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ADVANCES IN DISEASE MECHANISMS AND TRANSLATIONAL TECHNOLOGIES

Clinicopathologic Significance of Inflammasome Activation in Autoimmune Diseases

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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 damage-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, including infectious, metabolic, autoinflammatory, and autoimmune diseases. The inflammasome generally comprises a PRR, procaspase 1, and an adaptor molecule connecting the PRR and procaspase 1. Upon inflammasome activation, procaspase 1 becomes active caspase 1 that converts pro–interleukin-1β (proIL-1β) and proIL-18 into mature and active IL-1β and IL-18, respectively. The cytokines IL-1β and IL-18 have multipotent effects on immune and nonimmune cells and induce and promote systemic and local inflammatory responses. Human studies have shown increased levels of these cytokines, altered activation of inflammasome-related molecules, and/or the presence of inflammasome activators in rheumatic diseases, including systemic lupus erythematosus, rheumatoid arthritis, crystal-induced arthropathies, and Sjögren's syndrome. Such changes are found in the primary target organs, such as the kidneys, joints, and salivary glands, as well as in the cardiovascular system. In animal models of rheumatic diseases, inflammation and tissue damage improve upon genetic or pharmacologic targeting of the inflammasome, supporting its pathogenic role. Herein, we review the clinicopathologic significance and therapeutic targeting of inflammasome activation in rheumatic diseases and related conditions based on recent findings.

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. Germline-encoded pattern-recognition receptors (PRRs), like Toll-like receptors (TLRs), expressed by innate immune cells recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (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 such as interleukin-1β (IL-1β) and IL-18, whose maturation and secretion are regulated by multiprotein complex inflammasomes (1,2). An increasing body of evidence supports the notion that the inflammasome plays a role in rheumatic diseases such as SLE, crystal-induced arthropathies, and RA. In this review, we discuss the biologic processes, clinical significance, and therapeutic targeting of inflammasome activation in rheumatic diseases and related conditions, focusing on recent advances.

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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 procaspase 1 into active caspase 1 that converts proIL-1β and proIL-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 unconventional secretion of numerous cytosolic proteins (3). The inflammasome

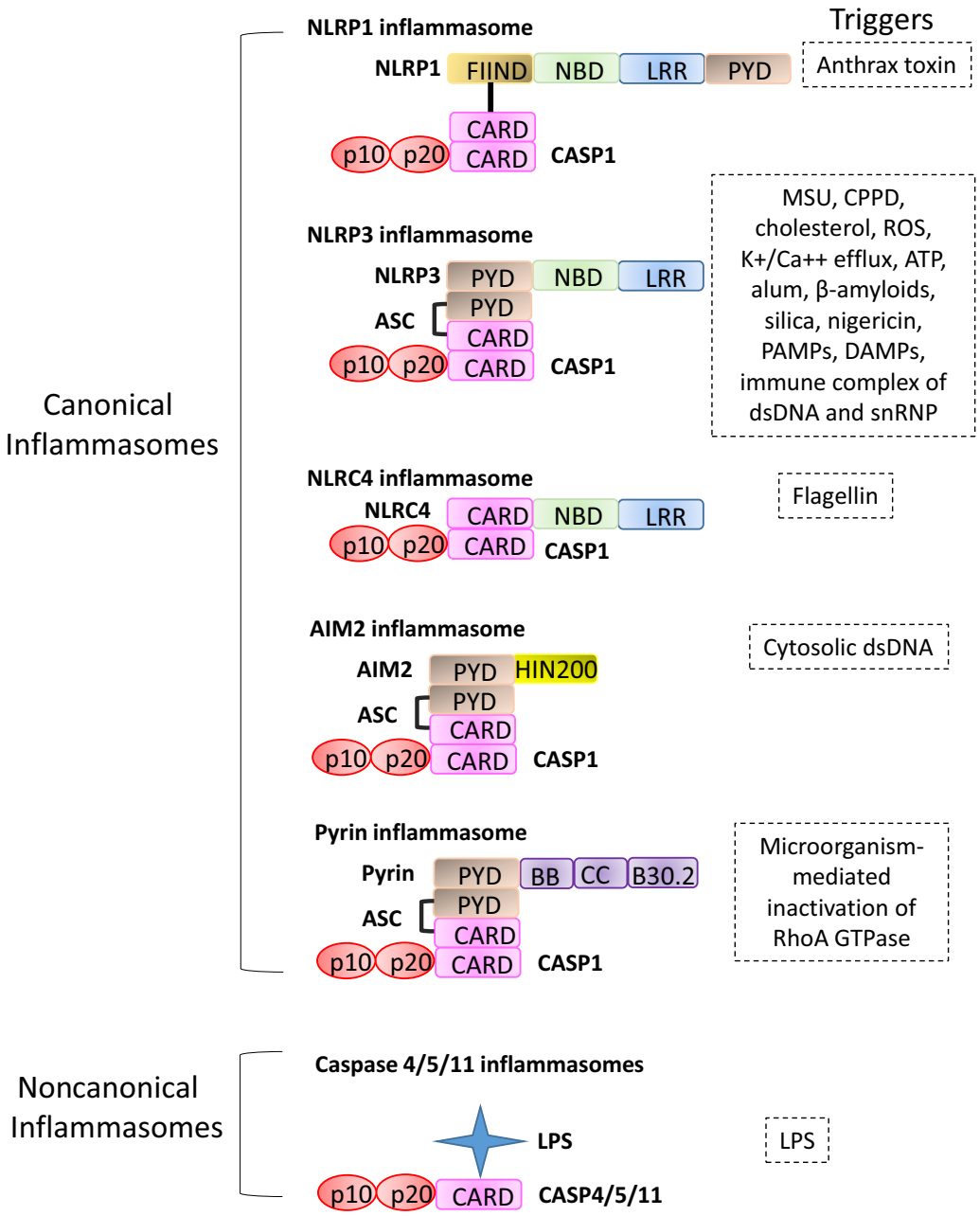

Figure 1. Structures and triggers of canonical and noncanonical inflammasomes. Canonical inflammasomes that contain caspase 1 can be classified into distinct types based on the presence of the sensor proteins NLRP1, NLRP3, NLRC4, AIM2, or pyrin, which recognize different triggers. Noncanonical inflammasomes that contain caspase 4 or 5 in humans and caspase 11 in mice can directly interact with the lipid A moiety of lipopolysaccharides (LPS). Triggers of individual inflammasomes are shown. FIIND = function to find domain; NBD = nucleotide-binding domain; LRR = leucine-rich repeat; PYD = pyrin domain; CARD = caspase activation and recruitment domain; p10 = caspase 1 p10; CASP1 = caspase 1; MSU = monosodium urate monohydrate; CPPD = calcium pyrophosphate dihydrate; ROS = reactive oxygen species; PAMPs = pathogen-associated molecular patterns; DAMPs = damage-associated molecular patterns; dsDNA = double-stranded DNA; snRNP = small nuclear RNP; HIN200 = hematopoietic interferon-inducible nuclear protein 200; BB = bBox zinc-finger domain; CC = coiled coin domain; B30.2 = B30.2 domain.

typically comprises 3 components: 1) a PRR sensing PAMPs or DAMPs, 2) procaspase 1, and 3) an adaptor molecule like ASC that links the sensor and procaspase 1 (1,2). Based on the types of PRRs present in individual inflammasomes, they can be classified into nucleotide-binding oligomerization domain–like receptor (NLR), absent in melanoma 2 (AIM2)–like receptor (ALR), and pyrin inflammasomes (Figure 1). The NLR inflammasome family members, which include NLRP1, NLRP3, and NLRC4, have a central nucleotide-binding domain, a C-terminal leucine-rich repeat, and a pyrin or caspase activation and recruitment domain (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, noncanonical inflammasomes containing caspase 4 or 5 and caspase 11 are observed in humans and mice, respectively. The CARD motif of caspases 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).

The best-characterized inflammasome is the NLRP3 inflammasome (3). While intracellular levels of ASC and procaspase 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 up-regulated 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 ($P2X_7$ purinoceptor) channel. Many NLRP3 triggers increase mitochondrial ROS production, and NLRP3 inflammasome activation is inhibited by preincubation with some antioxidants (3). Never in mitosis gene–related protein kinase 7 plays an essential role in the formation of the NLRP3 inflammasome in murine macrophages by directly interacting with NLRP3 (6). Bruton's 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 posed to the host through interacting with multiple cellular and molecular pathways.

The inflammasome and rheumatic diseases

Inflammasomes regulate the maturation and secretion of IL-1β. IL-1β has pleiotropic effects on multiple immune and nonimmune cells and is responsible for many clinical manifestations in autoimmune and inflammatory diseases (8). As an endogenous pyrogen, IL-1β induces fever, which is frequently seen in rheumatic diseases. IL-1β serves as an upstream regulator of innate and adaptive immune responses by promoting the production of other inflammatory cytokines, such as IL-6, tumor necrosis factor (TNF), and IL-17 (8,9). Similarly, IL-18 is known to enhance interferon-γ (IFNγ) production by Th1 cytokines. Thus, it is natural to consider the potential role of the inflammasome in 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 molecules known to be causative of or pathogenic for rheumatic diseases can activate inflammasomes, leading to the production of IL-1β and IL-18. These include monosodium urate monohydrate and calcium pyrophosphate dihydrate (CPPD) crystals, which are responsible for gout and pseudogout, respectively (10), as well as double-stranded DNA (dsDNA) and U1 small nuclear RNP (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 have been shown to be associated with susceptibility, severity, and/or treatment response in rheumatic diseases, including SLE and RA (15–20). Improvement in disease activity was observed in murine models of SLE, RA, crystal-induced arthropathies, and Sjögren's syndrome (SS) when inflammasome activation was targeted genetically or chemically (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.

The inflammasome and SLE

Possible dysregulation of inflammasome activation in lupus was identified as early as 3 decades ago. Those 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 mechanisms for these findings were not clear at that time, the discovery of the inflammasome 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 can activate the NLRP3 inflammasome in human monocytes, leading to the production of IL-1β and IL-18 (11,12). Several pathways, including ROS, K+ efflux, and TLRs, are involved in this phenomenon, as evidenced by the fact that 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 notion that inflammasome activation is implicated in dysregulated adaptive

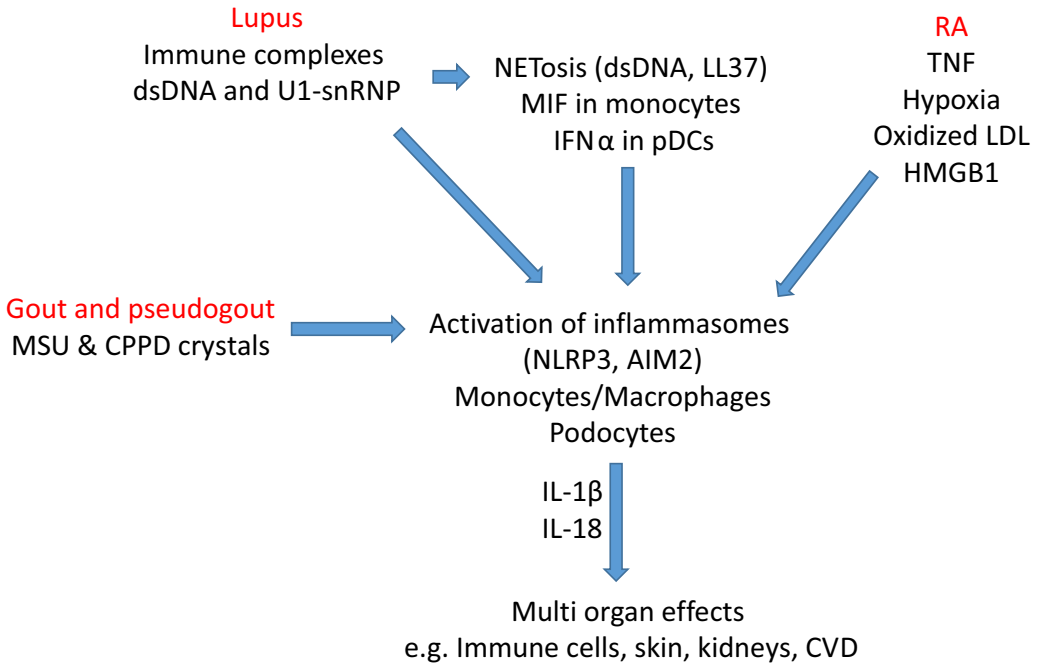

Figure 2. Schematic representation of the mechanisms of inflammasome activation in rheumatic diseases. Lupus immune complexes of double-stranded DNA (dsDNA) and U1 small nuclear RNP (U1 snRNP) affect inflammasome activation via inducing NETosis, macrophage migration inhibitory factor (MIF) in monocytes, and interferon-α (IFNα) in plasmacytoid dendritic cells (pDCs). In rheumatoid arthritis (RA), tumor necrosis factor (TNF), hypoxia, oxidized low-density lipoprotein (LDL), and high mobility group box chromosomal protein 1 (HMGB-1) affect NLRP3 expression and inflammasome activation. In gout and pseudogout, monosodium urate monohydrate (MSU) and calcium pyrophosphate dihydrate (CPPD) crystals activate the NLRP3 inflammasome. Monocytes, macrophages, and podocytes with activated inflammasome produce interleukin-1β (IL-1β) and IL-18, leading to inflammation and tissue damage in multiple organ systems. CVD = cardiovascular disease.

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 such as the antibacterial 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 feedforward 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 have been shown to improve 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 with SLE has been demonstrated in patients of different ethnic backgrounds, supporting the possible genetic implication of certain inflammasome-related genes in SLE (15–17).

Monocytes and macrophages from 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 is correlated with IFN scores, and IFNα enhances caspase 1 expression via IFN regulatory factor 1 (Figure 2). These findings support the notion of a positive interaction between type I IFN and the 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 correlate with serum levels of IL-1β, anti-dsDNA antibodies, and disease activity (25). Also, ATP-induced IL-1β production has been shown to be increased in the macrophages of patients with SLE (27). Recently, the role of macrophage migration inhibitory factor (MIF) in up-regulating NLRP3 expression was demonstrated 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 that MIF was implicated in activating the NLRP3 inflammasome through its interaction with NLRP3 (5). These findings support the notion that MIF plays a role in lupus pathogenesis, which is

further substantiated by human and animal studies showing the relationship of MIF genotypes to SLE and improvement in murine lupus upon blocking MIF, respectively (28,29).

Consistent with the results of human studies, animal studies indicate a pathogenic role for inflammasomes in lupus. In one study, 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, 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 have been shown to have increased expression of $P2X_7$, NLRP3, ASC, active caspase 1, and IL-1β in the kidneys (32). Blockade of $P2X_7$ purinoceptor 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 TLR-7 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 and reduced anti-dsDNA antibody levels and renal disease in a study using MRL/*lpr* and NZB × NZW F1 mice (34). This finding could be related to the suppressive effect of TDZD-8 on NF-κB activation, which up-regulates NLRP3 expression (35). A20, encoded by TNF-induced protein 3, 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 mice with pristane-induced lupus 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 ameliorated 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 the intracellular calcium concentration, which regulates NLRP3 inflammasome activation (38). In contrast to the results of most studies, a few studies have shown decreased levels of inflammasome activation or related molecules in lupus. NZB mice that develop autoimmune hemolytic anemia express high levels of the AIM2 antagonist p202 and an *NLRP3* gene mutation, leading to impaired IL-1β production, while lupus-prone (NZB × NZW)F1 mice have been shown to have reduced NLRP3 and AIM2 inflammasome responses (39). Also, lupus-like autoimmunity became more severe in C57BL/6-*lpr*/*lpr* mice deficient in *Nlrp3* and *Asc* (40). Another study identified decreased expression of *NLRP3* and *ASC* genes in peripheral blood mononuclear cells (PBMCs) from lupus patients but increased expression of *CASP1*, *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.

The inflammasome and RA

Joint inflammation is initiated by inflammasome activation, as is seen in crystal arthropathies such as gout and CPPD crystal 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 of a more indirect nature. Interest in inflammasome biology in RA is longstanding, as anakinra, a soluble IL-1 receptor antagonist, was the first biologic agent approved for the treatment of RA. The success of anakinra as an RA therapy was modest at best (42); thus, the links between the inflammasome and RA continue to be a subject of debate and a topic for further research.

Genetic evidence provides hints, but no definitive links between RA and inflammasome biology. Polymorphisms and subsequent overexpression of NLRP1 have been linked to an increased risk of RA (18). Minor polymorphisms in both NLRP3 and CARD-8 (an inflammasome-regulating protein) have been shown to be associated with seropositivity and increased disease severity (43). Cytokine polymorphisms have not been definitive either. Polymorphisms of IL-1β may be associated with the development of RA in certain ethnic populations (19), and IL-18 polymorphisms may also increase the risk of RA (20). Overall, the relationship between RA and the inflammasome may reflect the inflammatory activity in the joint itself, rather than a true genetic etiology of the disease.

Data from human studies support the notion that the inflammasome plays a role 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 up-regulates key components of the inflammasome (45), partially through transforming growth factor β–activated kinase 1. Hypoxia, a feature of the inflamed synovium, induces IL-1β protein and NLRP3 expression (46). Oxidized low-density lipoprotein, a modified lipid that is increased in RA patients, primes for inflammasome activation in macrophages, which results in increased IL-1β release (47). High mobility group box chromosomal protein 1, an alarmin that is associated with the development of RA, 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 nonoxidized 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 versus IL-1 receptor antagonist production was noted nearly 25 years ago in human RA synovial explants (51). IL-1β activates synovial fibroblasts and induces the production of TNF, IL-6, and matrix metalloproteinases (52). IL-1α, which is active in its full-length and 18-kd 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 the notion that the inflammasome plays a role 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 $P2X_7$ purinoceptor is also protective in a rat streptococcal wall model of arthritis (54). Genetic data have 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, have demonstrated a role for NLRP3 in CIA, since inhibition of NLRP3 via MCC950 is protective in a CIA model (56). Another orally available NLRP3 inhibitor, OLT1177, suppresses inflammation in zymosan-induced arthritis (57). Myeloid-specific deletion of *A20/Tnfaip3* causes erosive polyarthritis, similar to RA. In this model, NLRP3, caspase 1, and the IL-1 receptor are also required for full disease expression (58). A comparison of the role of the inflammasome in RA and its role in SLE is shown in Table 1.

Table 1. Comparison of inflammasome involvement in SLE and RA*

	SLE	RA
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	PIA, MRL/*lpr*, (NZB × NZW)F1, NZM2328	CIA, A20/*Tnfaip3* myeloid deletion
Triggers to prime/activate inflammasome response	Type I IFNs, MIF, dsDNA, RNP immune complexes	TNF, IL-6, Oxidized LDL, HMGB-1
Important pathogenic cells	Podocytes, monocytes, endothelial cells	Macrophages, endothelial cells

* SLE = systemic lupus erythematosus; RA = rheumatoid arthritis; PIA = pristane-induced arthritis; CIA = collagen-induced arthritis; type I IFNs = type I interferons; MIF = macrophage migration inhibitory factor; dsDNA = double-stranded DNA; TNF = tumor necrosis factor; IL-6 = interleukin-6; LDL = low-density lipoprotein; HMGB-1 = high mobility group box chromosomal protein 1.

The inflammasome and other rheumatic autoimmune diseases

Sjögren'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 those with severe SS) compared to healthy controls (59,60). In addition, increased expression of NLRP3 inflammasome components is detectable 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 control monocytes. In a murine model of autoimmune exocrinopathy, inhibition of $P2X_7$ purinoceptor is protective against induction of salivary gland inflammation (61). In addition, ocular dryness (as seen in 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 the development of celiac disease through genome-wide association studies (63), and this link has been validated in both pediatric and adult-onset celiac disease (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), IFN can stimulate intestinal epithelial cells to promote inflammasome activation and disruption of epithelial barriers (65). In addition, circulating monocytes from patients with celiac disease mount a more robust NLRP3-dependent inflammatory response to gluten peptides than monocytes from healthy controls (66). Further research is required to determine whether the inflammasome is pathogenically activated in patients with celiac disease, 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 interstitial lung disease 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 lead to an increased risk of cardiovascular disease, and the inflammasome contributes to this risk through its known effects on plaque progression, destabilization of plaque (for review, see ref. 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. Pharmaceutical advances in cytokine and inflammasome inhibitors are beneficial for patients with autoimmune diseases, and they provide tools, as the science evolves, to link inflammasome activity to autoimmunity. Therapies can be classified into two categories: cytokine inhibition to block the end result of inflammasome activity, or inhibition of the inflammasome itself, which may be important for cytokine- and noncytokine-related functions of the inflammasome that contribute to disease.

Cytokine inhibition. IL-1 antagonism has been a long-standing biologic approach to the management of inflammatory diseases (for comprehensive review of drugs, see ref. 71) (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 approved by the Food and Drug Administration, but it has orphan designation for the treatment of hemophagocytic lymphohistiocytosis as well as Breakthrough Therapy designation for NLRC4 macrophage activation syndrome and X-linked inhibitor of apoptosis protein 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 been shown to be beneficial in RA (77) and possibly lupus (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 nonsteroidal antiinflammatory drugs have been shown 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 the autoimmune diseases they are used to treat remains to be determined.

Direct inhibitors of inflammasome activation are 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 2 diabetes mellitus and cryopyrin-associated periodic

Table 2. Strategies for targeting the inflammasome*

Drug	Mechanism	Target	Disease
Cytokine neutralization			
Anakinra	Soluble IL-1Ra	IL-1α and IL-1β	RA, CAPS, gout†
Canakinumab	Neutralizing IL-1β antibody	IL-1β	CAPS, colchicine-resistant FMF, MKD, TRAPS, systemic JIA
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

* IL-1Ra = interleukin-1 receptor antagonist; RA = rheumatoid arthritis; CAPS = cryopyrin-associated periodic syndromes; FMF = familial Mediterranean fever; MKD = mevalonate kinase deficiency; TRAPS = tumor necrosis factor receptor–associated periodic syndrome; JIA = juvenile idiopathic arthritis; IL-1RAcP = IL-1R accessory protein; HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome; XIAP = X-linked inhibitor of apoptosis protein; CLE = cutaneous lupus erythematosus; † Not approved by the Food and Drug Administration (FDA) for this indication.

syndromes (84). OLT1177, a β-sulfonyl nitrile compound, inhibits assembly of the NLRP3 inflammasome and has been shown to exert beneficial effects on zymosan-induced murine arthritis (57). Small molecule inhibitors of other inflammasomes have not yet been identified. Human trials of MCC950 or CY-09 have not been developed as of yet. Other methods of blocking inflammasome activation, including 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.

Conclusions

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 insight into 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.

AUTHOR CONTRIBUTIONS

Drs. Kahlenberg and Kang drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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