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## INTRODUCTION

The inflammasome is a multiprotein complex that serves an important proinflammatory role in the innate immune system. The primary component of the inflammasome is the nucleotide oligomerization domain (NOD)-like receptors (NLR). There are over 20 known human NLRs and over 30 mice NLRs.<sup>[1-6]</sup> It is unclear how many of these NLRs function as organizers of inflammasome formation. Till date, only four inflammasomes have been characterized: NLRP1, NLRP3, Ipaf and AIM2 inflammasomes. It has also been suggested that NLRP2 NLR, has the ability to form an inflammasome.<sup>[7]</sup> The NLRs that make up the central organizing component of the inflammasomes are divided into two major groups, the NLRPs and the NODs, and a third smaller group, the Ipafs. The NLRs all share some attributes in common. All NLRs have an active region containing a repetitive amino acid pattern rich in leucine [Figure 1]. This region is termed leucine-rich repeat (LRR) and is important in functioning of NLRs as inflammasome organizers. LRR domain is believed to play a role in ligand-sensing/binding and regulating inflammasome activation.<sup>[8]</sup> Another active site common to all NLRs is NACHT (found in neuronal apoptosis inhibitory protein (NAIP), Class II transactivator (CIITA), incompatibility locus protein from *Podospora anserina* (HET-E), and

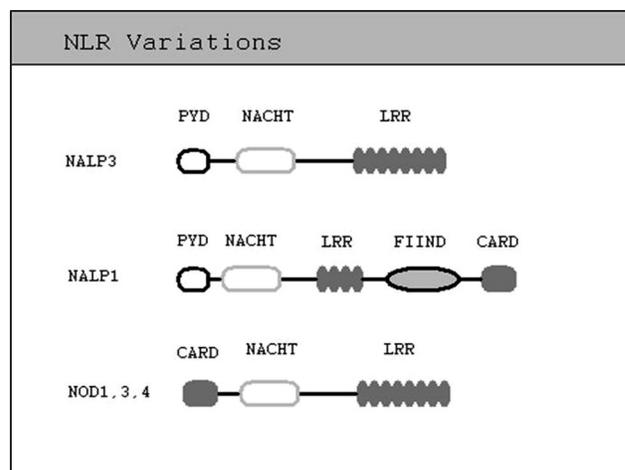
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**Figure 1: Prototype of NLR structure showing the major interaction domains: The ligand sensing leucine-rich repeats, NACHT or the oligomerization domain, pyrin domain or caspase recruitment domain, acting as the effector domain and function to find domain**

telomerase-associated protein (TP-1) domain. The NACHT domain shows catalytic activity as an NTPase and is similar in structure and function to a group of apoptosis-associated proteins known as the STAND family of NTPases.<sup>[9]</sup> The crucial function of NACHT domain is believed to be its activity as a mediator of oligomerization, a function that has been documented in other members of STAND family.<sup>[10,11]</sup> The final essential component of NLR is a binding domain capable of recruiting adapter proteins and/or effector caspases. This domain varies among the NLRs and can be a caspase recruitment domain (CARD), as seen in NLRP1 NLR or a PYD (pyrin domain).<sup>[7]</sup> Caspases involved in inflammasome signal cascade have been the topic of much recent research. Inflammatory caspases (caspases 1, 4 and 5), play a pivotal role in processing of inflammatory cytokines. Evidence suggests that, caspase 5 alone is not a very effective activator of IL-1 $\beta$ , synergistic activity of caspase 5 and caspase 1 seems to be very efficient at IL-1 $\beta$  processing, which may be indicative of the coactivation of caspases 1 and 5 that occurs in the NLRP1 inflammasome. It has also been suggested that caspase 5 may play a role in upstream regulation and activation of caspase 1.<sup>[12,13]</sup> In a study

by Salskov-Iverson, *et al.*<sup>[14]</sup> findings suggested that expression of caspase 5 is upregulated in lesional psoriatic skin as compared to nonlesional psoriatic, healthy skin and in other inflammatory skin diseases. Their findings also suggested that caspase 5 expression subsides along with psoriatic symptoms after anti-TNF- $\alpha$  treatment.

Although inflammasome formation is quite established in the NLRP family and Ipaf family, the role of NOD family in inflammasome activity is still unclear. However, it has been shown that NOD signalsomes can activate inflammasome-related gene transcription through the NF- $\kappa$ B (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway.<sup>[7,10,11,15]</sup> Evidence suggests that both NOD2 and NAIP, from the Ipaf family, are critical in inflammasome formation in some cases and may even be able to form inflammasomes on their own or through dimerization.<sup>[16,17]</sup>

Recently, AIM2 inflammasome has been characterized.<sup>[18]</sup> It is the only inflammasome which functions without a member of the NLR family as an organizing component.<sup>[19-22]</sup> AIM2 has been shown to be an activator of caspases 1 and IL-1 $\beta$  in the presence of endogenous and exogenous double-stranded DNA (ds DNA)<sup>21</sup> and is believed to be associated with systemic lupus erythematosus (SLE).<sup>[18]</sup> Recently, Dombrowski *et al.*<sup>[23]</sup> demonstrated that cytosolic DNA is an important disease-associated molecular pattern that can trigger AIM2 inflammasome and IL-1 $\beta$  activation in psoriasis.

## ROLE OF INFLAMMASOMES IN INFLAMMATION

The primary role of inflammasome is to function as a detector of cytosolic signals of either tissue damage or the presence of a pathogen and to activate innate and adaptive immune responses. The cytosolic NLRs (and specifically, their LRR portions) have specificity for common pathogenic motifs known as pathogen-associated molecular patterns (PAMPs) [Table 1] and endogenous signals of distress or damage known as danger-associated molecular patterns (DAMPs) such as excess K<sup>+</sup> levels or cytosolic DNA.<sup>[24-26]</sup> Upon detection of its particular danger signal by LRR domain, the NLR initiates oligomerization via a CARD or PYD interaction with adapter proteins like ASC (Apoptosis-associated Speck-like Protein Containing a Caspase Recruitment Domain) which then recruit

**Table 1: The most fully characterized NOD-like receptors and their known activating pathogen-associated molecular patterns and danger-associated molecular patterns**

Ligands of inflammasomes		
NLRP3	Microbial motifs	Bacterial muramyl dipeptide, bacterial RNA, antiviral compounds, double-stranded RNA and viral RNA
	Bacteria	<i>Staphylococcus aureus</i> , <i>Listeria monocytogenes</i>
	Viruses	Sendai and influenza
	Toxins	Maitotoxin, nigericin, aerolysin
	Host danger signals	Uric acid, ATP, low intracellular potassium levels, UVB-induced activation of keratinocytes
	Fungal $\beta$ glucans (curdlan)	<i>Candida albicans</i> , <i>Aspergillus fumigatus</i> and <i>Saccharomyces cerevisiae</i>
Ipaf	Protozoal	Plasmodium species
	Microbial motifs	Cytosolic Flagellin
	Bacteria	<i>Salmonella typhimurium</i> , <i>Legionella pneumophila</i>
NLRP1 (Murine)	Toxins	<i>Bacillus anthracis</i> lethal toxin

and activate effector inflammatory caspases.<sup>[10,12]</sup> The activated caspases then cleave pro-IL-1 $\beta$ , pro-IL-18, and possibly pro-IL-33 into their active, proinflammatory forms [Figure 2]. The activated cytokines are then secreted into the interstitial fluid to initiate inflammation.<sup>[7]</sup> IL-1 $\beta$  has an extremely powerful inflammatory and pyrogenic effect. It also induces the release of TNF, inducible nitric oxide synthase, COX-2 (Cyclooxygenase-2), prostaglandin E2, nitric oxide, type 2 phospholipase A, and even IL-1 $\beta$  itself depending on the type of cell.<sup>[27]</sup> IL-1 $\beta$  blockade has been used successfully to treat a number of inflammatory diseases such as; gout, familial Mediterranean fever (FMF), and several diseases in the family of inflammatory diseases known as cryopyrin-associated periodic syndrome (CAPS).<sup>[28]</sup> Additionally, the well-characterized inflammasomes (NLRP1, NLRP3, Ipaf, and AIM2) were all recently implicated in the process of pyroptosis in monocyte-derived cells.<sup>[20,29-32]</sup>

## PYROPTOTIC CELL DEATH

Pyroptosis is a form of programmed cell death. Earlier it was termed as 'apoptosis' due to morphologic similarities (apparent blebbing) and presence of DNA fragmentation, chromatin condensation and necessity for a caspase.<sup>[33-37]</sup> Subsequently it was shown to be different from apoptosis.<sup>[38-40]</sup> In contrast to apoptosis, it occurs after Caspase-1 activation, does not involve

proapoptotic caspases (caspase 3,8,9) and does not cleave target proteins poly ADP ribose polymerase (PARP)1 and intercellular adhesion protein D (ICAD).<sup>[36,38,41-44]</sup>

### REGULATORY ROLE OF INFLAMMASOME IN CONFINEMENT OF INFECTION AND HOST CELL REPAIR

Gram negative bacterial infection lead to caspase-1 activation and IL-1 $\beta$ , IL-18 release. NLRC4/IpaB deficient macrophages infected with salmonella are unable to activate caspase 1 and mature IL1 $\beta$  and IL18. *Legionella*, *Pseudomonas* and *Shigella* also induce caspase1 activation and phagosome maturation in a NLRC4 dependant manner.<sup>[45,46]</sup> Activation of proinflammatory cytokines induce inflammation and confine infection. In addition, activation of caspase 1 leads to secretion of nuclear DAMP high-mobility group box 1 (HMGB1) from infected macrophages.<sup>[47]</sup> Decreased metabolic rate in infected cells due to loss of enzymatic activity of glyceraldehyde-3-phosphate dehydrogenase by Caspase 1<sup>[48]</sup> limits intracellular pathogen replication and dictates host cells to undergo pyroptosis. Moreover, caspase 1 heals and repairs damage in host cells caused by bacterial pore forming toxins. Healing is regulated by activation of sterol regulatory element-binding protein 1 (SREBP1) and SREBP2 by NLRP3 and NLRC4 [Figure 3]. Studies have also confirmed that maturation of procaspase 7 by NLRP3 and NLRC4 control intracellular replication of *Legionella*.<sup>[45]</sup>

### RELATIONSHIP BETWEEN NLRP AND REACTIVE OXYGEN SPECIES

The precise mechanism behind lysosomal activation of NLRP3 inflammasome is still indistinct. Earlier it was reported that crystal-induced activation of inflammasome was due to nicotinamide adenine dinucleotide phosphate (NADPH) oxidase mediated reactive oxygen species (ROS) production.<sup>[49,50]</sup> However, some studies show that mutations in NADPH oxidase components and ineffective ROS production in patients with chronic granulomatous diseases still lead to inflammasome activation.<sup>[51]</sup> Recent reports suggest that mitochondrial ROS generation due to stress or defect in respiratory chain lead to upregulated IL-1 $\beta$  maturation through NLRP3 stimulation.<sup>[52-54]</sup> The precise mechanism of ROS-induced inflammasome activation is presumed

to occur through interaction of thioredoxin-interacting protein (TXNIP) and NLRP3.<sup>[55]</sup>

### REGULATION OF INFLAMMASOME

Two known major areas of regulation on NLR are CARD domain and PYD domain. Blockade of CARD motif prevents efficient recruitment of effector caspases and, thereby, inhibits inflammasome cascade.<sup>[56-59]</sup> Binding of PYD domain on NLR to ASC adapter protein is thought to be regulated by pyrin or other pyrin-only proteins (POPs). Pyrin and POPs bind directly to PYD site and inhibit inflammasome formation by competing for ASC.<sup>[60,61]</sup> But pyrin also has a proinflammatory function and ability to actively assemble an inflammasome complex.<sup>[62]</sup> Guarda *et al.* demonstrated that NLRP1 and NLRP3 inflammasome activation could be blocked by memory and effector T cells.<sup>[63]</sup>

Nerve growth factor (NGF) and neuropeptides also induce IL-1 $\beta$  secretion and increases its mRNA expression in murine peritoneal macrophages and monocytes.<sup>[4]</sup> Raychaudhuri *et al.* demonstrated that IL-1 $\beta$  and other proinflammatory cytokines can induce NGF as well as its receptor expression in fibroblast like synoviocytes.<sup>[5]</sup> So it is a matter of debate as to whether NGF is responsible for proinflammatory cytokine secretion by activation of inflammasome cascade and whether the secreted cytokines induce secretion of NGF in an autocrine manner.

### EXPRESSION OF INFLAMMASOME COMPONENTS

Yin *et al.* showed NLR expression in lymphoid system, lymph nodes, spleen and thymus, peripheral blood, trachea, placenta, and brain with lymph nodes and trachea expressing the highest levels of NLRP1, and bone marrow and thymus tissue expressed the highest levels of NLRP3.<sup>[64]</sup> They reported a tiered system for determining inflammasome readiness of different tissues. First tier contains brain, blood, placenta and thymus. All these tissues constitutively express the components to form a fully functional inflammasome at any time. Second tier contains tissues (brain, pancreas, vascular, lymph nodes, trachea and spleen) that lack only one inflammasome component that can be readily induced. Lastly, third tier tissues (cardiac muscle) lack at least two (potentially inducible) inflammasome components. Potential inflammasome activity has been shown in many immune as well as

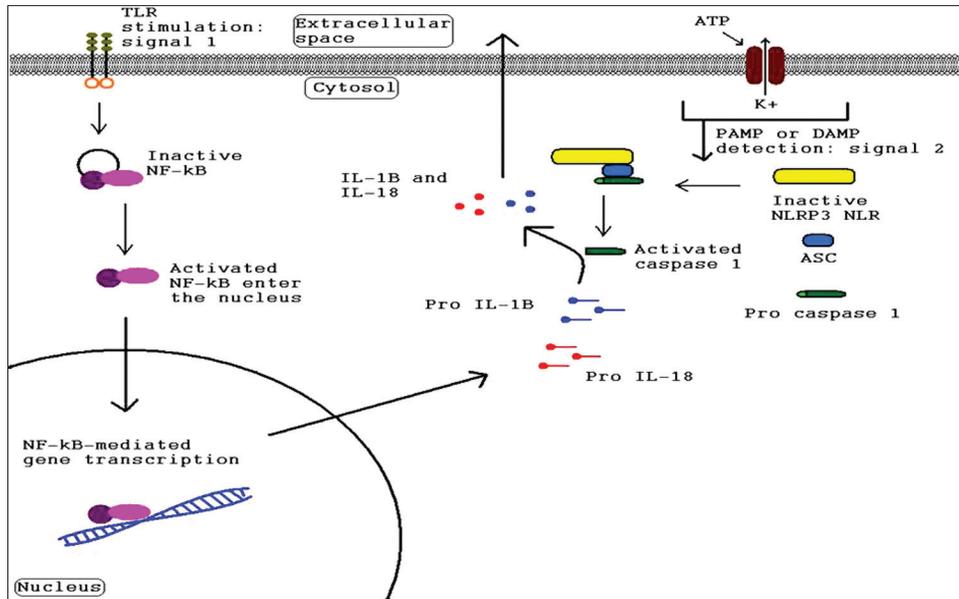


Figure 2: Diagram illustrating the signals needed for inflammasome-related gene transcription and for inflammasome complex formation by pathogen-associated molecular patterns or damage-associated molecular patterns as well as the signal cascade leading to inflammatory cytokine secretion

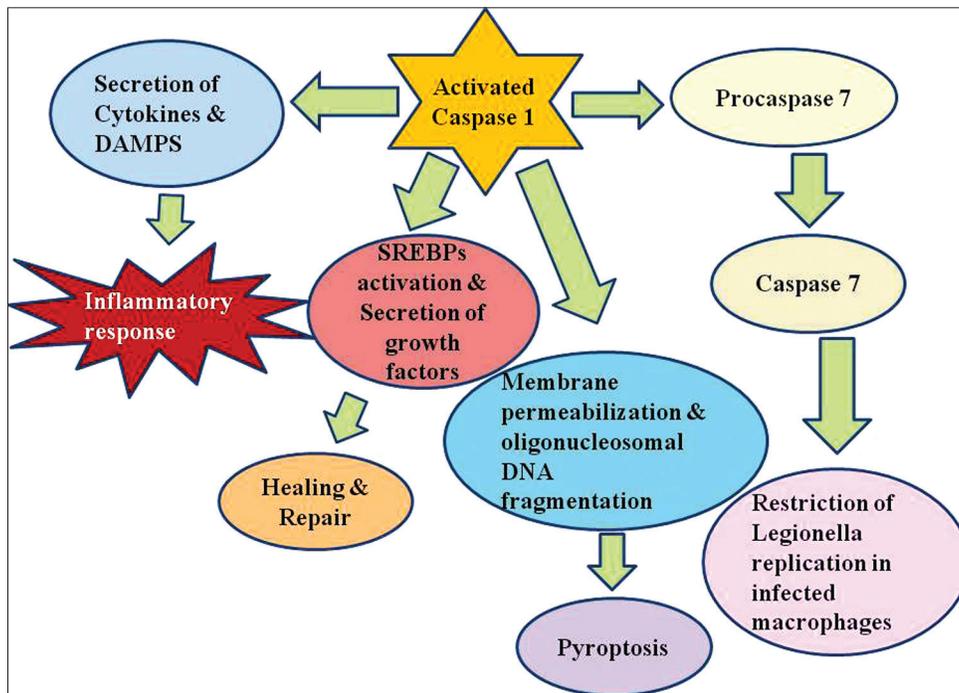


Figure 3: Inflammasome assembly is triggered by pathogen assault of macrophages and dendritic cells, which ultimately leads to Caspase 1 activation. Activated caspase 1 regulates the release of numerous proinflammatory cytokines such as interleukin-1β (IL-1β), IL-18 and IL-1a, and probably induces damage-associated molecular patterns such as high mobility group box 1 giving rise to inflammation. Caspase 1 also activates sterol regulatory element binding proteins, induces secretion of growth factors like fibroblast growth factor 2 and encourages repair and healing. Caspase 1 also prepares host cells to undergo pyroptosis, a form of programmed cell death involving membrane permeabilization and DNA fragmentation resulting in elimination of infected immune cells. Moreover caspase 7 activation by the inflammasome complex prevents bacterial replication in Legionella-infected macrophages

nonimmune cells. Pancreatic β cells secrete IL-1β in response to chronic hyperglycemia which is presumed to be inflammasome dependant.<sup>[65]</sup> Keratinocytes express NOD1 and NOD2 and were able to produce

IL-6 upon stimulation.<sup>[66]</sup> NLRP1 and NLRP3 were both detectable in neutrophils, monocytes, dendritic cells, B cells and T cells.<sup>[67,68]</sup> However, macrophages and neutrophils only produced NLRP3 when induced

with LPS.<sup>[68,69]</sup> Nucleocytoplasmic staining<sup>[68]</sup> showed that NLRP1 was found in mononuclear cells in T-cell-related areas of tonsils, lymph nodes, spleen and also in Langerhans cells in mucosal tissues and in skin. Cytoplasmic staining revealed that epithelial cells in gastrointestinal tract, respiratory tract, endometrial and endocervical glands, gall bladder, and prostate all expressed detectable quantities of NLRP1. NLRP1 was also found in nuclei of pyramidal neurons and oligodendrocytes in brain as well as in cytoplasm of spermatogonia in testis. Cells that express cytoplasmic NLRP3 in detectable amounts are keratinocytes in oral, esophageal, and ectocervical mucosa, Hassall's corpora in thymus and stratified epithelial cells in bladder and ureter.

### IDENTIFICATION OF INFLAMMASOME ACTIVITY

Martinon *et al.*, used an immunoprecipitation technique to confirm inflammasome oligomerization and caspase activation.<sup>[12]</sup> Target proteins (caspases 1, 2, 4, 5 and 9, NLRP1, Pycard, and Apaf) were tagged with a FLAG protein and then precipitated out of solution using anti-FLAG antibodies. These immunoprecipitation assays showed strong interactions between NLRP1 and caspases 5, as opposed to caspases 1, 2, 4, or 9. Inflammasome activation was also correlated to activation of caspases 1 and 5 which was demonstrated by detection of the cleavage products using western blot. Another indicator of inflammasome activation is simply to conduct a Western blot analysis of cell lysate, staining for NLR. Martinon *et al.* adapted a technique used by Cain *et al.* to determine whether there is inflammasome complex formation.<sup>[12,70]</sup> Cell lysate was analyzed using Western blot staining with antibodies specific for the NLR whose mass was 165 kDa. Appearance of band at 700 kDa indicated NLR association with a large inflammasome complex. Similarly, staining with caspases 1 and 5 antibodies showed a shift from their theoretical weights to those associated with NLRP1 inflammasome.

Using mice or human cells deficient in one or more inflammasome components also appeared to be an effective way to be assured of their activity. Mice deficient in either one or both of NLRP3 inflammasome components NLRP3 and ASC were unable to mount an effective immune response.<sup>[71]</sup>

PCR and subsequent Western blot was used for mRNA

and protein expression of caspases, ASC and NLRs.<sup>[14]</sup>

### ROLE OF THE INFLAMMASOME IN CUTANEOUS AUTOIMMUNE AND AUTOINFLAMMATORY DISEASE

Studies linking inflammasomes to adjuvanicity and inflammasome product blockade to remission of symptoms in gout, FMF, Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS) suggest a central role of inflammasomes and their accessory caspases in autoimmune and autoinflammatory diseases.<sup>[14,72-76]</sup> Here, we describe some cutaneous diseases like contact dermatitis, psoriasis, vitiligo and atopic dermatitis and how inflammasomes may be participating in their pathophysiology.

#### CAPS and autoimmune cold urticaria

CAPS family of diseases include MWS, FCAS, and neonatal-onset multisystem inflammatory disease (NOMID). They are associated with missense mutations in NACHT oligomerization-regulating domain of NLRP3 NLR.<sup>[74,78]</sup> These mutations, are responsible for upregulation of NLRP3 inflammasome and overproduction of mature IL-1 $\beta$ .<sup>[31]</sup> Nakamura *et al.*<sup>[79]</sup> demonstrated NLRP3-associated mutations in the pathophysiology of MWS. Mast cells (MCs) are concentrated in areas commonly affected by CAPS-associated urticaria; the skin, the joints and the central nervous system.<sup>[80]</sup> They showed that MCs from healthy tissue constitutively express caspase 1 and ASC. Moreover, studies show that anti-IL-1 $\beta$  therapy resulted in successful treatment of CAPS.<sup>[73,81,82]</sup>

#### Contact dermatitis

It has been reported that induction of epidermal hypersensitivity by chemical irritant is inflammasome-dependant.<sup>[83]</sup> Cavani *et al.* showed that inflammasome was involved in development of contact hypersensitivity, a T-cell-mediated reaction, and therefore had been exerting influence over the adaptive immune system. Inflammasome participation in this reaction is also implied by the discovery that sensitization phase of the hypersensitivity reaction is dependent on activated caspases-1, IL-1 $\beta$ , and IL-18.<sup>[84-87]</sup> Furthermore, a study was conducted using mice deficient for ASC and NLRP3 in which the mice displayed a reduced capacity to generate a hypersensitivity reaction to certain irritants.<sup>[71]</sup> This demonstrated the importance of inflammasome in overall hypersensitivity response and the fact that

these immune-deficient mice were able to mount normal elicitation phase contact hypersensitivity reactions upon inoculation with presensitized T-cells solidified the hypothesis that the inflammasome was only crucial in the sensitization phase.<sup>[88]</sup> In other words, the phase of the hypersensitivity reaction in which antigen-presenting cells (APCs) take up antigen and migrate from skin to lymph nodes to present it to naïve T-cells is mediated by inflammasome activity.

### Psoriasis

Experimental results suggest that caspase 5, an effector caspase in the NLRP1 inflammasome, is a powerful promoter of psoriatic pathology.<sup>[14]</sup> The results showed that there was increased mRNA expression of caspase 5 and a smaller, but still significant, upregulation of ASC (a NLRP1 inflammasome component) in lesional psoriatic tissue. Caspase 5 upregulation is showed to be an indicator of high immunogenic activity and its expression is not increased in other inflammatory skin diseases (contact hypersensitivity and atopic dermatitis). Moreover, psoriasis patients have lesser cutaneous infections compared to other inflammatory skin diseases implying inflammasome hyperactivity to be a major contributing factor. Recently Dombrowski *et al.*, demonstrated that cytosolic DNA is an important disease-associated molecular pattern that can trigger AIM2 inflammasome and IL-1 $\beta$  activation in psoriasis, providing new potential targets for treatment of this chronic skin disease.

### Vitiligo

The precise role of the inflammasome in vitiligo and vitiligo-associated autoimmune diseases is still a point of speculation. It was shown by Jin *et al.*<sup>[89]</sup> that mutations in NACHT region of the NLRP1 NLR gene, as well as a mutation in the regulatory region of that gene, were correlated to expression of vitiligo phenotype. Taïeb<sup>[90]</sup> suggested that the pathological inflammasome activity in vitiligo is altering adaptive immunity by prioritizing melanocyte clearance. This hypothesis is supported in part by a finding of slightly elevated T-cell infiltrates in skin of vitiligo patients.<sup>[91]</sup> Furthermore, vitiligo is known to often coincide with autoimmune diseases such as rheumatoid arthritis, SLE, and diabetes which, by extension, suggest a role for the NLRP1 inflammasome in these diseases.<sup>[89]</sup>

### Atopic dermatitis

Atopic dermatitis is a complex disease with environmental factors, impaired recruitment of innate immune cells and decreased anti-microbial peptide

secretion contributing both to autoinflammatory pathology as well as susceptibility to infection.<sup>[92]</sup> NLRP1, NLRP3, NOD1, and NOD2 are all believed to be responsible for innate detection of bacterial motifs in pathogens commonly associated with atopic dermatitis infections such as certain Gram-negative bacteria and *Staphylococcus aureus*.<sup>[93]</sup> The inability of patients with atopic dermatitis to cope with pathogens suggests that some deficiency in the inflammasome signal cascade. Additionally, the gene encoding NOD1 is located in a region that has been linked with atopy and mutations in NOD1, NOD2, and NLRP12 have all been correlated to diagnoses of atopic dermatitis.<sup>[94-96]</sup> Nakanishi *et al.*<sup>[97]</sup> illustrate the importance of IL-18 in the pathogenesis of atopic dermatitis. IL-18 influences adaptive immune response by stimulating Th1 cells to “super Th1 cells” that produce both Th1 and Th2 cytokines.<sup>[98]</sup> These “super Th1 cells” were identified in mice with induced atopic dermatitis. IL-18 was also demonstrated to be present and originating from keratinocytes. IL-18 blockade successfully prevented both development of induced atopic dermatitis and generation of “super Th1 cells”.<sup>[99]</sup>

## CONCLUSIONS

In this review, we summarized the role of inflammasomes and their activation in cellular damage or stress. Activation of inflammasomes require ‘priming’ with lipopolysaccharide and a second signal in the form of low intracellular potassium, increased mitochondrial ROS levels, lysosomal destabilization, or other unknown factors. A better understanding about the regulatory role of inflammasomes in host defense, autoinflammatory conditions and cell repair will open new therapeutic targets for infectious and inflammatory diseases. The role of inflammasome in the pathogenesis of gout and rheumatoid arthritis has reached the point where therapeutic targets are being identified and tested in humans. Some unanswered questions regarding inflammasome activation and function still remain, which over the years is expected to be solved.

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