

Inflammasomes and autoimmune and rheumatic diseases: A comprehensive review[☆]



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ABSTRACT

Inflammasomes are a multi-protein platform forming a part of the innate immune system. Inflammasomes are at standby status and can be activated when needed. Inflammasome activation is an important mechanism for the production of active interleukin (IL)-1 β and IL-18, which have important roles to instruct adaptive immunity. Active forms of inflammasomes trigger a series of inflammatory cascades and lead to the differentiation and polarization of naïve T cells and secretion of various cytokines, which can induce various kinds of autoimmune and rheumatic diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), gout, Sjögren's syndrome, Behçet's disease, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and IgA vasculitis (former Henoch-Schönlein purpura). In this review, we summarize studies published on inflammasomes and review their roles in various autoimmune diseases. Understanding of the role of inflammasomes may facilitate the diagnosis of autoimmune diseases and the development of tailored therapies in the future.

1. Introduction

An inflammasome, first reported by Tschopp and his team in the year 2002, is a multiprotein platform which is formed in response to various physiologic and pathogenic stimuli [1]. Activation of inflammasome is an essential component of the innate immune response and is important for the clearance of pathogens or damaged cells. It should be tightly regulated to appropriately defend against the pathogens and to prevent the pathological host damage [2]. However, excess activation of inflammasome can also drive autoimmune diseases ranging from rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE) and metabolic disorders such as type 1 and 2 diabetes, and therefore, it is important to understand this process in physiological and pathological contexts [2–4].

Inflammasomes have critical roles in both innate and adaptive immunity. An immune response begins with sensing of conserved

molecular patterns derived from pathogens and host tissue damage, which are called pathogen associated molecular patterns (PAMPs) and damage (danger) associated molecular patterns (DAMPs), respectively, and the innate immune system activates the adaptive immune system primarily through the actions of antigen presenting cells (APCs). Inflammasomes and interleukin (IL)-1 family cytokines have been implicated in the generation of adaptive immunity via T and B lymphocytes [2,4].

PAMPs, such as cell wall components and nucleic acids of microbial pathogens, are recognized by pattern recognition receptors (PRRs) which can be divided into membrane-bound PRRs (eg. toll like receptors (TLRs) and c-type lectin receptors (CLRs)) and cytoplasmic PRRs (eg. NOD-like receptors (NLRs)). Interaction of TLRs with their specific PAMPs is mediated through either MyD88-dependent pathway and triggers the signaling through nuclear factor-kappaB (NF- κ B) and the mitogen-activated protein (MAP) kinase pathway and therefore the

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secretion of pro-inflammatory cytokines and co-stimulatory molecules or TIR-domain-containing adapter-inducing interferon- β (TRIF)-dependent signaling pathway [2,4,5]. PRRs can also detect structurally related chemical moieties from damaged host cells and DAMPs act as endogenous PRR ligands. Recognition of PAMPs and DAMPs can not only lead to the induction of pro-inflammatory and anti-microbial activity but also result in the adaptive immune response [4]. In addition to these processes, APCs, such as dendritic cells (DCs), become mature in response to recognition of microbial products and participate on the several activities which are important for the initiation of T cell-mediated adaptive immune responses such as (1) presentation of processed microbial antigen to T cells with major histocompatibility complexes (MHCs) on their surfaces, (2) increase the expression of co-stimulatory molecules (CD80 and CD86) on the cell surface which are required for appropriate T cell activation and (3) release of cytokines (e.g. IL-12), which adaptive immune response are necessary to differentiate naïve T cells into their effector and memory cells. Inflammasome-dependent cytokines (IL-1 β and IL-18) have important roles to instruct these adaptive immunity [2,4].

Inflammasomes typically comprise caspase-1, the nucleotide-binding and oligomerization (NACHT), leucine rich repeat (LRR), and pyrin domain (PYD)-containing proteins and the apoptosis-associated speck-like protein containing a carboxy-terminal caspase activation and recruitment domain (ASC) [2,4,5]. Assembled inflammasomes can include a nucleotide-binding oligomerization domain and leucine-rich repeat-containing receptors and may be absent in melanoma 2 (AIM 2)-

like receptors (ALRs). The exact composition depends on the type of initiating molecules that trigger their assembly [5,6]. Serving as a platform for recruiting and activating caspase-1, inflammasomes lead to maturation of the pro-inflammatory cytokines IL-1 β and IL-18 [7]. The cytoplasmic complex eventually results in the secretion of these cytokines, thus modulating various inflammatory responses [8]. Inflammasome activation can also lead to pyroptosis, a type of pro-inflammatory cell death programmed to end the replication of pathogens within a cell [9]. Detailed process of NLRP3 and AIM2 inflammasome activation are presented in Fig. 1.

A variety of inflammasome subsets are reported to date: the NLR family subset including NLRP1, NLRP3, NLRP6, NLRP12, and caspase activation and recruitment domains (CARD)-containing protein 4 (NLRP4), and the non-NLR family subset including AIM 2 [10]. Among these, the NLRP3 inflammasome is the most studied subtype and its assembly can be triggered by TLR agonists. TLR agonists such as lipopolysaccharides (LPS) and lipid A can regulate inflammatory responses by inducing assembly of the NLRP3 inflammasome via pro-inflammatory cytokines including tumor necrosis factor (TNF)- α [11]. A more recently reported scaffold of a different kind is the AIM 2 inflammasome and its activation depends upon the recognition of host- and pathogen-associated double-stranded deoxyribonucleic acid (dsDNA) [12].

Once activated, the inflammasome can trigger an inflammatory cascade. A fully assembled inflammasome induces the recruitment and processing of pro-caspase-1 [1]. Recruited pro-caspase-1 proteins cleave themselves via oligomerization to form active caspase-1 [13]. Active

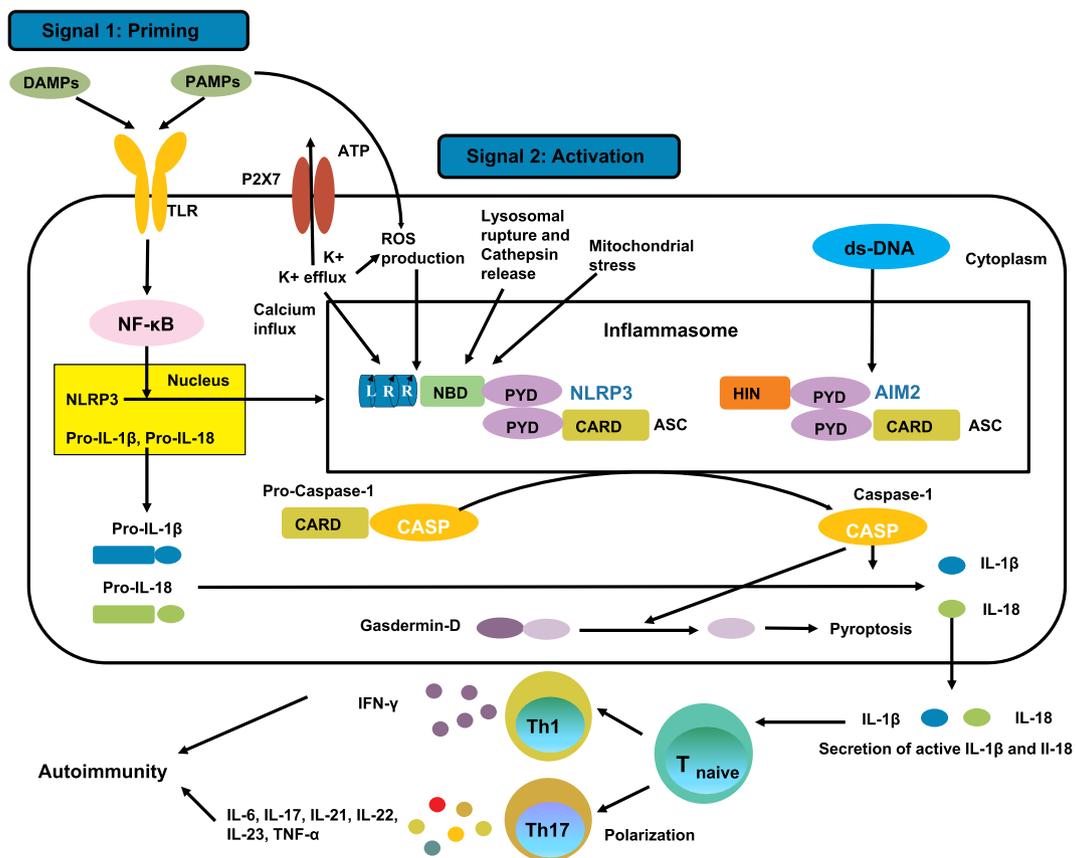


Fig. 1. Mechanisms for assembly and activation of NLRP3 and AIM2 inflammasomes. Inflammasomes are formed by two signals of priming and activation. Pathogen-associated molecular patterns (PAMPs) or endogenous damage-associated molecular patterns (DAMPs) are recognized by toll-like receptors (TLRs) and NF- κ B (nuclear factor κ B) is activated, which mediate priming of NLRP3 (nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3) inflammasome. The functional NLRP3 inflammasome is formed by various secondary signals such as potassium efflux, ROS (reactive oxygen species) production, lysosomal rupture and mitochondrial stress. AIM2 (absent in melanoma-2) inflammasome is sensed by dsDNA (double stranded DNA). Finally, caspase-1, IL (interleukin)-1 β , and IL-18 are produced on the platform of NLRP3 or AIM2 inflammasomes. Pyroptosis (gasdermin-mediated necrotic cell death) acts as an immune defense against infection. Active forms of inflammasomes lead to the differentiation and polarization of naïve T cells and secretion of various cytokines, which can induce various kinds of autoimmunity.

caspase-1 generates mature interleukin (IL)-1 β and IL-18 via cleavage of their respective precursors, pro-IL-1 β and pro-IL-18 [14–17].

Inflammasomes are reported as important molecules in understanding the pathogenesis of inflammation [18–20], which can be closely associated with the development and progression of various kinds of autoimmune diseases. In this article, we comprehensively reviewed the role of various inflammatory molecules in relation to inflammasomes, and their associated molecules in autoimmune diseases.

2. Inflammasome and systemic lupus erythematosus (Table 1 and Supplemental Table 1S)

2.1. Animal studies on inflammasomes using “lupus prone mice”

Several animal studies have demonstrated the relevance of inflammasomes in SLE. Two studies revealed that activation of the AIM2 inflammasome plays a key role in SLE pathogenesis via apoptotic DNA (apopDNA)-induced macrophage activation and IL-1 β production [21,22]. In contrast, one study suggested that decreased activity of the AIM2 inflammasome contributes to lupus by producing interferon (IFN)

Table 1
List of studies related to the role of inflammasomes in lupus.

Main study findings
Genetic variant
SNP in IL1B gene [33]
SNP in NLRP1 gene [34]
SNP in CARD8 gene [45]
NLRP3 inflammasome
Pathogenic role of NLRP3 inflammasome
Activated by <i>anti</i> -dsDNA Abs mediated by TLR4 and mitochondrial ROS [36] or potassium efflux [37]
Activated by endogenous RNA-containing U1-snRNP [38]
Activated by IRF-1 through long term type I IFN exposure [39]
Activated by NETs [52]
Activated by P2X7 signal [46]
Associated with podocyte injuries and proteinuria in lupus nephritis [27]
A role of GSK3- β in pathogenesis of lupus nephritis by activating NLRP3 inflammasome [29]
Serum IL-18 represents the activity of SLE, including renal flares [41]
Protective role of NLRP3 inflammasome
Inactivation of NLRP3 inflammasome leads to progression of lupus [30]
Downregulation of NLRP3/NLRP1 inflammasome is associated with lupus [40]
AIM2 inflammasome
Pathogenic role of AIM2 inflammasome
Activated in MRL/lpr mice [21].
Activated in SLE patients with high disease activity [21].
Important role in apopDNA-induced macrophage activation [22]
Protective role of AIM2 inflammasome
Decreased activity of AIM2 inflammasome in some mouse strains by p202 [23].
AIM2 deficiency plays a role in female lupus pathogenesis by activating Ifi202gene [42]
Gender-dependent regulation of inflammasomes
AIM2 and p202 differently regulated according to the cell type and gender [43]
Mechanism of NLRP3 inflammasome activation is different in male and female SLE patients [45]
Therapeutic targets for NLRP3 inflammasomes
Bay11-7082: NF- κ B in MRL/lpr mice [47]
TLR 7, 8 and 9 antagonists: in lupus-prone NZB/W F1 mice [50]
EGCG: in lupus-prone mice [51]

Abbreviations: NLRP: Nucleotide-binding oligomerization domain, Leucine rich Repeat and Pyrin domain containing, SNP: single nucleotide polymorphism, IL: interleukin, CARD8: caspase recruitment domain family, member 8; dsDNA: double strand DNA, TLR: Toll-like receptor, ROS: reactive oxygen species, snRNP: small nuclear ribonucleoproteins, IRF1: Interferon Regulatory Factor, IFN: interferon, NET: neutrophil extracellular trap, P2RX7: P2X purinoceptor 7, GSK3: glycogen synthase kinase 3, SLE: systemic lupus erythematosus, AIM: absent in melanoma, apopDNA: apoptotic DNA, Ifi: interferon inducible, NF- κ B: Nuclear factor-kappa B, TLR: Toll-like receptor, EGCG: epigallocatechin-3-gallate.

[23]. Three studies have shown that NLRP family inflammasomes are important in SLE pathogenesis [24–26]. In lupus prone mice, the NLRP inflammasome, which is activated by disinhibition of Deoxyribonuclease 1 Like 3 (Dnase1L3) [24] and deficiency of adenosine triphosphate binding cassette transporter A1/G1 (ABCA1/G1) gene [25], activates the cascades including caspase-1 [26].

Regarding the NLRP3 inflammasome, four studies have demonstrated its relationship with lupus nephritis or cardiopulmonary manifestations [27–30]. Fu et al. reported that NLRP3 activation has an impact on podocyte injuries and the pathogenesis of proteinuria [27]. Lu et al. reported that NLRP3-R258W mutation of myeloid cells induces proteinuria and mesangial cell destruction in pristine challenged lupus-prone mice [28]. Zhao et al. showed that activation of the NLRP3 inflammasome induces lupus nephritis through activation of glycogen synthase kinase 3- β (GSK3- β) [29]. On the other hand, Lech et al. demonstrated that inactivation of the NLRP3/(NLRP3/ASC) inflammasome induces exacerbation of lupus nephritis by inhibiting transforming growth factor (TGF)- β signaling [30] and reported a link between lung infiltration and the inactivation of NLRP3/ASC inflammasomes [30]. However, one study reported that inflammasomes are not associated with the induction of diffuse alveolar hemorrhage [31]. Two other studies explained that the risk of cardiovascular disease increases in SLE patients via inflammasome activation [26,32]. IFN- α causes activation of inflammasomes, which activates caspase-1 and IL-18, resulting in a reduced number of endothelial progenitor cells and circulating angiogenic cells leading to premature atherosclerosis [26,32].

2.2. Human studies on inflammasomes and lupus using human immune cells

Several human studies have demonstrated a strong correlation of inflammasomes with human SLE using several methods including genetic, cellular, and molecular analyses. Among these, two studies analyzed single nucleotide polymorphisms (SNPs) in inflammasome genes [33,34]. Pontillo et al. reported that polymorphisms of the inflammasome receptor gene NLRP1 play a significant role in the pathogenesis of SLE [33]. Furthermore, they revealed that among NLRP1, NLRP3, CARD8, IL-1 β , NLRC4, AIM2, and NLRPX genes, the IL-1 β gene plays a crucial role in juvenile SLE pathogenesis [34]. Although not tested in lupus, genetic variations of inflammasome genes were associated with inflammasome mRNA levels in peripheral blood mononuclear cells [35].

Human studies on inflammasomes so far have mostly used monocytes or macrophages from SLE patients. Three studies revealed that the autoantibodies that are commonly present in SLE patients lead to activation of inflammasomes [36–38]. Zhang et al. and Shin et al. demonstrated that *anti*-dsDNA antibodies could affect inflammasome activation via mitochondrial reactive oxygen species (ROS) and the potassium efflux signaling pathway [36,37]. Further, Shin et al. reported that the presence of *anti*-U1-SnRNP could influence the clinical progression of SLE patients [38].

Three other studies have investigated the correlation between the type 1 IFN response and the inflammasome pathway [32,39,40]. Liu et al. showed that long term type I IFN exposure leads to marked inflammasome activation related to IRF-1 in SLE patients [39]. In contrast, Yang et al. reported that NLRP1/3 protein and mRNA levels in peripheral blood mononuclear cells (PBMCs) are inversely proportional to the occurrence and severity of SLE [40]. Interestingly, Kahlenberg et al. discovered that IFN- α activates inflammasomes and matures IL-18, but suppresses IL-1 β [32].

In addition, two studies showed that AIM2 inflammasomes contribute to SLE progression by using human myeloid-derived suppressor cells with monocytic morphology (M-MDSCs) [21] and apopDNA-induced macrophages, respectively [22]. In addition, Wu et al. reported that serum IL-18 levels could be an indicator of clinical outcomes including lupus renal flares in pediatric-onset SLE [41].

2.3. Gender-dependent regulation of inflammasomes in SLE

Panchanathan et al. reported that female sex hormone increases the susceptibility of lupus by inducing p202 protein, which further

stimulates IFN- β , signal transducer and activator of transcription 1 (STAT1), and other molecules in immune cells [42]. On the other hand, the same group demonstrated that male sex hormone prevents lupus by inducing AIM2, which is in inverse correlation with p202 [43]. Furthermore, they also demonstrated that exposure to bisphenol A, an environmental estrogen, increases the risk of SLE by activating IFN signaling, p202 expression, and NLRP3 inflammasomes [44]. Yang et al. reported that the mechanisms of NLRP3 inflammasome hyperactivation in male and female SLE patients are similarly inducing IL-1 β production, but differences exist between them [45]. NLRP3 mRNA is overexpressed in females, whereas AIM2 mRNA is overexpressed and the CARD8 variant allele is associated with the male sex [45].

2.4. Inflammasome modulation for the treatment of SLE

The idea that SLE patients could be treated by blocking the NLRP3 inflammasome pathway has triggered the search for promising therapeutic agents. There have been three studies using MRL/lpr mice treated with isoflurane, P2X7 antagonist brilliant blue G (BBG), and I-kappaB kinase- β inhibitor (bay 11-7082), respectively [18,46,47]. These agents restricted the formation of NLRP3 inflammasomes and sequentially downregulated the release of IL-1 β [18,46,47].

Furthermore, four studies examined the influence of related factors such as A20, citral, TLR antagonists, epigallocatechin gallate (EGCG) on inflammasomes [48–51]. Li et al. reported that overexpression of A20 suppresses lupus nephritis via inhibiting NF- κ B-mediated NLRP3 inflammasomes activation [48]. Ka et al. showed that treatment with citral inhibited the activation signal of NLRP3 inflammasomes and stimulated activation of Nrf2 antioxidant signaling [49]. In addition, NZBW/FL lupus-prone mice treated with TLR 7, 8, and 9 receptor antagonists also demonstrated restriction in forming NLRP3 inflammasomes [50]. Further, Tsai et al. showed that EGCG has a preventive effect on lupus nephritis via anti-oxidation of Nrf2 and inactivation of NLRP3 inflammasomes [51]. The potential therapeutic targets for inflammasome pathways are presented in Fig. 2.

In patients with SLE, targeting IL-1 β receptor using anakinra led to clinical and serological improvement in 4 patients with lupus arthritis,

but one patient had an arthritic flare after 6 weeks, suggesting that anakinra could be an interesting alternative in individual patients with lupus arthritis not responding to conventional treatments [35].

2.5. Interaction between NETs and inflammasomes in SLE

Neutrophil extracellular traps (NETs) are known to be significant defenders against microorganisms. However, unregulated NETs could be toxic to the endothelium and lead to organ damage. Kahlenberg et al. suggested that NETs are hyper-stimulated especially in SLE patients through NLRP3 inflammasomes [52]. They showed that macrophages of SLE patients stimulated by NETs through P2X7 receptors, sequentially activate the NLRP3 inflammasomes pathway and release IL-18 [52]. Furthermore, IL-18 could reactivate NETs, causing NETosis by a ‘feed-forward’ reaction [52]. This study provided a new insight into NETs, which could potentially contribute to SLE pathogenesis [53,54].

In summary, NLRP3 inflammasome may have an important role in the pathogenesis of both lupus prone mice and human lupus through various inflammasome-driven pathways, but there have also been some reports on the protective role of inflammasomes in SLE models, requiring cautious interpretation and further additional studies will be necessary in the future. There were some reports on different gender-dependent regulation of inflammasomes in SLE and some variants in inflammasome genes (e.g. NLRP1 and IL-1 β) were found to be associated the susceptibility of SLE. Though several studies have suggested inflammasomes as potential therapeutic targets in experimental models of SLE, the results may be partial and preliminary, requiring further validations in the future. The studies on the use of IL-1 β receptor antagonist were also limited in human SLE, requiring prospective randomized controlled trials (RCTs) in the future.

3. Inflammasomes and rheumatoid arthritis (Table 2 and Supplemental Table 2S)

3.1. Animal studies on inflammasomes and RA

Several studies have suggested a role of inflammasomes in RA using

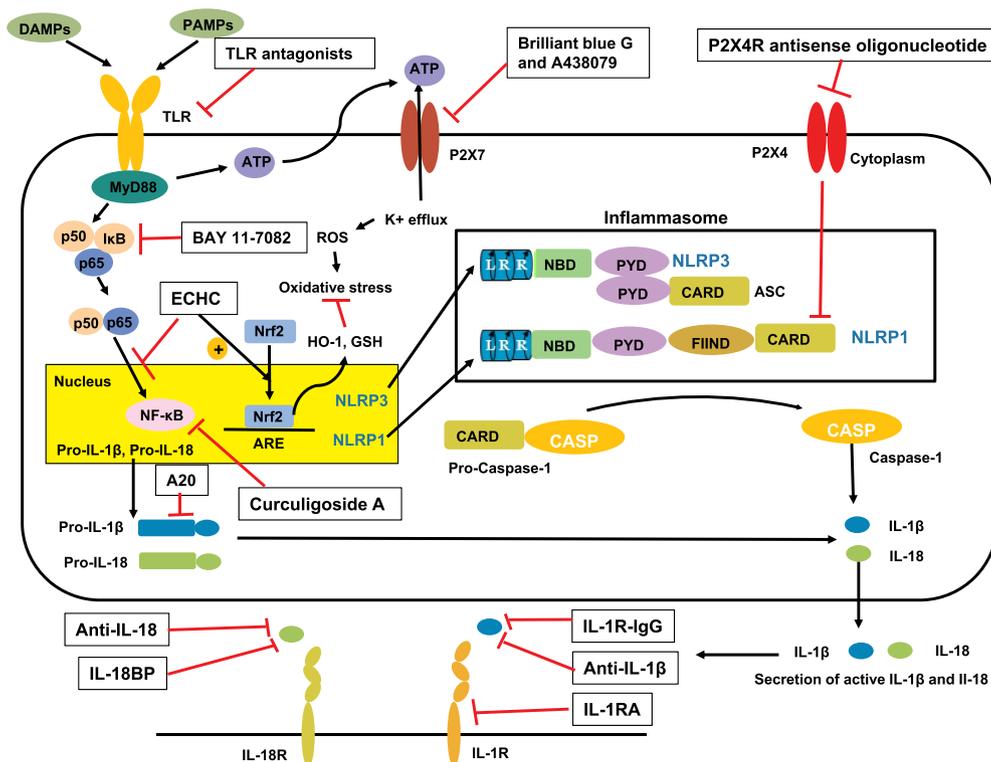


Fig. 2. Potential therapeutic targets for various activation pathways of NLRP1 and NLRP3 inflammasomes. Various cascades for inflammasome activation have been targeted through toll-like receptors (TLRs), P2X7 (P2X purinoceptor 7), P2X4 (P2X purinoceptor 4), ROS (reactive oxygen species), NF- κ B (nuclear factor κ B) pathways, IL (interleukin)-1 β , and IL-18 and IL-1 β receptor. Abbreviations: HO-1: heme oxygenase-1, GHS: glutathione, Nrf2: the nuclear factor erythroid 2-related factor 2, ARE: antioxidant response element

animal models or gene knock-outs [55–64]. One study showed a positive correlation between NLRP3 expression and clinical/radiographic severity in the mouse model of collagen induced arthritis (CIA) [55]. In another study, the NLRP3 signaling pathway was upregulated in a mouse model of adjuvant-induced arthritis (AIA) [59]. Although little is

Table 2

List of studies related to the role of inflammasomes in rheumatoid arthritis.

Main study findings
Genetic mutation
NLRP1 mutation: NLRP1-associated autoinflammation with arthritis and dyskeratosis [73]
Genetic variant
Susceptibility of RA
SNPs in NLRP1 gene: Han Chinese [76]
SNPs in NLRP3 gene: Sweden [74], Brazil [75], Caucasian [77]
SNPs in CARD8 (TUCAN) gene: Sweden [74], Brazil [75], Caucasian [77]
Disease course or activity (severity)
SNPs in NLRP3 gene: Slovenia [78], Sweden [80]
SNPs in CARD8 gene: Slovenia [78] early RA from northern Sweden [81]
Response to treatment (e.g. anti-TNF-α)
SNPs in NLRP3 gene: Caucasian [77], naïve RA from Denmark [79]
SNPs in CARD8 gene: Caucasian [77]
Comorbidities
SNPs in NLRP3 gene: atherosclerosis in Sweden [80]
No effect of genetic variant on RA
SNPs in NLRP3 gene: RA susceptibility in France and Tunisia [82]
SNPs in CARD8 gene: RA susceptibility in France and Tunisia [82] and Spain [83], cardiovascular events in Spain [83]
NLRP3 inflammasome
Pathogenic role of NLRP3 inflammasome
Animal models
Correlated with clinical/radiographic severity in CIA mouse model [55]
Upregulated in AIA mice model [59]
ASC (–/–) mice were protected from CIA, while Nlrp3(–/–) and caspase-1(–/–) mice were not [62]
ASC (–/–) mice were protected from AIA, while mice deficient in NALP-3, IPAF, or caspase-1 were not [64]
Overexpressed in IL-10KO synovium [60]
RA inflammation was reduced by deletion of NLRP3, caspase-1, and IL-1 receptor in A20 (myel-KO) mice [63]
RA patients
IL-1 β secretion and NLRP3 expression were significantly enhanced in RA [66]
MiR-33 activated NLRP3-caspase-1-IL-1 pathway in RA patients [67]
IL-1 β and IL-18 were markedly increased in patients with rheumatoid lung [68]
NLRP3 expression was increased via TLR 3 and 4 but not TLR 2 in active RA patients [70]
Hyperactivated caspase-1 in neutrophils of RA and high level of IL-18 but not IL-1 β in RA patients [72]
Protective role of NLRP3 inflammasome
NLRP1 and caspase-1 mRNA in PBMC of RA group were lower in RA [71]
No difference in NLRP3 and ASC mRNA between RA and controls [71]
NLRP3, caspase-1 and ASC mRNA in granulocyte were lower in RA [71]
A negative correlation of NLRP1 mRNA with anti-rheumatoid factor antibody [71]
Therapeutic targets for NLRP3 inflammasomes
11 β -HSD 1 inhibitor: inhibition of NF- κ B activation and NLRP1 assembly [85].
P2X4 inhibition: suppression of NLRP 1 activation, serum IL-1 β and disease activity in CIA mice [86]
Curculigoides A: reduction of NF- κ B/NLRP3 pathway activity and serum IL-1 β [87]
Prognostic indicator
Gene signature score of inflammasome gene predicted the treatment outcome of biologics [69]

Abbreviations: NLRP: nucleotide binding domain and leucine rich repeat containing proteins, CIAS1: cold-induced autoinflammatory syndrome 1 gene encoding NLRP3, TUCAN (CARD8): caspase recruitment domain family, member 8, SNP: single nucleotide polymorphism; RA: rheumatoid arthritis, CIA: Collagen-induced arthritis, AIA: Adjuvant-Induced Arthritis, ASC: Apoptosis-Associated Speck-Like Protein Containing CARD, NALP: The NACHT, LRR and PYD domains containing protein, IPAF (NLRC4): NLR family CARD domain-containing protein 4, IL: interleukin; KO: knock-out, A20 (TNFAIP3): TNF α -induced protein 3, MiR: microRNA, TLR: Toll-like receptor, mRNA: messenger RNA, PBMC: peripheral blood mononuclear cell, HSD: Hydroxysteroid dehydrogenase, P2X4: P2X purinoceptor 4, NF- κ B: Nuclear factor-kappa B, SDH: succinyl dehydrogenase.

known about the role of NLRP3 in synovial tissue, one study that used IL-10 knock out AIA mice suggested that the degree of bone erosion by synovial regulation of the NLRP3 inflammasome was associated with IL-10 [60]. In another study using mice with a myeloid-cell-specific deletion of the A20/Tnfaip3 gene, deletion of NLRP3, caspase-1, and IL-1 receptor resulted in decreased RA-associated inflammation and cartilage destruction [63].

On the other hand, two studies suggested that caspase-1 inhibition had no therapeutic effect in RA [62,64]. One study revealed that NLRP3 and caspase-1 knock-out mice were prone to CIA whereas ASC knockout mice were not, as ASC plays an independent role in T cell priming of CIA [62]. One study revealed no therapeutic difference in joint inflammation in mice deficient for NALP-3, IPAF, and caspase-1, which are inflammasome components, whereas ASC knockout mice showed decreased inflammation in AIA, indicating that ASC is independent of caspase-1, NALP-3, and IPAF [64]. Because IL-1 β is activated by caspase-1 as well as by serine proteinases, especially PR3, dual inhibition of caspase-1 and serine proteinase may have a therapeutic effect on inflammatory diseases such as RA [61].

3.2. Human studies on inflammasomes and RA

The human studies on inflammasomes suggest their important roles in RA pathogenesis [65–72]. Some studies have revealed that stimulation of the NLRP3 pathway induces IL-1 β production and caspase-1 activation in RA patients [66–68,72]. In one study with RA patients, IL-1 β and TNF production from peripheral blood monocytes was increased compared to that in healthy controls, and IL-1 β secretion and NLRP3 expression in monocytes was elevated [66]. Another study found significant upregulation of IL-1 β in bronchoalveolar lavage fluid macrophages of patients with RA-usual interstitial pneumonia (RA-UIP) [68]. Further, levels of microRNA (miR)-33, which is supposed to enhance the expression of NLRP3 and activate caspase-1 as well as NLRP3 inflammasomes, were enhanced in peripheral blood monocytes of RA patients [67]. In neutrophils, unlike in monocytes or macrophages, the expression of NLRP3, ASC, and pro-caspase-1 was decreased, whereas the expression of activated caspase-1 was increased [72]. This study showed no correlation between RA severity and serum IL-1 β , but showed a positive correlation with serum IL-18 [72].

3.3. Genetic studies on inflammasomes and RA

Several studies have investigated various kinds of inflammasome-associated genes in relation to disease susceptibility, severity, or comorbidity of RA [73–83]. Grandemange et al. identified 3 patients from two unrelated families with diffuse skin dyskeratosis, autoimmunity, autoinflammation, arthritis, and high transitional B-cell levels, and called this type of disease as NAIAD (NLRP1-associated autoinflammation with arthritis and dyskeratosis), using a next generation sequencing approach and by analyzing NLRP1 mutations [73].

One study suggested that polymorphisms in genes encoding TUCAN (CARD8) and cryopyrin (CIAS1) are associated with RA susceptibility and severity [74]. Addobbati et al. analyzed six inflammasome genes (AIM2, CARD8, CASP1, NLRP1, NLRP3, NLRC4) along with IL-1 β , IL-18, IL-1R genes and their gene expression levels in monocytes of an Eastern Brazilian population, and suggested that CARD8 and NLRP3 polymorphisms are related to RA development, and that RA patients showed high activity of IL-1 β , IL-1R, and CASP1 genes [75]. One study showed that NLRP1 gene polymorphism enhances NLRP1 expression and risk of RA in Han Chinese [76]. Several other studies showed that NLRP and CARD8 are associated with RA susceptibility, high anti-TNF treatment response rate, or high disease activity [77–81]. However, variations in CARD8 and NLRP3 genes showed no effect on RA susceptibility in the French and Tunisian populations [82]. The association with genetic variants between NLRP3 inflammasomes and the risk of developing stroke/transient ischemic attacks (TIA), but not myocardial

infarction (MI)/angina, was reported in Swedish patients with established RA [80]. One study from northern Sweden concluded that progression in early RA is associated with the presence of CARD8-X [81]. However, it is still controversial whether inflammasomes are associated with comorbidities of RA such as cardiovascular disease (CVD). According to a study from Spain that assessed the CARD8 polymorphism in 1530 RA patients with cardiovascular disease or cardiovascular risk factors, the genotype for CARD8 gene variants between patients with RA and controls was not significantly different [83]. Therefore, they suggested that the CARD8 polymorphism did not influence the development of CVD nor did it increase the risk of cardiovascular events during the entire lifetime [83].

3.4. Inflammasome targeted treatment in RA

Animal studies for inflammasome-targeted RA treatment have been reported [56,84–88]. Human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) have the potential as a novel therapeutic strategy, inactivating NLRP3 inflammasomes and differentiating naïve macrophages to the M2 phenotype [56]. One study suggested NALP1 inflammasomes, which are activated in synovial tissues from AIA rats, as a therapeutic target [84]. BVT-2733, a selective 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) inhibitor, reduced the severity of arthritis and the levels of serum IL-1, IL-6, IL-1 β , and TNF- α in CIA mice by inhibiting NF- κ B and NLRP1 inflammasome signaling pathways [85]. In another study, purinergic receptor P2X4 (P2X4R) antisense oligonucleotide, which suppresses NLRP1 inflammasome activation, was injected into CIA mice resulting in a decrease in both the disease severity and serum levels of IL-6, IL-17, IL-1 β , and TNF- α [86]. Another study demonstrated the effect of curculigoside A on AIA rats by inhibiting NF- κ B/NLRP3 activation [87]. The potential therapeutic targets for inflammasome pathways are presented in Fig. 2.

In summary, there have been great advances in the genetic studies of inflammasome-associated genes in RA. Mutations in the inflammasome genes such as NLRP1 and NLRP3 were gain of function and caused several kinds of autoimmunity in humans. It has been reported that SNPs in NLRP3 and CARD8 genes were associated with the susceptibility, disease course or activity, predicted response to treatment (e.g. anti-TNF- α) or comorbidities of RA, but some discrepant results were shown possibly due to ethnic differences. Although animal models of RA have shown the pathogenic role of NLRP3 inflammasome in its pathogenesis, there have been controversial results in patients with RA. There have been several studies showing inflammasomes as potential therapeutic targets in experimental models of RA, but the results are still preliminary, requiring further validations in the future. Targeting IL-1 β receptor using anakinra was shown to be relatively safe and modestly efficacious biologic therapy for RA, but the degree of improvement is less pronounced compared to studies using other biologic therapies [88].

4. Inflammasomes and gout (Table 3 and Supplemental Table 3S)

Deposition of monosodium urate (MSU) crystals in human tissues, especially in the joints is the main cause of gout [89]. It induces inflammatory reactions in the body, causing severe pain and fever [89]. In this section, we summarize the previous published studies on gout, particularly focusing on the relationship between inflammasomes and gout.

4.1. *In vitro* studies on inflammasomes and gout using human cells

To understand the relationship between inflammasomes and gout, *in vitro* studies using human cells have been performed [90–99] by activating or inhibiting inflammasome-mediated immune response pathways. Several investigators have demonstrated inflammasome-mediated immune response pathway activation by serum amyloid A,

TLR-2 ligands, various nucleotides including Adenosine triphosphate (ATP), soluble uric acid, and TNF- α [90–95]. NLRP3 inflammasomes were activated by these molecules and showed increased secretion of IL-1 β [90–95]. In another study, NLRP3 inflammasome-mediated immune response pathway was inhibited by knockdown of the Nrf2 gene, using a heme oxygenase (HO)-1 inhibitor and knockdown of the Nek7 gene, resulting in decreased secretion of IL-1 β [96]. One study demonstrated that neither MSU crystals nor soluble UA had any effect on activation of NF- κ B and precipitation of UA into MSU crystals was essential for activation of the NLRP3 inflammasome and subsequent release of IL-1 β in human monocytes [97].

In another *in vitro* study, phagocytosis of MSU by NLRP3 expressing osteoblasts was found [98]. MSU crystals were internalized in human osteoblasts via phagocytosis and NLRP3-mediated autophagy in this study, which can explain the presence of MSU in the bone tissue of chronic gout patients [98]. Moreover, accumulation of p62 protein by MSU and the resulting increased activity of inflammasome-mediated immune response pathway was found in another *in vitro* study [99].

4.2. *In vivo* studies on inflammasomes and gout using animal models

Several studies have investigated inflammasomes in gout using *in vivo* models [100–114]. Some genes thought to play a key role in the inflammasome-mediated immune response pathway were investigated by constructing genetically modified mice with defects in the pathway by removing the function of these genes including macrophage migration inhibitory factor (MIF), cryopyrin (Cryo), CD-14, small heterodimer partner (SHP), and miR-146a [100–105]. The results of these *in vivo* studies suggest that MIF, Cryo, and CD-14 genes play a positive role in the inflammasome-mediated immune response pathway because knockout mice for these genes produced low IL-1 β [100,101,103]; in contrast, SHP and miR-146a play a negative role in the inflammasome-mediated immune response pathway because knockout mice for these genes produced high IL-1 β levels [104,105].

In other *in vivo* studies, researchers have analyzed the inflammasome-mediated immune response pathway in mice using some well-known molecules like MSU and TNF- α [106,107]. They found that the MSU-induced inflammasome-mediated immune response pathway is induced by activating leukotriene B4 (LTB4) and C5a [106,107], and that the pathway is thought to be activated by low intracellular potassium concentration [108]. It was also found that the transmembrane form of TNF- α and MSU stimulation combined with free fatty acids (FFAs) or granulocyte-macrophage colony-stimulating factor (GM-CSF) are effective to activate the inflammasome-mediated immune response pathway [109–111], whereas exogenous or endogenous hydrogen sulfide (H₂S), PMN-ecto (neutrophil-derived microvesicles), and antibiotics have an inhibitory effect on this immune response pathway [112–114].

4.3. Characteristics of genetic variants and gene expression levels in patients with gout

There have been some studies on genetic variants and gene expression levels in gout patients. Researchers have tried to find correlations between molecules – some genes and proteins – which are components of the inflammasome-mediated immune response pathway and gout [115–124].

One study showed functional variants in IL-1B and CARD8 genes, providing evidence suggesting that inflammasome activity could be related to gout severity by interaction between IL-1 β and CARD8 genes [119]. In this study, the level of IL-1 β was dependent on the gout-associated allele of IL1B and the multiplicative interaction between CARD8 and IL-1B was consistent with the synergy of greater inflammasome activity combined with higher levels of pre-IL-1 β , causing overproduction of IL-1 β in gout [119]. In another study, CARD 8 gene and P2X purinoceptor 7 (P2X7R) gene polymorphisms were partly

Table 3

List of studies related to the role of inflammasomes in gout.

Main study findings
In vitro experiments
MSU stimulation alone
MSU stimulation alone cannot result in IL-1 β secretions in synovial fibroblasts [90].
MSU crystals alone failed to induce IL-1 β in PBMCs of both primary gouty patients and control groups [91]
MSU crystals or soluble uric acid alone cannot activate NF- κ B in primary human monocytes [97]
Soluble uric acids induced NALP3, caspase-1 and IL-1 β in proximal tubule epithelial cells [94]
MSU + priming with others
SAA: activation of caspase-1 and production of active IL-1 β in synovial fibroblasts [90]
TLR-2 ligand: production of IL-1 β in PBMCs of gout and healthy controls [91]
TNF- α : secretion of IL-1 β in human neutrophils [95]
Soluble UA: activation of NLRP3 inflammasome in PBMCs [97]
Potential mechanisms
K (+)- and Ca (2+)- mediated dysfunction of mitochondria leading to iATP loss in macrophages [92]
Purinergic receptor signaling in macrophages [93]
TLR4-dependent ways in proximal tubule epithelial cells [94]
Nrf2 was found to be crucial in MSU crystal-induced inflammations [96]
Phagocytosis, autophagy and interrupted functional regulations of OBs [98].
p62 accumulation through disruption of proteasomal degradation in autophagy [99]
In vivo experiments
Knock-out animals showing decreased MSU-induced inflammation
Inflammasome components-deficient mice: impaired neutrophil influx [102]
Inflammasome components-deficient mice: MSU/FFA-induced release of IL-1 β was dependent on activation of caspase 1 and ASC, but not NLRP3 [110]
Inflammasome components-deficient mice: a role of LTB4 for the activation of NLRP3 inflammasome [106]
Cryo(-Z/-Z) and Cryo (DeltaLRR Z/DeltaLRR Z) mice: an important role of cryopyrin LRR domain [101]
CD14(-/-) mouse s.c. air pouches [103]
Complements (-/-) mice: an important role of C5a for the activation of NLRP3 inflammasome [107]
GPR43(-/-) mice: the role of microbiota to respond to an inflammasome-dependent stimulus [114]
Knock-out animals showing increased MSU-induced inflammation
SHP (-/-) mice: a negative regulatory role for SHP in NLRP3 inflammasome pathway [104]
miR-146a (-/-) mice: a negative regulatory role for miR-146a in NLRP3 inflammasome pathway [105]
Activation of NLRP3 inflammasome
The decrease in K (+) in air pouch MSU-injected mouse model [108]
Transmembrane form of TNF- α in murine gout model using C57BL/6J with joint injection of MSU crystals [109]
GM-CSF is important in MSU-recruited monocyte differentiation [111]
Inhibition of NLRP3 inflammasome
Exogenous or endogenous H2S: inhibitory effects on NLRP3 inflammasome [112]
Neutrophil microvesicles: inhibiting C5a-mediated priming of the inflammasome [113]
Genetic studies for gout
SNPs in PPARGC1B gene in gout [115]
MEFV gene mutations carriage: higher frequency [117], no association [121]
SNPs in P2X7R [118] and CARD8 gene [118,119]
SNPs in IL1B gene [119]
SNPs in TLR4 gene: increased risk in European and decreased the risk in Polynesians [120]
Human studies for gout
IL-18 levels were elevated in gout [122]
Negative association of NLRP3 levels serum uric acid levels [123]
No differences in synovial caspase-1 levels between gout and other arthritides [124]
Targeted treatment for gout with IL-1 receptor blocker
Anakinra: Improvement of renal function [125], pain and CRP [126], sign and symptoms of arthritis [127]
Rilonacept: Improvement of pain visual analogue scale, CRP and joint scores [128]

Abbreviations: MSU: monosodium urate, IL: interleukin, PBMC: peripheral blood mononuclear cell, NF- κ B: Nuclear factor-kappa B, NALP: The NACHT, LRR and PYD domains containing protein, SAA: Serum Amyloid A, TLR: toll like receptor, TNF: tumor necrosis factor, UA: uric acid, NLRP: nucleotide binding domain and leucine rich repeat containing proteins, iATP: intracellular ATP, Nrf2: nuclear factor E2-related factor 2, OB: osteoblast, free fatty acids: FFAs, ASC: apoptosis-associated speck-like protein containing a CARD, LTB4: Leukotriene B4, LRR: leucine-rich repeat, CD14: cluster of differentiation 14, GPR43: G-protein coupled receptor 43, SHP: small heterodimer partner, MiR: microRNA, GM-CSF: granulocyte-macrophage colony-stimulating factor, H2S: hydrogen sulfide, SNP: single nucleotide polymorphism, PPARGC1B: Peroxisome proliferator-activated receptor gamma coactivator 1-beta, MEFV: Mediterranean fever, P2X7R: P2X ligand-gated ion channel 7, CARD8: caspase recruitment domain 8, CRP: C-reactive protein.

associated with gout susceptibility [118]. Similarly, polymorphisms of PPARGC1B, MEFV, and TLR4 genes, which are involved in the inflammasome-mediated immune response pathway, were found to be associated with gout pathophysiology [115,117,120]. There was one study showing the effect of gene variants of mitochondrial DNA on inflammasome activity [116].

In addition to genetic variants, increased gene expression levels may affect the pathophysiology of gout. One study compared the cytokine levels produced by the inflammasome-mediated immune response pathway [122]. This study found increased IL-6 and IL-18 in gouty

patients and showed that IL-6 is more related with the clinical features of gout (articular deformity, presence of tophi etc.), whereas IL-18 is more related with inflammatory activity in gout [122].

However, there are some studies providing contradictory evidence about the correlations between these genetic variants or increased gene expression levels and the pathophysiology of gout. The study by Rasheed et al. [120] showed a discrepant result on the association of TLR4 polymorphism according to race and Sari et al. [121] suggested that correlations between variants of the MEFV gene and the pathophysiology of gout are uncertain, because the clinical features of gouty

arthritis do not depend on the presence of MEFV variants. Besides, the caspase-1 levels in synovial fluid of gouty arthritis were not as high as those in other arthritis forms [124].

4.4. Effective inflammasome targeted treatment and potential treatment in gout

Some effective inflammasome targeted treatment options have been investigated in gout [125–128]. Inflammasome-targeted treatment is aimed to relieve and alleviate the severity of gout by blocking specific stages of the inflammasome-mediated immune response pathway [126–128]. Anakinra, an IL-1 receptor antagonist, is one of the effective inflammasome targeted treatments that acts by blocking IL-1 (product of inflammasome mediated immune response pathway) binding to the IL-1 receptor [126]. In this manner, it suppresses the immune response and greatly relieves the symptoms of patients with gout within 48 h after injection [127]. Anakinra was also effective in improving the renal function of diabetic patients suffering from gout [125]. Another drug, riloncept, also known as an IL-1 trap, was developed to treat gout and was proven to be effective [128], but it has not been approved by United States Food and Drug Administration for the treatment of gout, because the benefits did not outweigh the risks associated with the drug.

There are some studies on the treatments of gout patients, including butyrate, ferulic acid, beta-hydroxybutyrate, sulforaphane, tranilast, EGCG, CY-09 (a NLRP3 inhibitor that blocks NLRP3 inflammasome assembly and activation), chondroitin sulphate, and doliroside A [129–138]. Each of these agents has their own inflammasome-targeting mechanisms similar to anakinra and riloncept, which have been investigated using *in vivo* studies or in clinical trials. The potential therapeutic targets for inflammasome pathways are presented in Fig. 2.

In summary, MSU stimulation alone could not result in IL-1 β secretions or inflammasome activation in various cells, but MSU primed with other factors could activate production of IL-1 β . NLRP3 could be activated by dysfunction of mitochondria, purinergic receptor, TLR and autophagy. Studies on various kinds of knock-out animal models have found several molecules involved in the pathogenesis of MSU-induced inflammation. There have been several reports on the effect of several SNPs in IL1B, P2X7R, TLR4 and CARD8 genes on the susceptibility of gout. The studies on the levels of inflammasome-driven cytokines are limited, but several clinical trials have demonstrated that blocking IL-1 receptor (e.g. anakinra) lead to the improvement of symptoms and inflammatory markers such as C-reactive protein (CRP) in patients with gouty arthritis. Further studies are also necessary to evaluate whether targeting various pathways of inflammasome activation could be beneficial in the treatment of gout.

5. Inflammasomes and Behçet's disease (Supplemental Table 4S)

5.1. *In vitro* studies on inflammasomes and Behçet's disease using human cells

It has been controversial whether inflammasomes play a significant role in the pathogenesis of Behçet's disease (BD). Several *in vitro* studies using human cells support their role in the pathogenesis of BD [139–141]. Monocyte-derived macrophages (MDMs) obtained from BD patients showed increased TLR2/4 expression and IL-1 β /ROS production, and showed inhibition of IL-1 β production when the NLRP3 inflammasome was suppressed using RNA interference [140]. PBMCs from BD patients, when stimulated with LPS, expressed larger amounts of NLRP3 inflammasome components and produced more IL-1 β compared to cells from healthy controls [139]. These results imply a possible link between the ROS-NLRP3-dependent pathway and IL-1 β production in BD. On the other hand, dendritic cells and neutrophils from

BD patients, which were stimulated with two types of PRRs revealed an insignificant difference in caspase-1 activity compared to healthy controls, suggesting a lack of association between the caspase-1-dependent pathway and BD pathogenesis [141].

5.2. Inflammasome-related genetic variants in patients with Behçet's disease

The mutational profile of inflammasome-related genes in BD has been partially elucidated so far [142–144]. One study showed that the NLRP3/cryopyrin V200 M mutant, found in some BD patients, induces IL-1 β production [143]. SNPs in gamma-interferon-inducible protein (IFI16) and AIM2 genes were found to influence the risk of BD [142]. In this study, risk haplotype was associated with lower IFI16 expression compared to the protective counterpart, suggesting that IFI16 variant types may influence BD susceptibility [142]. A recent study screened seven candidate genes related to autoinflammatory diseases (AIDs) in BD patients, of which mevalonate kinase (MVK), nucleotide-binding oligomerization domain-containing protein 2 (NOD2), and proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1) were proven to be associated with AIDs by multiple different statistical methods [144].

In summary, PBMCs from BD patients show higher expression of NLRP3 inflammasome components and larger IL-1 β secretion compared to healthy controls and BD patients also showed increased levels of IL-1 β , suggesting an important role of inflammasome activation in BD. There have been several reports on the effect of the SNP in AIM2 and NLRP3/cryopyrin mutations in the susceptibility of BD. Although prospective RCTs for the treatment of Behçet's disease are still limited, the data from retrospective studies showed that there have also been acceptable results with IL-1 inhibitors for the management of refractory ocular disease, and with apremilast, anakinra, and ustekinumab for refractory mucocutaneous involvement [145].

6. Inflammasome and Sjögren's syndrome

6.1. *In vivo* study of inflammasome and Sjögren's syndrome using animal models

Researchers have suggested that the NLRP3 inflammasome pathway plays a role in the pathogenesis of Sjögren's syndrome (SS) [146–150]. Khalafalla et al. demonstrated the role of inflammasomes in SS in mouse models, and tested a potential therapeutic strategy by *in vivo* targeting of the inflammasome pathway [150]. P2X7R activation induced assembly of the NLRP3 inflammasome and IL-1 β secretion in primary submandibular gland cells from wild-type mice, but not in the P2X7R-deficient strain [150]. *In vivo* injection of A438079, a P2X7R antagonist, was tested in an autoimmune salivary gland exocrinopathy mouse model, which resulted in reduced salivary gland inflammation, and enhanced saliva secretion, suggesting that P2X7R antagonism could be an effective therapeutic strategy for SS patients [150].

6.2. Human studies on inflammasomes and Sjögren's syndrome

In a study conducted by Baldini et al. [146], the gene expression levels of inflammasome components (NLRP3, ASC, and caspase-1) were significantly higher in primary SS gland specimens, and this was paralleled by the increased expression of mature IL-18 in primary SS saliva samples. The same group also showed that the expression levels of inflammasome components (NLRP3, ASC, and caspase-1) were even higher in patients later developing mucosa-associated lymphoid tissue non-Hodgkin's lymphoma (MALT-NHL) due to SS progression [147]. Another group demonstrated an increase in ASC, caspase-1, and IL-1 β expression in SS patients, with IL-1 β mRNA/protein levels being correlated with NLRP3 mRNA levels [148]. These evidences support the

hypothesis that the P2X7R-NLRP3 inflammasome-caspase-1 axis is involved in the pathogenesis of SS exocrinopathy and lymphomagenesis.

6.3. Mechanism underlying NLRP3 inflammasome activation in Sjögren's syndrome

A recent study proposed a mechanism for NLRP3 inflammasome activation in severe SS, suggesting that extranuclear accumulation of inflammagenic DNA and impaired DNA degradation may be the culprit [149]. In SS patients at risk of lymphoma and in those with established lymphoma, extranuclear DNA accumulation was found in the serum, PBMCs, and salivary gland tissues, with diminished DNaseI activity and DNaseII expression [149]. Evidences of NLRP3 inflammasome pathway activation were found in the monocytes and macrophages of these patients [149]. Addition of cell-free nucleic acids obtained from patients or DNaseII gene-silencing both effectively activated inflammasomes in healthy monocytes *in vitro* [149].

Although recent studies regarding inflammasomes have shed a light on their pathogenic roles and potentially new therapeutic options in SS, one randomized, double-blind, placebo-controlled trial of anakinra did not find a significant reduction of fatigue in pSS its primary endpoint [151]. The reported inefficacy of anakinra in SS could be due to the reason that other immunologic pathways such as B cells which are considered to be a central actor of primary SS pathogenicity, germinal center-like structures which are likely to support auto-Ab (*anti*-SSA/Ro) production, and T cell co-stimulation might be more important in the pathogenesis of SS [152].

7. Inflammasome and ANCA-associated glomerulonephritis

7.1. Inflammasome suppression by the effect of ROS in ANCA-associated glomerulonephritis

Experiments with the anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (AAGN) mouse model revealed that ROS generated by ANCA-induced phagocyte NADPH oxidase (phox) suppresses caspase-1 activity, thus inhibiting inflammasome action and reducing ANCA-induced inflammation [153]. In an *anti*-myeloperoxidase (*anti*-MPO) antibody-mediated disease model, mice transplanted with either gp91(phox)-deficient or p47(phox)-deficient bone marrow showed accelerated disease with increased crescents, necrosis, glomerular monocytes, and renal IL-1 β levels compared to mice transplanted with wild-type bone marrow, suggesting that ROS could limit the ANCA-induced inflammation [153]. In this study, IL-1 β receptor blockade ameliorated the disease in gp91(phox)-deficient mice, implicating IL-1 receptor blockade as a promising strategy in AAGN [153].

7.2. NLRP3 inflammasome induced tubulointerstitial injury in ANCA-associated glomerulonephritis

Another study [154] in which kidney biopsy was performed in AAGN patients, showed that the NLRP3 inflammasome pathway plays a key role in tubulointerstitial injury (TII) [154]. IL-1 β levels and TLR4/NLRP3 expression levels correlated with TII severity. NLRP3 protein and TLR4 protein were exclusively detected in tubulointerstitial infiltrating cells, and almost none were detected in the glomerular area [154]. These results imply that NLRP3 inflammasome-dependent processing in tubulointerstitial macrophages produces IL-1 β , resulting in TII [154]. Since the NLRP3 inflammasome pathway seems to act only in the tubulointerstitial area, inhibiting the action of IL-1 β may be a strategy for treating AAGN [154]. However, the role of inflammasomes in the pathogenesis of AAGN is currently limited due to the small number of studies in this field.

8. Inflammasomes and IgA vasculitis (Henoch-Schönlein purpura)

8.1. An inflammasome-related genetic variant in IgA vasculitis (Henoch-Schönlein purpura) patients

He et al. [155] reported a variant in the pyrin-encoding MEFV gene associated with IgA vasculitis (Henoch-Schönlein purpura) susceptibility. MEFV E148Q polymorphism (G > C) increased the risk of IgA vasculitis by an odds ratio of 2.76, and the allele was correlated with joint involvement in the disease [155].

9. Conclusion

In this study, we attempted to expand our understanding of the role of inflammasomes on the links between inflammasomes and autoimmune diseases through a comprehensive review of the literature. We also reviewed the central function of inflammasomes between innate and adaptive immunity. Inflammasome activation is an important mechanism for the production of active IL-1 β and IL-18, which have important roles to instruct adaptive immunity. Activated cells of the innate immune system upregulate inflammatory mediators and induce increased expression of costimulatory and adhesion molecules which can also lead to the activation of the adaptive immune system. During this process, APCs, such as DCs have important roles for the initiation of T cell-mediated adaptive immune responses which are necessary to differentiate naïve T cells into their effector and memory cells. Therefore, the complex interplay between innate and adaptive immunity is critical in the development of various autoimmune and rheumatic diseases and therefore, they could be a potential therapeutic target for drug development.

Recently, there have been great advances in the genetic studies of inflammasome-associated genes in various kinds of autoimmune and rheumatic diseases, but some discrepant results were shown possibly due to ethnic differences. Some studies have revealed an association between inflammasomes and disease severity, complications, and treatment response. Nevertheless, many of these studies have been conducted in animal studies, and therefore, more studies in humans are needed. Despite these limitations, the current evidence implies a crucial role of inflammasomes in some autoimmune and rheumatic diseases.

Further studies that focus on effective inflammasome-targeted treatment are needed. Although some drugs like anakinra are in use and some are in clinical trials, further studies are necessary to evaluate their efficacy and safety. If targeting IL-1 β is not effective in some autoimmune diseases such as SS, the pathogenesis may involve other crucial immunological pathways, such as B cells, germinal center-like structures which are likely to support auto-Ab (*anti*-SSA/Ro) production, T cells and co-stimulatory molecules which could be more important pathogenesis of SS. In addition, the pleiotropic actions of inflammasomes and potential harms after targeted treatments should also be considered. Although targeting inflammasomes and IL-1 has been shown to be highly effective in the treatment of rheumatic diseases, such as gout, the long-term safety profile has not been determined. Also, if the inflammasome is targeted, other adverse events, such as infection or development of other autoimmune diseases by imbalance of cytokines, should also be closely monitored because it is an important component of the innate immune system [156].

Conflicts of interest

All authors state that they have no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations.

Authorship

All authors made substantial contributions to all of the following:

(1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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