major contributor to mortality in human lupus (30). Also, Nlrp3-R258W mice carrying the gain of function mutation exhibited significantly higher mortality and renal damage upon pristane challenge (31). Lupus-prone MRL/*lpr* mice had increased expression of P2X7, NLRP3, ASC, activate caspase-1, and IL-1β in the kidneys (32). Blockade of P2X7R suppressed lupus

nephritis in MRL/*lpr* mice by inhibiting NLRP3 inflammasome activation with decreased IL-1β and IL-17 levels (32). A recent study showed no effect of IL-1β deficiency on lupus nephritis in NZM2328 mice injected with the TLR7 agonist R848 (33). Given the role of inflammasomes in regulating multiple immune molecules, including IL-18, it is likely that targeting only IL-1β may not be sufficient to suppress disease activity. The serine/threonine kinase glycogen synthase kinase 3β (GSK-3β) is a positive regulator of NF-κB activation. Thiadiazolidinone 8 (TDZD-8), a selective inhibitor of GSK-3β, inhibited caspase-1 activation and IL-1β production along with reduced anti-dsDNA Abs and renal disease in MRL/*lpr* and NZB x NZW F1 mice (34). This finding could be related to the suppressive effect of TDZD-8 on NF-κB activation, which upregulates NLRP3 expression (35). A20, encoded by TNF-α-induced protein 3 (TNFAIP3), is a potent negative regulator of inflammation, and its gene polymorphisms are associated with autoimmunity including SLE. A20 was found to suppress NF-κB and caspase-1 activity (36), and its overexpression reduced nephritis in pristane-induced lupus mice by inhibiting NF-κB and NLRP3 (37).

The NLRP3 inflammasome contributes to the development of proteinuria in lupus nephritis by affecting podocyte function. NLRP3 inflammasome activation was detected in podocytes from patients with lupus nephritis and lupus-prone mice, and the selective NLRP3 inhibitor MCC950 ameliorates proteinuria and renal histologic lesions in lupus-prone mice (21). Pim-1, a member of the Pim family of serine/threonine kinases, promotes NLRP3 inflammasome activation in human podocytes in response to anti-dsDNA antibody-positive serum by increasing intracellular calcium concentration, which regulate NLRP3 inflammasome activation (38). In contrast to the results of most studies, a few studies report decreased levels of inflammasome activation or related molecules in lupus. NZB mice that developed autoimmune hemolytic anemia express high levels of the AIM2 antagonist p202 and an *NLRP3* gene mutation, leading to impaired IL-1β production, while the lupus-prone NZB x NZW F1 mice were reported to have reduced NLRP3 and AIM2 inflammasome responses (39). Also, lupus-like autoimmunity became more severe in C57BL/6-*lpr*/*lpr* mice deficient of Nlrp3 and Asc (40). Another report identified decreased expression of *NLRP3* and *ASC* genes in PBMCs of lupus patients but increased expression of *caspase-1*, *IL1B* and *IL18* in PBMCs (41). Nevertheless, a large set of animal and human data clearly support the notion that inflammasomes, especially the NLRP3 inflammasome, play a role in the pathogenesis of lupus.

Inflammasome and Rheumatoid Arthritis

Joint inflammation is activated by inflammasome activation, as is seen in crystal arthropathies such as gout and CPPD deposition disease. In RA, which is characterized by chronic inflammation and synovial activation that results in bony erosions, the role of the inflammasome may be through a more indirect nature. Interest in inflammasome biology in RA is longstanding as anakinra, a soluble IL-1R antagonist, was the first biologic approved for treatment of RA. The success of anakinra for RA was modest at best (42), thus the links between the inflammasome and RA have remained available for debate and further research.

Genetic evidence provides hints, but no definitive links between RA and inflammasome biology. Polymorphisms and subsequent overexpression of NLRP1 has been linked to increased risk of RA (18). Minor polymorphisms in both NLRP3 and CARD8 (an inflammasome regulating protein) were associated with seropositivity and increased disease severity (43). Cytokine polymorphisms have not been definitive either. Polymorphisms of IL-1β may be associated with development of RA in certain ethnic populations (19), and IL-18 polymorphisms may also increase risk of RA (20). Overall, the relationship between RA and the inflammasome may reflect the inflammatory activity in the joint itself, rather than on a true genetic etiology of the disease.

Human data support a role for the inflammasome in RA. Expression of inflammasome-associated proteins in the joint is increased but varies with the cell population analyzed. Endothelial and inflammatory cells in the RA synovium express all components needed for inflammasome activation, but synovial fibroblasts do not express NLRP3 (44). Importantly, many RA-associated joint changes prime for inflammasome activation. TNF-α upregulates key components of the inflammasome (45) partially through transforming growth factor beta activated kinase 1 (TAK1). Hypoxia, a feature of the inflamed synovium, is able to induce IL-1β protein and NLRP3 expression (46). Oxidized LDL, a modified lipid that is increased in RA patients, primes for inflammasome activation in macrophages, which results in increased IL-1β release (47). HMGB1, an alarmin with associations to RA development, primes for inflammasome activation as well (48). All of these features of RA lead to a state where the inflammasome is ready for activation (Figure 2).

Adaptive immune responses in RA are also regulated by the inflammasome. T cells from RA patients express elevated levels of active caspase-1 (49, 50) which can be triggered by oxidized and non-oxidized mitochondrial DNA. Intriguingly, this inflammasome activation contributes to Th17 skewing in vitro (50). These data suggest that T cell inflammasome activation may also be an important target for RA treatment.

The cytokines produced by inflammasome activation contribute to the inflammatory phenotype in the RA joint. An imbalance of IL-1β vs IL-1 receptor antagonist (IL-1RA) production was noted nearly 25 years ago in human RA synovial explants (51). IL-1β activates synovial fibroblasts and induces production of TNF-α, IL-6 and matrix metalloproteinases (52). IL-1α, which is active in its full-length and 18 kDa cleaved (by caspase-1) mature form, also has inflammatory effects on the joint. IL-1α can promote the maturation of cathepsin B and cathepsin S and works in synergy to increase chondrocyte cathepsin B activation and secretion (52).

Murine models support a role for the inflammasome in inflammatory arthritis, but most research has focused on infection or gout-related arthritis. In collagen-induced arthritis (CIA), a murine model with features of RA, inhibition of NLRP1 inflammasome activation is protective (53). Inhibition of P2X7R is also protective in a rat streptococcal wall model of arthritis (54). Genetic data has not supported a role for either caspase-1 or NLRP3 in CIA as absence of either protein was not protective; however, a functional ASC molecule was required for disease activity (55). Inhibitor data, however, has demonstrated a role for NLRP3 in CIA as inhibition of NLRP3 via MCC950 is protective in a CIA model (56). Another orally available NLRP3 inhibitor, OLT1177, is also able to suppress inflammation in zymosan-induced arthritis (57). Myeloid-specific deletion of *A20/Tnfaip3* causes an erosive polyarthritis, similar to RA. In this model, NLRP3, caspase-1 and the IL-1 receptor are also required for full disease expression (58). Comparisons between the role of the inflammasome in RA and SLE can be viewed in Table 1.

Inflammasome and Other Rheumatic Autoimmune Diseases

Sjögren's Syndrome

Sjogren's syndrome (SS) incorporates pathologic and clinical features of both SLE and RA, thus, it is not surprising to note that the inflammasome has been implicated in its pathogenesis as well. Circulating levels of IL-1β and IL-18 as well as inflammasome components such as ASC are elevated in SS patients (especially severe SS) compared with healthy controls (59, 60). In addition, increased expression of NLRP3 inflammasome components are detectible in SS salivary gland macrophages *in situ* (59). Both AIM2 and NLRP3 inflammasomes may be involved in SS as stimulation with DNA or NLRP3 agonists induces greater IL-1β production in SS monocytes than controls. In a murine model of autoimmune exocrinopathy, inhibition of P2X7R is protective from induction of salivary gland inflammation (61). In

addition, ocular dryness (as seen with primary or secondary SS) has been documented as a trigger for the NLRP3 inflammasome in murine models (62).

Celiac Disease

IL-18 signaling has been linked to development of celiac disease (CD) through GWAS studies (63) and this link has been validated in both pediatric and adult-onset CD (64). There are data to support a role for inflammasome activation in both disruption of epithelial barriers and in more generalized inflammation in response to gluten. Similar to its inflammasome promoting effects in SLE monocytes and endothelial cells (14, 22), IFNα can stimulate intestinal epithelial cells to promote inflammasome activation and disruption of epithelial barriers (65). In addition, circulating monocytes from celiac disease patients mount a more robust NLRP3-dependent inflammatory response to gluten peptides than monocytes from healthy controls (66). Further research is required to know whether the inflammasome is pathogenically activated in CD patients, contributes to disease phenotypes, and should be a target for treatment.

The Inflammasome and Complications of Autoimmunity

Other complications of autoimmune disease are also influenced by inflammasome activation. NLRP3 may be involved in lung fibrosis, and increased circulating levels of IL-18 have been identified as a potential biomarker for ILD in RA patients (67). Increased circulating levels of IL-1β have been documented in patients with severe scleritis (68), and importantly, a recent small pilot trial has shown efficacy for anakinra in the treatment of refractory scleritis associated with systemic inflammatory disorders (69). Many autoimmune diseases also display an increased risk of cardiovascular disease, and the inflammasome contributes to this risk through its known effects on plaque progression, destabilization of plaque, (reviewed in (70)) and promotion of endothelial dysfunction

Therapeutic Targeting of the Inflammasome

Interest in inflammasome inhibition is high for many diseases. This has been most pronounced for the plethora of autoinflammatory syndromes linked to genetic causes of aberrant inflammasome activation. These pharmaceutical advances in cytokine and inflammasome inhibitors are beneficial to autoimmune diseases, and they provide tools, as the science evolves, to link inflammasome activity to autoimmunity. Therapies can be considered in two categories: cytokine inhibition to block the end result of inflammasome activity or inflammasome inhibition itself, which may be important for cytokine and non-cytokine-related functions of the inflammasome that contribute to disease.

Cytokine Inhibition

IL-1 antagonism has been a longstanding biologic approach to management of inflammatory diseases (drugs are comprehensively reviewed in (71) and are listed in Table 2). New developments in cytokine blockade include several drugs. Lutikizumab, which is a dual IL-1α and IL-1β antibody is being evaluated in several diseases including erosive hand osteoarthritis (OA) (72) and knee OA (73). While trial results do not support use of IL-1 blockade in OA, the drug may have other indications. Bermekimab is a new human IL-1α antibody that is in trials for cancer therapy (74). IL-18 inhibition is available via the drug tadekinig alfa, which is a recombinant human IL-18 binding protein that can bind IL-18 and inhibit its function. Tadekinig alfa is not FDA approved, but it has orphan designation for the treatment of hemophagocytic lymphocytic histiocytosis as well as Breakthrough Therapy Designation for NLRC4-macrophage activation syndrome and XIAP deficiency (71). In addition, tadekinig alfa is being studied in adult onset Still's disease (75).

Inflammasome Inhibition

As research has progressed, inflammasome inhibition has been identified as a mechanism for several commonly used medications in the treatment of rheumatic diseases. Colchicine interrupts inflammasome activation by interfering with microtubule assembly (76). Hydroxychloroquine interferes with immune complex-triggered activation of the inflammasome in monocytes (11, 12). Omega 3 fatty acids, which have shown benefits in RA (77) and possibly lupus patients (78), inhibit inflammasome activation through numerous mechanisms (79, 80). Thalidomide, which has off-label therapeutic benefit in cutaneous lupus (81), inhibits inflammasome activation via repression of caspase-1 (82). Even non-steroidal anti-inflammatory drugs (NSAIDs) have been identified to have caspase inhibiting properties. Caspase-4, but not caspase-1, is inhibited by ketorolac and ibuprofen (83). Whether inflammasome inhibition has direct links to the efficacy of these drugs in their respective autoimmune diseases remains to be determined.

Direct inhibition of inflammasome activation is also being developed. MCC950, a specific inhibitor of the NLRP3 inflammasome (although the exact target has not been localized), inhibits inflammasome activation and protects against a myriad of inflammatory and autoimmune diseases in many murine models, including murine lupus nephritis (21) and CIA (56). CY-09 is another small molecule that binds to the ATP-binding motif of NLRP3 and can block inflammasome activation in murine models of type II diabetes and CAPS (84). OLT1177, a β-sulfonyl nitrile compound, inhibits assembly of the NLRP3

inflammasome and has shown beneficial effects on zymosan-induced murine arthritis (57). Small molecule inhibitors for other inflammasomes have not yet been described. Human trials for MCC950 or CY-09 have not been developed as of yet. Other methods for blocking inflammasome activation, include inhibiting upstream activators such as NF-κB, or increasing negative regulators such as HSP70 (85) also work in murine models, but human trials are still pending.

Conclusion

The accelerating pace of inflammasome research has demonstrated important roles for inflammasome activation in many diseases, both autoinflammatory and autoimmune (Figure 2). While single cytokine inhibition of IL-1β may not be overwhelmingly effective in autoimmune syndromes, further studies into the role of IL-18 blockade and general inflammasome inhibition may identify effective treatment strategies for diseases such as RA or SLE or may offer mechanisms by which resulting complications of autoimmunity can be averted. Further research will continue to shed light on this ubiquitous inflammatory pathway in diseases of the immune system.

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Figure legend

Figure 1. Structures and triggers of canonical and non-canonical inflammasomes. Canonical inflammasomes that contain caspase-1 can be classified into distinct types based on the presence of the sensor proteins NLRP1, NLRP3, NLRC4, AIM2, and Pyrin which recognize different triggers. Non-canonical inflammasomes that have caspase-4/5 and -11 in humans and mice, respectively, can directly interact with the lipid A moiety of lipopolysaccharides (LPS). Triggers of individual inflammasomes are provided in dashed boxes. PYD, pyrin domain; LRR, leucine-rich repeat; NBD, nucleotide-binding domain; FIIND, function to find domain; CARD, caspase activation and recruitment domain; CASP, caspase; HIN200, hematopoietic interferon-inducible nuclear protein 200; ASC, apoptosis-associated speck-like protein containing CARD; Bb, bBox zinc finger domain; CC, coiled coin domain; B30.2, B30.2 domain; MSU, monosodium urate; CPPD, calcium pyrophosphate dihydrate; ROS, reactive oxygen species; PAMP, pathogen-associated molecular pattern; DAMP, danger-associated molecular pattern; snRNP, small nuclear ribonucleoprotein.

Figure 2. Schematic summary showing the mechanisms of inflammasome activation in rheumatic diseases. Lupus immune complexes of dsDNA and U1-snRNP can affect inflammasome activation via inducing NETosis, macrophage migration inhibitory factor (MIF), and IFN-α. In RA, TNF-α, hypoxia, oxidized LDL, and High mobility group box 1 (HMGB1) can affect NLRP3 expression and inflammasome activation. Monosodium urate (MSU) and calcium pyrophosphate dehydrate (CPPD) crystals can activate the NLRP3 inflammasome. Monocytes, macrophages, and podocytes with activated inflammasome can produce IL-1β and IL-18, leading to inflammation and tissue damage in multiple organ systems. CVD, cardiovascular disease.

Table 1. Comparison of inflammasome involvement in RA and SLE

	Systemic Lupus Erythematosus	Rheumatoid Arthritis
Disease-associated polymorphisms	*NLRP1, IL1B, IL18*	*NLRP3, NLRP1, CARD8, IL1B, IL18*
Inflammasomes involved	NLRP1?, NLRP3, AIM2	NLRP3, NLRP1?
Murine models that improve with inflammasome inhibition	Pristane, MRL/*lpr,* NZB x NZW $F_{1,}$ and NZM2328	Collagen-Induced Arthritis, A20/*Tnfaip3* myeloid deletion
Triggers to prime/activate inflammasome response	Type I interferons, Macrophage migration inhibitory factor (MIF), DsDNA and RNP Immune complexes	TNFα, IL-6, Oxidized LDL, HMGB1
Important pathogenic cells	Podocytes, Monocytes, Endothelial Cells	Macrophages, Endothelial Cells

Table 2: Strategies for targeting the inflammasome

	Drug	Mechanism	Target	Disease
Cytokine Neutralization	Anakinra	Soluble IL-1 receptor antagonist	IL-1α and IL-1β	RA, CAPS, gout*
	Canakinumab	Neutralizing IL-1β antibody	IL-1β	CAPS, crFMF, MKD, TRAPS, sJIA
	Rilonacept	Soluble IL-1R1/IL-1RAcp	IL-1α and IL-1β	CAPS
	Lutikizumab	Dual IL-1α and IL-1β antibody	IL-1α and IL-1β	Not yet FDA approved
	Bermekimab	IL-1α antibody	IL-1α	Not FDA approved
	Tadekinig alfa	Soluble IL-18 binding protein	IL-18	HLH*, MAS*, XIAP deficiency*
Inflammasome Inhibition	Colchicine	Interferes with microtubule assembly	NLRP3	gout
	Thalidomide	Inhibits caspase-1	Caspase-1	CLE
	CY-09	Binds ATP-binding motif	NLRP3	Not FDA approved
	MCC950	Mechanism unclear	NLRP3	Not FDA approved
	β-sulfonyl nitrile	Inhibits inflammasome assembly	NLRP3	Not FDA approved

*=not FDA approved for this indication. CAPS=cryopyrine-associated periodic fever syndrome; CLE-cutaneous lupus erythematosus; FMF=colchicine resistant familial Mediterranean fever; HLH=hemophagocytic lymphocytic histiocytosis; MAS=macrophage activation syndrome; MKD=mevalonate kinase deficiency; RA-rheumatoid arthritis; sJIA=systemic juvenile idiopathic arthritis; XIAP=X-lined inhibitor of apoptosis