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The Inflammasome and lupus- another innate immune mechanism contributing to disease pathogenesis?

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Abstract

Purpose of review—The role of innate immunity in systemic lupus erythematosus (SLE) has been a rapidly expanding area of research over the last decade. Included in this rubric is the concept that activation of the inflammasome, a molecular complex that activates caspase-1 and in turn, the cytokines IL-1 β and IL-18, is important in lupus pathogenesis. This review will summarize recent discoveries exploring the role of the inflammasome machinery in SLE.

Recent findings—Immune complexes can activate the NLRP3 inflammasome, and SLE-derived macrophages are hyper-responsive to innate immune stimuli, leading to enhanced activation of the inflammasome and production of inflammatory cytokines. Work in several murine models suggests an important role for the NLRP3 inflammasome in mediating lupus nephritis. Caspase-1, the central enzyme of the inflammasome, is essential for development of type I interferon responses, autoantibody production and nephritis in the pristane model of lupus. The AIM2 inflammasome may have protective and pathogenic roles in SLE.

Summary—Recent evidence suggests that the inflammasome machinery is dysregulated in SLE, plays an important role in promotion of organ damage, and may mediate cross-talk between environmental triggers and the development of lupus. Further research should focus on whether inhibition of inflammasome components may serve as a viable target for therapeutic development in SLE.

Keywords

Inflammasome; lupus; IL-18; caspase-1; NLRP3

Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune syndrome characterized by formation of autoantibodies to nuclear components, immune complex deposition and inflammatory cell-mediated organ damage. Significant progress has been made over the past decade describing the putative role of innate immune processes in disease pathogenesis. These abnormalities include stimulation of toll-like receptor (TLR) signaling by immune complexes, activation of persistent type I interferon (IFN) responses, and hyperproduction of

neutrophil NETs(1–4). In the past few years, another innate immune signaling complex, the inflammasome, has garnered support for a role in promoting organ damage and contributing to the SLE phenotype. This review will discuss the recent evidence that implicates the inflammasome in SLE pathogenesis.

The inflammasome

The inflammasome is a term used to describe a complex of molecules that, when induced to oligomerize, result in the activation of caspase-1, the primary enzyme responsible for activation of the pro-inflammatory cytokines IL-1 β and IL-18 (reviewed in (5)). Activation of the inflammasome, particularly in the context of intracellular infections, may also result in an inflammatory form of cell death dependent on caspase-1, termed pyroptosis(6). Most inflammasomes involve a NOD-like receptor (NLR), such as NLRP3, which contains a C-terminal leucine rich repeat domain, a central NACHT nucleotide binding domain and an N-terminal PYRIN domain, which is able to interact with the PYRIN domain of the adaptor ASC. ASC is able to recruit caspase-1 via its CARD domain resulting in oligomerization of multiple caspase-1 molecules that in turn cleave and activate each other (reviewed in(7)). Other inflammasomes are formed from scaffolds not related to the NOD-like receptor. These include Absent in Melanoma 2 (AIM2), IFN- γ inducible protein 16 (IFI16) and retinoic acid inducible gene I (RIG-I). These proteins are able to assemble inflammasomes in response to cytosolic nucleic acids. They also play important roles in induction of antiviral type I interferon (IFN) responses. How the cytokine activation and IFN regulating roles of non-NLR inflammasomes are regulated is still an area of investigation (7).

Regulation of inflammasome activity occurs at multiple levels. NLRP3 and IL-1 β are not constitutively expressed. They require a “priming” step, usually stimulation by toll-like receptor (TLR) ligands, which subsequently activate NF κ B and their transcription (8). De-ubiquitination of NLRP3 has also been reported as an important intermediate step for inflammasome priming(9). Final activation of the inflammasome depends on the presence of unique ligands or cellular metabolic changes which result in assembly of the complex. These include stimuli as diverse as bacterial peptidoglycans, nucleic acids and crystalline materials (10–12).

The inflammasome is a recognized central pathogenic player in several rheumatologic diseases. The inherited cryopyrinopathies stem from activating mutations in NLRP3 leading to increased IL-1 β production(13). Gout and pseudogout involve joint inflammation secondary to activation of the NLRP3 inflammasome by monosodium urate and calcium pyrophosphate crystals respectively(12). Research is also ongoing into the role of the inflammasome in diseases such as inflammatory bowel disease, type II diabetes and metabolic syndrome(14–16). Importantly, a role for inflammasome in SLE pathogenesis is emerging (Table 1).

Genetic Evidence for a Role for the Inflammasome in SLE

Advanced genetic techniques have enhanced autoimmune disease research by finding important targets for study. Polymorphisms in the inflammasome scaffold, NLRP1, have previously been highly associated with vitiligo and type I diabetes(17). The same

polymorphisms in this gene are also highly associated with the development of SLE and correlate with the phenotypes of nephritis, arthritis and cutaneous lesions(18). These polymorphisms lead to increased IL-1 β production from circulating monocytes (19). Other inflammasome genes, including NLRP3, AIM2, NLRC4 and CASP1 were not associated with increased risk for SLE in the same study(18). The role of genetic polymorphisms in the cytokines activated by the inflammasome has also been examined. Several polymorphisms in the promoter of IL18 have been related to increased risk of SLE in several different ethnic populations(20*, 21*). Despite several studies, no convincing evidence for IL-1 β polymorphisms contributing to SLE risk has been documented(18, 22).

Activation of the Inflammasome in SLE

Increased expression of inflammasome components, including NLRP3 and caspase-1 has been reported in lupus nephritis biopsies(23), suggesting that this tissue may be primed for inflammasome activation. How the inflammasome is triggered in SLE is an important concept for understanding its role in this disease. Immune complexes formed secondary to antibody recognition of DNA or RNA antigens, have been shown to stimulate inflammasome activation through upregulation of TLR-dependent activation of NF κ B and subsequent activation of the NLRP3 inflammasome(24, 25**). Importantly, the use of chloroquine, an antimalarial that interferes with TLR7 and 9 activation in the lysosomal compartment, is able to block the stimulation of IL-1 β release following stimulation of monocytes with RNA or DNA immune complexes(24, 25**). C3a, which is released during complement activation in tissues, promotes inflammasome activation through upregulation of ATP secretion(26*). Together, these results support the notion that immune complex deposition and complement consumption in organs affected by SLE promote activation of the inflammasome and may contribute to organ damage through this mechanism. Neutrophil extracellular traps (NETs) have also been proposed to play a pathogenic role in SLE. These structures are released spontaneously by a subset of proinflammatory lupus neutrophils termed low density granulocytes (LDGs) (4) and contribute to immune complex formation and type I IFN synthesis(27). Recently, NETs have been shown to activate caspase-1, resulting in release of IL-1 β and IL-18, and this activation was enhanced in macrophages derived from SLE patients(28*). Importantly, IL-18 is able to induce NETosis, suggesting that NET activation of the inflammasome can result in a feed-forward loop in which inflammasome-activated IL-18 stimulates a perpetual cycle of NET formation and inflammasome activation(28*). This mechanism yields an intriguing possibility as to how infection or other triggers can spark a disease flare in SLE patients.

C1q, the deficiency of which is a strong risk factor for development of SLE(29), has important inhibitory functions on type I IFN responses in plasmacytoid dendritic cells(30). Recently, C1q, when presented in the context of apoptotic lymphocytes, was also demonstrated to repress the expression of NLRP3 in human monocyte-derived macrophages(31). Importantly, following phagocytosis of C1q-coated apoptotic lymphocytes, activation of the NLRP3 inflammasome by LPS and ATP was inhibited(31). These results suggest that the absence of C1q may contribute to SLE development through multiple pathways, including release of suppressive effects on inflammasome activation during phagocytosis.

Lupus Nephritis

The NLRP3 inflammasome has received a significant amount of attention as a contributor to lupus nephritis in murine models. Daily treatment of NZB/NZW F₁ mice with epigallocatechin-3-gallate, a major bioactive polyphenol in green tea, reduced renal inflammation and suppressed upregulation of NLRP3 and activation of IL-1 β and IL-18 in the kidneys of these mice. No suppression of anti-dsDNA antibodies or activation of T or B cells was observed in this model(32). Signaling through many TLR receptors activates NLRP3 expression via activation of NF κ B(8) and thus acts as an important priming step for inflammasome inhibition. Recently, it has been suggested that the beneficial effects of TLR7, 8 and 9 inhibition in NZBW/F1 murine lupus models stem at least partially through blockade of NLRP3 upregulation(33*). Further demonstrating the importance of this pathway, inhibition of NLRP3 expression by use of inhibitors of NF κ B was able to protect MRL/lpr mice from nephritis and demonstrated a 50% reduction in anti-dsDNA titers(34*). NLRP3 inflammasome activation has also been demonstrated in other models of renal injury(35), so it remains to be determined whether inhibition of NLRP3 function will benefit more than lupus-related renal injury.

In addition to NLRP3, the importance of caspase-1 in the development of murine lupus has also been recognized. In a recent study, caspase-1 $-/-$ mice were shown to be resistant to develop lupus using the pristane model. Compared to wild-type mice, caspase-1 $-/-$ mice had significant reductions in both anti-dsDNA and anti-RNP autoantibody titers, abrogation of a type I IFN signature and were protected from both renal immune complex deposition and kidney inflammation(36**). Inhibition of the P2X7 receptor, a well-studied activator of NLRP3 and caspase-1(37), has also shown beneficial effects in lupus nephritis in both MRL/lpr and NZM 2328 mice. Indeed, inhibition of this receptor via brilliant blue G or via siRNA knockdown of P2X7 blocked development of anti-dsDNA antibodies, immune complex deposition and renal inflammation (38**). Blockade of High-mobility group box 1 protein (HMGB1), a danger signal that circulates on nucleosome and NET-derived complexes at higher levels in SLE(3, 39) has also shown success in abrogating caspase-1 activation and lupus nephritis in BXSB mice(40*).

The inflammasome scaffold AIM2 has also been studied for its role in SLE pathogenesis. AIM2 binds cytoplasmic DNA and induces inflammasome activation through recruitment of the adaptor molecule ASC through its pyrin domain(41). Balb/c mice induced to develop a lupus-like syndrome by repeated injection of apoptotic DNA have elevated levels of AIM2 expression in multiple organs, which correlates with disease progression. Further, these mice have a diminished lupus-like phenotype when AIM2 is knocked down(42*). Others, however, have demonstrated that inhibition of AIM2 may promote lupus pathogenesis. In mice, another interferon-inducible p200 family member, p202, is upregulated in many lupus-prone strains(43, 44). p202 negatively regulates AIM2 inflammasome activation, consequently decreasing cell death and promoting prolonged type I IFN production in response to cytosolic DNA(45*). Inhibition of AIM2 results in upregulation of p202(46). Importantly, in T and B cells, type I IFN exposure results in suppression of AIM2 and upregulation of p202(47). This could thus lead to a vicious cycle of type I IFN production.

Thus, the inhibition of AIM2 may be a double edged sword with regards to lupus pathogenesis.

Cutaneous Lupus (CLE)

While the inflammasome itself has not been well-studied in cutaneous lupus, the inflammasome-activated cytokine IL-18 has been proposed as an important pathogenic mediator of cutaneous lupus lesions. IL-18 appears to play an important role in atopic dermatitis (reviewed in (48)), but is less well-studied in lupus. This cytokine is highly upregulated in the epidermis of cutaneous lupus, but not control, skin biopsies(49). IL-18 exposure induces upregulation of MHC class II and the chemokine CXCL10, which may be important for recruitment and activation of inflammatory cells(50). Additionally, keratinocytes isolated from subacute cutaneous lupus lesions upregulate TNF- α after IL-18 stimulation, which increases keratinocyte sensitivity to apoptosis, leading to enhanced exposure of modified autoantigens. These effects of IL-18 were not noted in control keratinocytes(49). Interestingly, UV light has been reported to activate the inflammasome in keratinocytes(51), but whether this contributes to enhanced photosensitivity in SLE patients remains to be determined.

Cardiovascular Disease

SLE patients demonstrate up to a 50-fold increased risk of cardiovascular disease (CVD) (52). The detrimental effects of type I IFNs in the vasculature of SLE patients has been proposed to be a primary pathogenic mediator of this risk (reviewed in(53). One mechanism in which type I IFNs impact vascular health is through their detrimental effects on growth and differentiation of endothelial progenitor cells, which are important for vascular repair(54). Type I IFNs repress expression of the pro-angiogenic cytokine IL-1 β (55). Importantly, type I IFNs have also been shown to upregulate NLRP3, caspase-1 and IL-18 in human EPC cultures, which results in enhanced production of IL-18. IL-18, in turn, has inhibitory effects on EPC differentiation to mature endothelial cells(23). Inhibition of caspase-1 in these cultures prevents the detrimental effects of type I IFNs (23), and absence of functional caspase-1 also renders murine bone marrow EPC cultures resistant to the detrimental effects of pristane-induced lupus on EPC function and improves endothelial function in vivo(36**). Thus, the balance of IL-1 β and IL-18 production via inflammasome activation, as influenced by type I IFN exposure, may have important consequences for vascular health in SLE.

Cholesterol crystals, which accumulate in atherosclerotic plaques, are able to stimulate inflammasome activation, and this activation is required for atherosclerosis development in the LDL-receptor knockout model of atherosclerosis(14). Interestingly, a role for complement activation in enhancing the activation of the inflammasome in response to cholesterol crystals has recently been documented(56*). Whether immune complex mediated complement activation and deposition can enhance inflammasome activation in SLE CVD remains to be explored.

The Importance of Inflammasome-generated cytokines in SLE

IL-18 has been postulated as important in SLE as noted above. Serum levels of this cytokine are elevated in SLE patients and correlate with disease severity, autoantibody profiles and the presence of lupus nephritis (23, 57–59). Moreover, IL-18 transcripts are elevated in glomeruli and tubulointerstitial compartments from patients with lupus nephritis(60), and serum levels correlate with the severity of lupus nephritis and degree of proteinuria(61*). Inhibition of IL-18 function in the murine lupus model MRL-Fas^{lpr} suggests a role for IL-18 in SLE nephritis and skin disease(62, 63), and reductions in IL-18 transcripts have been associated with improvement in murine lupus nephritis models(64). Unlike IL-18, increased serum levels of IL-1 β are not commonly observed in SLE patients and have not been sufficiently linked to lupus pathogenesis(65).

Modulation of Inflammasome Activity in SLE

Therapeutic intervention for SLE patients may have modulating effects on inflammasome activity. Hydroxychloroquine has not been shown to significantly modify inflammatory cytokine levels in patients after six months of therapy(65). However, others have shown that chloroquine is able to reduce inflammasome activation by immune complexes(24, 25). Glucocorticoids induce expression of NLRP3 and enhance its activation and IL-1 β secretion by ATP in vitro (66). In vivo, glucocorticoids may also have a positive effect on NLRP3, NLRP1, caspase-1 and IL-1 β expression in SLE patients(67). A recent paper suggests that methotrexate is able to stimulate IL-1 β production in a cultured monocytic cell line, but it is unclear whether this is related to induction of cell death. These findings were not able to be replicated in primary human PBMCs(68), thus the in vivo effects of methotrexate on inflammasome activity remain unclear. Further exploration into how treatments for SLE impact inflammasome activity are needed.

Conclusion

SLE is a heterogeneous disease with wide-ranging manifestations. The research discussed above suggests that the inflammasome is emerging as an important player in lupus pathogenesis (Figure 1). Consideration of the role of the inflammasome in further mechanistic studies of this disease is warranted. Targeting of the NLRP3 inflammasome appears to be a promising therapeutic avenue for lupus nephritis and further research is needed to understand whether other organ damage can be prevented with inhibition of this complex.

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Key Points

1. Activation of the inflammasome by SLE-specific immune complexes, complement activation or neutrophil NETs may contribute to organ inflammation and propagation of aberrant immune responses.
2. Inhibition of NLRP3, caspase-1 and IL-18 has shown benefit to nephritis in various murine models of lupus.
3. Activation of caspase-1 contributes to endothelial progenitor cell dysfunction and may promote vascular damage in SLE.

Figure 1.

The inflammasome is activated in SLE and contributes to disease pathogenesis. Immune complexes, neutrophil NETs and type I IFN responses may enhance inflammasome activation in SLE. This results in increased production of IL-18, which contributes to cutaneous lesion development, cardiovascular disease risk and nephritis. A role for caspase-1 in promoting type I IFN responses and autoantibody generation has also been noted in the pristane model of lupus. The NLRP3 inflammasome has also been implicated as an important contributor to lupus nephritis. CVD=cardiovascular disease, IFN=interferon.

Table 1

Summary of inflammasome scaffolds and their links to SLE.

Inflammasome Scaffold	Activation Triggers	Links to SLE
NLRP1	<i>Bacillus anthracis</i> lethal toxin	Genetic polymorphisms associated with SLE
NLRP3	Crystalline material, potassium efflux, immune complexes, C3a, UVB radiation, microbial PAMPs, mitochondrial destabilization	Upregulated in diseased tissue, inhibition improves disease in murine models
NLRC4/IPAF	<i>Salmonella typhimurium</i> , <i>Pseudomonas aeruginosa</i> , <i>Legionella pneumophila</i> , <i>Shigella flexneri</i> infection	None reported
AIM2	Double-stranded DNA; DNA viruses, <i>Francisella tularensis</i> and <i>Listeria monocytogenes</i> infection	Inhibition provides resistance to apoptotic DNA-induced lupus phenotype but also increases type I IFN responses through upregulation of p202
IFI-16	DNA	None reported
RIG-I	RNA	May facilitate CCL5 upregulation in nephritis but no links with its inflammasome activity known

CCL5=chemokine ligand 5, PAMPs=pathogen-associated molecular patterns, SLE=systemic lupus erythematosus