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Review article

NLRP3 inflammasome in Different Autoimmune Diseases

Inflammasome NLRP3 Dans Différentes maladies auto-immunes

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Abstract

Inflammasome is an intracellular protein composed of a multimeric complex. It is an integral part of the innate immune system targeting the immune cellular homeostasis. The dominant particles/domains in the complex guide its name and function. Researches are ongoing for better understanding of inflammasomes function and their role in different pathologies, therefore the possibility of targeting them with therapeutic agents. NLRP3, specifically, was widely studied and identified in a group of autoinflammatory, autoimmune, degenerative and malignant disorders. Its activation can occur through different exogenous triggers such as microbial agents, or endogenous factors as cellular stress. The latter can explain the participation of NLRP3 in the pathogenesis of autoimmune disorders. Activation of NLRP3 promotes the cleavage of potent proinflammatory cytokines and, hence, forming the functioning form of caspase-1. This process is a part of the innate immune response and, in parallel, the signaling through activating IL-1 β and IL-18 is related to the adaptive immunity. In this review, we tried to delineate the importance of NLRP3 inflammasome and its downstream signals in selected autoimmune diseases, and to outline the possible future therapeutic strategy.

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Inflammasomes:

Inflammasomes are multimeric proteins reside in the cellular cytoplasm weighted molecularly 700 KDa. The main 3 components involved in the structure of

any inflammasome are sensor or adaptor protein, pattern recognition receptor (PRR) and the proinflammatory caspase-1 [1]. PRR works as an apoptosis-related speck-like component (ASC) with a caspase-recruitment domain (CARD). Inflammasome

complex guides the verified function of PRRs in recognizing pathogen-associated molecular pattern (PAMP) and damage-associated molecular pattern (DAMP) [2]. Both external and internal triggers can promote inflammasome activation and initiate the cascade of inflammasome self-cleavage, followed by activation of the proinflammatory cytokines interleukin (IL)-1 β and IL-18, and thereafter, promotion of caspase-1 into its active form [3,4]. Inflammasome activation and its downstream proteins function to keep the tissue homeostasis and repair [5].

The first described PRRs as parts of the inflammasome complex were (1) NLRs: nucleotide-binding oligomerization domain (NOD) and leucine-rich repeat (LRR)-containing receptors, (2) ALRs: the absent in melanoma-2 (AIM2)-like receptors and (3) proteins containing a tripartite motif (TRIM), including pyrin. Inflammasome cascade starts upon PAMP or DAMP recognition through one of the aforementioned PRRs, leading to ASC recruitment and generation of a new multimeric complex or 'speck'. Afterwards, cleavage of procaspase-1 into the bioactive caspase-1 follows, leading to stimulation of pro-IL-1 β and pro-IL-18 into their active forms. This process completes through activation of the pore-forming gasdermin D (GSDMD) and induction of pyroptosis or inflammatory cell death (Figure 1) [3,6]. Role of inflammasome can be outlined in defending against exogenous pathogens, removing the damaged cell debris, and cross-talking with the adaptive immune cells. Aberrant inflammasome activation is incorporated in many autoinflammatory and autoimmune disorders, infectious diseases and malignancies [3], due to the augmented injurious inflammation, such as in diseases like cryopyrin-associated periodic syndromes (CAPS), diabetes, obesity, atherosclerosis, crystal-related diseases (silicosis and gout), autoimmune diseases (multiple sclerosis, inflammatory bowel disease and lupus), and renal diseases, [acute kidney injury (AKI) and chronic kidney disease (CKD)] [7,8].

Inflammasomes assembly:

Domains of NLRs determine their designation. These domains are 1) a central nucleotide-binding domain (NBD), 2) LRR domain (except in NLRP10), 3) N-terminal (pyrin/CARD), and 4) C-terminal (LRR domain). N-terminal classifies NLRs into NLRP (leading to indirect caspase-1 activation) or NLRC (leading to direct caspase-1 activation) receptors. Inflammasome assembly requires either homotypic

CARD-CARD or PYD-PYD interactions, to induce oligomerization [10]. ASC adaptor protein gathers NLRP3, AIM2 and pyrin together in to the inflammasome complex [11]. Alternatively, inflammasome assembly can be mediated through the ALR family instead of LRR and the RIG-I-like receptor (RLR) family [12].

Inflammasome downstream proteins and caspase-1 activation:

NLRP1 inflammasome

Inflammasome containing NLR pyrin domain (NLRP)1 assembly occurs through two main ligands: muramyl dipeptide (MDP), a combined fragment from both Gram positive and negative bacteria, and *Bacillus anthracis* lethal toxin [13]. NLRP1 oligomerization requires the interaction between NLRP1, MDP and adenosine triphosphate (ATP), leading to caspase-1 cleavage. The process is enhanced by the adaptor protein ASC [14].

NLRP3 inflammasome

NLRP3 consists of a sensor PYD, an adaptor (ASC) and an effector (caspase 1). The N-terminal, PYD, is responsible for NLRP3 oligomerization and function. The T-terminal, LRR, promotes autoinhibition by folding back onto PYD. ASC is responsible for the domains' cross-talking [15]. NLRP3 assembly starts with ASC recruitment, followed by cleavage of caspase 1 and maturation of IL-1 β and IL-18, leading to pyroptosis. NLRP3 stimulation uniquely depends basically on PAMPs, DAMPs and environmental irritants recognition, through antigen presenting cells, Toll-like receptor (TLR), tumor necrosis factor (TNF)- α , a transcription regulator nuclear factor- κ B (NF- κ B) [14, 16].

NLRP3 oligomerization occurs through 3 models: the ion flux, the reactive oxygen species (ROS) and the lysosome rupture model. Other noncanonical cascades can participate in NLRP3 assembly involving caspase-11 cleavage by intracellular lipopolysaccharides (LPS), a mechanism associates the rupture of bacteria-loaded phagolysosomes [12].

In the ion flux model, changes in specific cytosolic cations, such as K $^{+}$, Ca $^{2+}$ and H $^{+}$, would activate NLRP3 [16]. Extracellular ATP activates the ATP-gated ion channel P2X7 and triggers rapid K $^{+}$ efflux; resulting in caspase-1 cleavage. This model can, additionally, stimulate NLRP1b and NLRC4 assembly [17]. Oxidative stress and release of ROS can activate NLRP3 oligomerization directly and indirectly via

ATP, alum, uric acid and Nigericin. However, the precise mechanism remains controversial. It is suggested that ROS inhibitors deactivate NLRP3 through inhibiting NF- κ B and pro-IL-1 β transcription [18]. Furthermore, the oxidized mitochondrial DNA released from dysfunctional mitochondria and ROS-independent mitochondrial cardiolipin can directly oligomerize the NLRP3 inflammasome [19]. Lysosomal rupture associating phagocytosis of large particulate materials, such as urate crystals, alum, silica, malaria, hydroxyapatite and amyloid- β , can activate NLRP3 inflammasome. Inhibitors of the lysosomal protease Cathepsin B deactivate NLRP3 and NLRP1b [20].

NLRP6 and NLRP12 inflammasomes

Co-expression of NLRP6 or NLRP12 with ASC results in synergistic activation of caspase-1 [21]. NLRP6, unlike NLRP3, is highly expressed in non-hematopoietic cells, mainly intestinal epithelial and goblet cells, to maintain intestinal homeostasis. It contributes in mucus secretion by goblet cells through activating IL-1 β - and IL-18, and the downregulation of NF- κ B and MAPK signaling [22]. NLRP12 approximates the functional features of NLRP6. It protects against colitis and colon cancer [22], and maintain intestinal homeostasis by negatively regulating inflammatory NF- κ B and MAPK.

AIM2-like receptors (ALRs) and RIG-I-like receptors (RLR)

AIM2 and ALRs are members of the pyrin family, containing PYD and DNA-binding domain. These proteins can theoretically bind nucleic acids and recruit ASC to form inflammasomes [23]. AIM2 stimulates inflammasome assembly through recognizing pathogenic or self-DNA [24]. The RIG-I like receptor (RLR), type I interferon (IFN) production inducer, can trigger inflammasome formation [25].

Role of NLRP3 inflammasome in systemic lupus erythematosus (SLE):

In SLE, the increased rate of apoptosis combined with an inefficient clearance of apoptotic cells leads to accumulation of DAMPs and activation of NLRP3. Other DAMPs can activate NLRP3 including nucleic acids, the main self-antigens in SLE, through TLR activation [26].

Neutrophil extracellular traps (NETs) are granule proteins bound to chromatin fibers and produced by activated neutrophils to kill extracellular pathogens. NETs are effective promoters of NLRP3

inflammasome in macrophages. SLE patients are more sensitive to NETs-related inflammasome assembly than healthy controls. Low-density granulocytes (LDGs) are a distinct subset of pro-inflammatory neutrophils detected in patients with SLE. LDGs promote NETosis and the related expression of proteins and enzymes, leading to a higher exposure of immunostimulatory molecules and inflammasome oligomerization. Active IL-18, released by NLRP3 assembly, induces NETosis [27].

Abnormal autophagy is another involved mechanism in NLRP3 stimulation among SLE patients. Physiologically, autophagy is a regulatory mechanism responsible for removing the excess or abnormal cellular components, leading to tuning inflammasome activation. SLE patients have downregulated macrophage autophagy, with hyperactivation of inflammasome in response to the crowded DAMPs and loss of degradation of inflammasome proteins and IL-1 [28]. In cutaneous SLE, NLRP3 assembly contributes to the chronic inflammatory status, through upregulation of IL-1 β [29].

NLRP3 is located in chromosome region 1q43-q44 and contains 3 kb upstream of the transcription exons and introns, and 2 kb downstream of the stop codon. Among 60 single nucleotide polymorphisms (SNPs) coding the NLRP3 gene, the five most studied in SLE were rs10754558, rs4612666, rs3806268, rs35829419 and rs4352135 [30]. The rs3806268 GG was associated with low C4 and the rs4612666 TT genotype was associated with anti-SSA positive rate. SNP rs2043211 increases the risk of SLE among males [31]. In a Brazilian study, rs10754558 was initially associated with SLE development, and rs10754558 G allele was significantly associated with lupus nephritis (LN) [32]. In an Iranian study, three NLRP3 SNPs were evaluated, two gain of function alleles (rs10754558 and rs4612666) and one loss of function SNP (rs6672995), were associated with underproduction of IL-1. SNP rs10754558 was associated with higher risk of SLE development. Lower age of onset was related to C and G alleles for rs4612666 and rs10754558, respectively. Patients with the C allele for rs4612666 had higher levels of ESR, anti-dsDNA, C3 and C4 [33]. However, G allele for rs10754558 caused lower levels of C3 and C4. SNPs rs4612666 and rs10754558 were associated with increased risk of neurological and renal involvement [34].

Role of NLRP3 inflammasome in lupus nephritis (LN):

NLRP3 overstimulation was involved in the pathogenesis and progression of LN and other kidney diseases. Renal mononuclear cells (dendritic cells and macrophages) and parenchymal cells (podocytes, endothelial, parietal and tubular epithelial cells) express the components of NLRP3 inflammasome in response to various PAMPs and DAMPs [28]. Ischemic reperfusion kidney injury can lead to cell damage and renal tubular cell necrosis, followed by release of endogenous DAMPs and NLRP3 cleavage [35]. In pediatric patients with LN, peripheral expression of NLRP3 was significantly correlated to SLE activity index [36].

Role of NLRP3 inflammasome in systemic juvenile idiopathic arthritis (SJIA) and recurrent macrophage activation syndrome (MAS):

An extremely rare heterozygous missense variant, c.482G>A, p.R161H was detected in the CASP1 gene encoding pro-caspase-1 in a patient with SJIA and recurrent MAS (single case report). This gain-of-function allele for both NLRP3 and NF- κ B augments the release of IL-6, IL-1 β and IL-18. LPS stimulation induces high expression of IL-6 and activation of the NLRP3 inflammasome and caspase-1. Expression of the CASP1 variant in an NF- κ B reporter luciferase assay stimulates NF- κ B activation through RIP2-dependent model [37].

Role of NLRP3 in rheumatoid arthritis (RA):

Rheumatoid arthritis (RA) is associated with overproduction of inflammatory cytokines in the sera and synovia, mainly TNF α , IL-6, and IL-1 β [38]. The latter expression in the synovial membrane activates chondrocytes and osteoclasts, leading to cartilage erosion and bone shedding, in addition to over-release of synovial IL-18 [39]. NLRP3 expression in mononuclear cells is upregulated in RA patients [40, 41], but not in the neutrophil, making the contribution of NLRP3 in the inflammatory status of RA debatable. Furthermore, IL-18 levels increase, but not IL-1, denoting that caspase-1 activation is mediated by IL-18 rather than NLRP3 assembly [42].

Role of NLRP3 in systemic sclerosis:

NLRP3 inflammasome is incriminated in the underlying pathogenesis of systemic sclerosis and its associated synovitis, arthritis, fibrosis and vascular damage, through the activation of proinflammatory Th2 cells, profibrotic M2 macrophages, B cells, fibroblasts and endothelial cells, leading to promotion

of fibro-necrotic changes [43]. NLRP3 and its cascade proteins were expressed profusely in sera and skin biopsies of patients with systemic sclerosis, with significant relevance to cutaneous and pulmonary affection [44]. NLRP3 contribution in systemic sclerosis can be summarized in 2 models: 1) the inhibitory influence on M2 macrophage activation, leading to suppression of the disease progression. It is known that M2 macrophages promote production of profibrotic cytokines including IL-4, IL-13, and transforming growth factor β (TGF- β), leading to overexpression of extracellular matrix (ECM) and fibrosis [45,46]. 2) the effect of NLRP3/IL-1 signaling activation on modulating Th1/Th2 balance and B cells-mediated expression of autoantibodies, pro-fibrosis cytokines and stimulation of fibrosis [46,47]. Notably, B cell activators such as tyrosine phosphatase N22 and BAFF, were reported to activate NLRP3, augment NF- κ B expression and upregulate ROS and K⁺ efflux [48].

The expression of NLRP3 in skin biopsies is positively relevant to levels of endothelin (ET)-1 [49]. Suppression of nitric oxide (NO), a potent vasodilator, and increasing ET-1 expression are the key modulators of vascular abnormalities in systemic sclerosis. NO acts as an inhibitor of NLRP3 inflammasome assembly through scavenging dysfunctional mitochondria [50,51]. MiR-155, an activator of NLRP3, is commonly expressed from the fibroblasts of systemic sclerosis patients [52]. Cutaneous NLRP3 was positively correlated with modified Rodnan skin thickness score [49].

Role of NLRP3 in autoimmune renal diseases:

Inflammasomes trigger autoimmune renal diseases using the influence of IL-1 β and IL-18 on deviating the T cell response, particularly T helper (Th) cells, towards Th17 and Th1. IL-1 inhibitors and two specific NLRP3 inflammasome inhibitors, MCC950 and β -hydroxybutyrate, showed promising results in the inflammasome-mediated conditions [8].

Puromycin amino-nucleoside (PAN) induces cellular stress in the podocytes through activation of NLRP3 inflammasome. PAN was commonly used to promote nephrotic syndrome (NS) in rodents. The excess of NLRP3, IL-1 β and IL-18, can injure the renal tubular cells leading to impaired kidney functions. IL-1 β induces inflammation through activation of NF- κ B, which in turn provokes a potentially fibrinogenic cascade including generation of protein kinase, ROS and TGF- β 1 [53].

Role of NLRP3 inflammasome in ANCA-associated vasculitis (AAV):

Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) can be stimulated by active IL-18 and IL-1 β , and the generated ROS by activated neutrophils. ANCA causes TNF-induced neutrophils degranulation and production of ROS. IL-18 is upregulated in the kidney in AAV. In myeloperoxidase glomerulonephritis (GN), Th1 and Th17 hyperstimulation, mediated by IL-1 β and IL-18, can induce glomerular injury in experimental anti-myeloperoxidase GN. Exposure to DAMPs or PAMPs in patients with AAV could activate inflammasome directly or through provocation of NETs. Notably, NETs are involved in the renal affection in AAV, rising the risk of GN [8].

NLRP3 inflammasome inhibitors:

NLRP3 inflammasome inhibitors can act directly by blocking the protein function or indirectly by targeting P2X7 receptor, ASC, caspase-1, IL-1 or RIP3. MCC950, a highly-selective NLRP3 inhibitor, can attenuate the severity of autoimmune encephalomyelitis, LN, steroid-resistant asthma and diabetic nephropathy in mice [54-56], through downregulation of NLRP3, caspase-1 and IL-1 production. It was associated with significant improvement in the podocyte effacement and heaviness of proteinuria in short time [57]. MCC950 blocks ATP hydrolysis and inhibits NLRP3 inflammasome formation and activation by directly interacting with the NACHT domain [58,59]. Phase II studies in RA was suspended due to drug toxicity [15].

Similar to MCC950, tranilast can bind to the NACHT domain of NLRP3, showing promising impact on reducing arthritis in mice with minimal side effects [60]. Another NLRP3 inhibitor, CY-09, specifically binds to the ATPase domain hindering the oligomerization of NLRP3, and reducing IL-1 β synovial expression in patients with gouty arthritis [61]. It can also decrease myocardial fibrosis induced by ischemia [62]. Besides, miRNAs combine with the 3' UTR sites of NLRP3 transcripts, causing NLRP3 inflammasome downregulation in RA and SLE mouse models [63].

Another NLRP3 direct inhibitor, Tris dibenzylidene acetone dipalladium (DBA), led to marked reduction of proteinuria, lower anti-dsDNA antibodies levels and improved kidney function in mice with LN compared with control mice [23]. Tris DBA acts through regulation of autophagy mediated by the

NLRP3 inflammasome and T-cell function along with phosphorylation inhibition of JNK, ERK and p38 MAPK signaling pathways via ROS-mediated inflammation [64].

A20, a TNF- α -induced protein 3, reduces NLRP3-mediated inflammation and pyroptosis, therefore, reducing the risk of pulmonary fibrosis in patients with RA [65]. Another promising NLRP3 suppressor is β -hydroxybutyrate (BHB), an oxidative metabolite of fat, which downstreams NLRP3 activation through inhibiting K⁺ efflux and ASC speck formation [66].

The ROS inhibitor, Citral (3,7-dimethyl-2,6-octadienal), an active component of the Chinese herbal *Litsea cubeba*, and M1, a bioactive ginseng, seem to be effective through inhibition of NLRP3 activation, ROS, COX-2 production and Nrf2 activation. M1 significantly suppresses NLRP3 inflammasome activation in podocytes through autophagy induction [67]. ROS-inhibition using chemical scavengers of ROS or inhibitors of NADPH oxidase could down-stimulate NLRP3 inflammasome in response to several stimuli [68].

BBG treatment can reduce the serum levels of IL-1, IL-17 and the Th17/Treg cell ratio. Its efficacy in reducing LN inflammation was confirmed in NZM2328 mice. In kidney tissue, RIP3 activation leads to podocyte necrosis and NLRP3 oligomerization. GSK872, an inhibitor of RIP3, MLKL and caspase-1, could reduce glomerular and tubulointerstitial inflammation with less IgG and C3 deposition in the kidney tissue [48].

AZD 1208, an inhibitor of PIM-1 in NZb/WF1 mice, suppressed the renal NLRP3 and caspase-1 activation with less IL-1 β and proteinuria, through reduction of the calcium influx [69]. Caspase-1 blockade is another strategy to downregulate NLRP3 inflammasome. YVAD-CHO is a reversible caspase-1 inhibitor, which reduces IL-1 β excretion in systemic sclerosis monocytes. Z-YVAD-FMK blocks overexpression of IL-1 β in fibroblasts from skin and lung of systemic sclerosis patients [70]. Sinkihwan-gamibang, a recent Korean therapeutic agent against PAN-induced renal injury and NS, showed promising clinical improvements in patients with chronic nephritis and NS [53].

Conclusion

NLRP3 inflammasome has gained marked interest in the last decade due to its fundamental role with its

downstream proteins in autoimmune diseases such as lupus, lupus nephritis, systemic sclerosis, ANCA-related vasculitis among others. Research is lacking as regards the young population; however, a new therapeutic hope has emerged based on the current studies on NLRP3.

Declaration on Interest

Authors declare that they have no conflict of interest.

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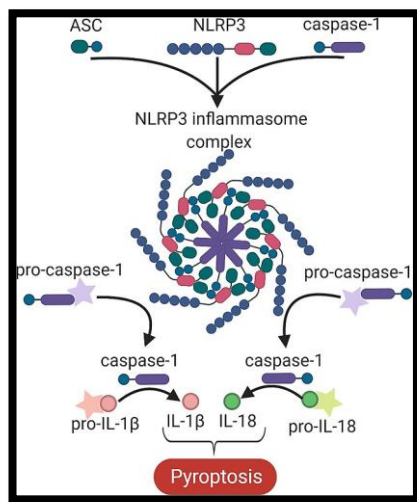


Figure (1): Formation of the NLRP3 inflammasome. NLRP3 inflammasome components (NLRP3, ASC and caspase-1) bind to form NLRP3 inflammasome complex, leading to the cleavage of pro-caspase-1 into its active isomer, caspase-1, which in turn activates pro-IL-1 β and pro-IL-18 into IL-1 β and IL-18 respectively. The excess in the downstream proteins leads to pyroptosis [9]

NBD: nucleotide binding domain
NETs: neutrophil extracellular traps
NF- κ B: transcription regulator nuclear factor β
NLRP: NLR containing pyrin domain
NLRs: NOD and LRR containing receptors
NO: nitric oxide
NOD: nucleotide-binding oligomerization domain
NS: nephrotic syndrome
PAMP: pathogen associated molecular pattern
PAN: puromycin amino-nucleoside
PRRs: pattern recognition receptors
PYD: pyrin domain
RA: rheumatoid arthritis
RLR: RIG-1 like receptors
ROS: reactive oxygen species
SJIA: systemic juvenile idiopathic arthritis
SLE: systemic lupus erythematosus
SNPs: single nucleotide polymorphism
Th: T helper cells
TLR: toll-like receptors
TNF: tumor necrosis factor
TRIM: tripartite motif

Abbreviations:

AAV: ANCA-associated vasculitis
AIM2: absent in melanoma-2
AKI: acute kidney injury
ALRs: AIM2-like receptors
ANCA: anti-neutrophil cytoplasmic antibody
ASC: apoptosis-associated speck-like protein containing a caspase-recruitment domain
ATP: adenosine triphosphate
BHB: β -hydroxybutyrate
CAPS: cryopyrin-associated periodic syndromes
CARD: caspase-recruitment domain
CKD: chronic kidney disease
DAMP: damage associated molecular pattern
DBA: dibenzylidene acetone
ECM: extracellular matrix
ET: endothelin
GN: glomerulonephritis
GSDMD: gasdermin-D
IFN: interferon
IL: interleukin
LDGs: low-density granulocytes
LN: lupus nephritis
LPS: lipopolysaccharides
LRR: leucine rich repeat
MAS: macrophage activation syndrome
MDP: muramyl dipeptide