REVIEW ARTICLE

Targeting the inflammasome in rheumatic diseases

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Activation of the inflammasome, a protein complex responsible for many cellular functions, including the activation of the proinflammatory cytokines interleukin (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. Furthermore, 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. (Translational Research 2015;■:1–13)

Abbreviations: AIM2 = Absent in Melanoma 2; *AOSD* = adult-onset Still's disease; AS = ankylosing spondylitis; ASC = apoptosis-associated speck-like protein containing a caspase recruitment domain; CAPS = cryopyrin-associated periodic syndrome; CARD = caspase-recruitment domain; CPPD = calcium pyrophosphate dehydrate; FA = fatty acids; FMF = familial Mediterranean fever; HIDS = hyperimmunoglobulinemia D syndrome; IL = interleukin; IL-1RA = IL-1 receptor antagonist; MSU = monosodium urate; NFκB = nuclear factor κB; NLR = nod-like receptor; NOMID = neonatal-onset multisystem inflammatory disease; NSAID = nonsteroidal anti-inflammatory drug; PAPA = pyogenic sterile arthritis, pyoderma gangrenosum and acne; PBMCs = peripheral blood mononuclear cells; RA = rheumatoid arthritis; RIG-I = retinoic acid–inducible gene I; ROS = reactive oxygen species; s-JIA = systemic onset juvenile idiopathic arthritis; SLE = systemic lupus erythematosus; TLR = toll-like receptor; TRAPS = tumor necrosis factor receptor–associated periodic syndrome

INTRODUCTION

For more than 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 US Food and Drug Administration-approved therapies, and more indications are in the pipeline. This review will summarize the mechanisms by which 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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Submitted for publication March 13, 2015; revision submitted June 2, 2015; accepted for publication June 4, 2015.

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1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2015.06.006

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 Lamkanfi and Dixit[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 uses a central scaffold, such as Nucleotide oligomerization domain-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, ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain [CARD]), which then interacts with the CARD on caspase 1, resulting in caspase 1 oligomerization and activation (reviewed in Latz et al,[3] summarized in Fig 1). Other inflammasome scaffolds not related to the NLR also serve similar functions in inflammasome assembly but their triggers for activation primarily include cytosolic nucleic acids. These include Absent in Melanoma 2 (AIM2), interferon gamma–inducible protein 16 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 nuclear factor kappa B (NF-κB) activation by toll-like receptor (TLR) ligands, stimulates NLRP3 and IL-1β transcription and prepares the cell for a vigorous response on activation.[5,6] Deubiquitination 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 colocalization of inflammasome components.[8] Other adaptor and signaling molecules, such as caspase 8, also participate in inflammasome regulation (reviewed in Man and Kanneganti[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 proinflammatory cytokine IL-1β (see Table I). 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 patients with cryopyrin-associated periodic syndrome (CAPS), and anakinra is also approved for use in rheumatoid arthritis (RA).[15] However, as described subsequently, 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 patients with rheumatic disease.

Other medications that were initially developed for noninflammasome-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 (ω-3FAs), 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 interfere with TLRs 7 and 9 activation in the lysosomal compartment, block inflammasome activation and IL-1β release after certain inflammasome activating triggers.[13,23] Colchicine, which inhibits microtubule assembly, is able to block inflammasome activation by preventing colocalization of ASC with NLRP3.[24,25] Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the NLRP3 inflammasome via blockade of cyclooxygenase (COX)-2 effects on this complex.[26] Some of these listed medications have been shown to have effects on rheumatic diseases, but further research is needed to