

NLRP3 Inflammasome: A Novel Therapeutic Target in Arthritis

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Editorial

Arthritis is a term used to mean an inflammation of one or more of your joints. The main symptoms of arthritis are joint pain and stiffness, which typically worsen with age. Other symptoms may include redness, warmth, and swelling and decreased range of motion of the affected joints. The most common types of arthritis are osteoarthritis and rheumatoid arthritis [1].

The inflammasome is a multiprotein intracellular complex that plays an important role in inflammation. It also induces a lytic form of regulated cell death termed pyroptosis [2].

Pyroptosis has been reported in macrophages infected with *Shigella flexneri* and *Salmonella enterica* serovar Typhimurium bacterial pathogens [3-5]. This term is used since 2001 to distinguish this inflammatory form of caspase-regulated necrosis from accidental necrosis and apoptosis [6].

Pyroptosis induction requires two types of receptors that sense harmful signals which can be given off by invasive pathogens or by an injury to a tissue. These receptors are Nod-like receptors (NLRs) and Toll-like receptors [7]. The nucleotide binding domain and leucine-rich repeat pyrin 3 domain (NLRP3 or cryopyrin) sensor protein, organizes the assembly of the best-characterized inflammasome, the NLRP3-inflammasome. NLRP3 is kept in an inactive state complexed with Heat Shock Protein 90 (HSP90) and suppressor of the G2 allele of *skp1* (SGT1) in the cytoplasm. Upon detecting harmful signals, HSP90 and SGT1 are released from NLRP3 which then recruits apoptosis-associated speck-like protein containing a CARD (ASC) protein and caspase-1 to the inflammasome complex. ASC contains a caspase activation and recruitment domain (CARD) that binds and facilitates activation of pro-caspase-1 through CARD-CARD interactions. Activated caspase-1 cleaves the precursors of interleukin (IL)-1 β and IL-18 converting them into the mature, secreted inflammatory cytokines [8]. Furthermore, the inflammatory caspases 1, 4 and 5 can induce pyroptosis directly by cleaving gasdermin D (GSDMD) into a pore-forming amino-terminal domain (GSDMDN) and an inhibitory carboxy-terminal (GSDMDC) domain. GSDMDN then oligomerizes and inserts in the plasma membrane inducing rapid cell lysis [9-12].

There is emerging evidence for involvement of the NLRP3-inflammasome/IL-1 β , IL18 axis in the inflammatory responses of arthritic disorders namely osteoarthritis [2,13], and rheumatoid arthritis [14]. The study of Sorge et al. [15] showed that active rheumatoid arthritis is associated with increasing NLRP3 expression and IL-1 β secretion in whole blood cells of mice upon stimulation via TLR3 and TLR4. In the same context, Choulaki et al. [14] revealed that IL-1 β secretion seems to be predominately driven by caspase-1 and caspase-8. They postulated that targeting NLRP3 or downstream caspases may be of benefit in suppressing IL-1 β production in rheumatoid arthritis.

In the recent study done by Zhao et al. [13], NLRP1 and NLRP3 inflammasomes expression was found to be high in human synovial samples obtained from knee osteoarthritis patients. When they isolated human fibroblast-like synoviocytes (FLSs) in vitro and stimulated them with lipopolysaccharide (LPS) and ATP, this resulted in cell pyroptosis. Interestingly, LPS+ATP-induced pyroptosis was attenuated by NLRP1 and NLRP3 siRNAs. Additionally, inhibition of NLRP1 and NLRP3 led to a remarkable reduction of pyroptosis-related cytokines.

In conclusion, NLRP3 inflammasome may have a potential role in the pathogenesis of arthritis. Targeting NLRP3 may represent a novel therapeutic target in arthritis.

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