

Review Article

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Inflammasomes in health and disease

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Abstract

Inflammation is a complex process that helps the body to eliminate invading pathogens or damaged cells, and initiates the repair process. The inflammasomes are a class of cytosolic large protein complexes that are responsible for the activation of inflammatory responses and inducing programmed cell death. Inflammasome activation has been implicated in the pathogenesis of various diseases, including infectious, autoimmune, and metabolic disorders. The mechanisms of inflammasome activation and regulation are complex and involve multiple pathways, and targeting inflammasomes has emerged as a potential therapeutic strategy for the treatment of inflammatory and immune-related diseases. This review provides an overview of inflammasome mechanisms, implications in disease, regulation, and therapeutic targeting.

Key words: Inflammation; Pattern recognition receptor; Inflammasomes.

Introduction

Definition of inflammasomes: Inflammasomes are multi-protein complexes that play a crucial role in the innate immune response to infection and tissue damage. They are primarily involved in the activation of inflammatory responses mediated by cytokines such as IL-1 β and IL-18 [1].

Structure of inflammasomes

The inflammasome complex is composed of three main components:

- **Sensor proteins:** Pattern recognition receptor (PRR) detect the presence of pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) in the cytosol [2].
- **Adaptor protein:** The ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain (CARD)) protein which is responsible for connecting the sensor proteins to the effector protein [3].
- **Effector protein:** The caspase-1 which is responsible for cleaving and activating pro-inflammatory cytokines IL-1 β and IL-18 as well as initiating pyroptosis [4].

In addition to these core components, several other proteins

can be involved in the assembly and regulation of inflammasomes, such as NEK7 (NIMA-related kinase 7), NLRP6, NLRP12, and PYCARD. These proteins can modulate inflammasome activation and downstream signaling [5].

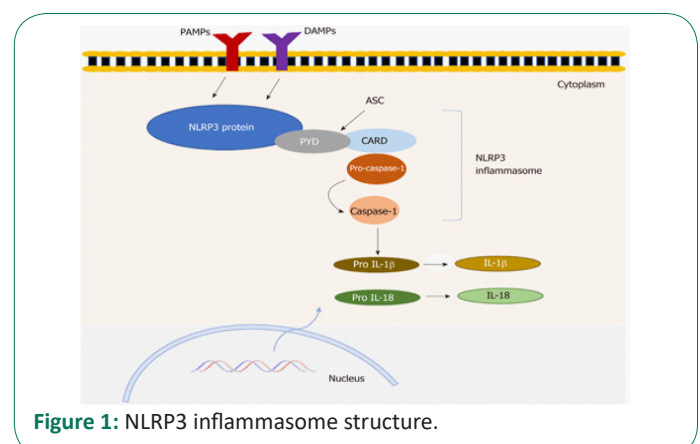


Figure 1: NLRP3 inflammasome structure.

NLRP3 inflammasome consists of three major components: the sensor NLRP3 protein, the adaptor apoptosis-associated speck-like protein (ASC) which contains a N-terminal PYRIN-PAAD-DAPIN domain (PYD) and a C-terminal caspase recruitment domain (CARD), and the effector protein-caspase-1. Activation of NLRP3 occurs when the cell is subjected to patho-

gen-associated molecular patterns and damage-associated molecular patterns. The stimulated NLRP3 interacts through PYD domain with ASC and pro-caspase-1 binds to ASC via CARD to assemble into a large cytosolic complex, which triggers activation of caspase-1. Active caspase-1 cleaves the pro-inflammatory cytokines IL-1 β and IL-18 from their precursors to their biologically active forms inducing inflammation [6].

Mechanism of inflammasome activation

Role of PRRs in inflammasome activation

The pathway of inflammasome activation is initiated when PRRs recognize PAMPs or DAMPs. PRRs can be divided into several categories, including Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I-like receptors (RLRs), and AIM2 (absent in melanoma 2)-like receptors (ALRs) [7].

- TLRs are transmembrane proteins that are located on the surface of immune cells and recognize PAMPs in the extracellular environment. TLRs can activate downstream signaling pathways that lead to the expression of pro-inflammatory cytokines and the priming of inflammasomes. For example, TLR4 recognizes lipopolysaccharide (LPS) from Gram-negative bacteria and induces the expression of pro-IL-1 β and pro-IL-18 [8].

- NLRs are cytoplasmic receptors that detect intracellular PAMPs and DAMPs. NLRs are composed of an N-terminal effector domain, a central nucleotide-binding oligomerization domain (NOD), and a C-terminal leucine-rich repeat (LRR) domain. Several NLRs, including NLRP1, NLRP3, and NLRC4 have been shown to activate inflammasomes [9].

- RLRs are cytoplasmic receptors that detect viral RNA and induce type I interferon responses. RLRs can also activate inflammasomes through the MAVS (mitochondrial antiviral signaling) pathway [10].

- ALRs are cytoplasmic receptors that recognize cytosolic double-stranded DNA (dsDNA) and induce the activation of inflammasomes. AIM2 is the only known member of the ALR family that can activate inflammasomes [11].

As PRRs recognize PAMPs or DAMPs, this leads to their oligomerization and the recruitment of adaptor proteins ASC [7]. ASC facilitates the assembly of the inflammasome complex by linking PRRs to effector caspases-1. Upon inflammasome assembly, the effector caspases are activated and cleave pro-inflammatory cytokines such as pro-IL-1 β and pro-IL-18 to generate the mature biologically active secreted forms of these cytokines [8]. This leads to the recruitment of immune cells and the promotion of inflammation at the site of infection or injury. In addition, effector caspases can also cleave gasdermin D (GSDMD), a pore-forming protein that mediates pyroptosis, leading to cell death and the release of pro-inflammatory intracellular contents [12].

The NLRP3 inflammasome is the most extensively studied inflammasome, and its activation involves a two-step process.

Two-step process of NLRP3 inflammasome activation

1. **Priming step:** Involves the upregulation of NLRP3 and pro-IL-1 β expression in response to a stimulus, such as a pathogen or a danger signal. This step requires the activation of PRRs, and the induction of transcription factors such as nuclear factor kappa B (NF- κ B) and interferon regulatory factor (IRF) [13].

2. **Activation step:** Involves the activation of the NLRP3 inflammasome itself, which requires a second stimulus, such as the release of intracellular ATP or the disruption of lysosomal membranes leading recognition of PAMPs or DAMPs by NLRP3 leading to their oligomerization and the recruitment of adaptor proteins, ASC, to form the inflammasome complex. This step results in the assembly of the NLRP3 inflammasome complex, the recruitment of pro-caspase-1, and the activation of caspase-1 [14].

Other stimuli that activate inflammasomes

In addition to the stimuli mentioned earlier, other factors have also been shown to activate inflammasomes include bacterial toxins, viral RNA, ATP, and crystals such as uric acid crystals [7]. For example, the NLRC4 inflammasome is activated by bacterial flagellin and type III secretion system (T3SS) components, while the NLRP1 inflammasome is activated by anthrax lethal toxin and muramyl dipeptide [15]. Moreover, the NLRP6 and NLRP12 inflammasomes have been implicated in the regulation of gut microbiota and intestinal homeostasis [9].

Furthermore, recent studies have suggested that environmental and lifestyle factors, such as diet and exercise, can modulate inflammasome activation. For example, high-fat diets and obesity have been shown to activate the NLRP3 inflammasome in various tissues, while exercise has been shown to inhibit inflammasome activation and reduce inflammation [16].

Inflammasomes in health and disease

Role of inflammasomes in the innate immune system: Inflammasomes play a critical role in both maintaining health and contributing to disease pathogenesis. In the context of health, inflammasomes are essential for innate immunity, providing a rapid and efficient response by detecting and responding to pathogens and cellular perturbations, including PAMPs, DAMPs and homeostasis-altering molecular processes (HAMPs), which are signals of infection or tissue damage [7]. Inflammasome activation leads to the production of pro-inflammatory cytokines, such as IL-1 β and IL-18, which recruit immune cells to the site of infection or injury, promote inflammation, and stimulate tissue repair. In addition, inflammasome-mediated pyroptosis leading to cell swelling and lysis that helps to eliminate infected or damaged cells, preventing the spread of infection. By activating these immune responses, inflammasomes contribute to the clearance of pathogens and the maintenance of tissue homeostasis [15].

However, dysregulation of inflammasome activation can contribute to the pathogenesis of various diseases, including infectious, autoimmune, and metabolic disorders. For example, inflammasome activation has been implicated in the pathogenesis of diseases such as gout and atherosclerosis. In gout, inflammasome activation in response to uric acid crystals leads to the production of IL-1 β , which contributes to the inflammatory response and joint damage [17]. In atherosclerosis, inflammasome activation in macrophages leads to the production of IL-1 β , which promotes the formation of atherosclerotic plaques [18].

Moreover, inflammasome activation has also been linked in the pathogenesis of some neurodegenerative diseases such as Alzheimer's Disease (AD) and Parkinson's Disease (PD). In AD, NLRP3 inflammasome activation in microglia in the brains of

patients with AD leads to the production of IL-1 β and IL-18 and the production of amyloid- β peptides, which contribute to the neuroinflammatory response and neuronal damage [19]. In PD, inflammasome activation has been linked to the production of pro-inflammatory cytokines and the activation of microglia, which can lead to neuroinflammation and neurodegeneration [20,21]. In addition, mutations in the NLRP3 gene, which encodes a component of the inflammasome, have been associated with autoinflammatory disorders such as Cryopyrin-Associated Periodic Syndromes (CAPS) and Familial Mediterranean Fever (FMF) [22].

Understanding the role of inflammasomes in health and disease is critical for the development of new therapies for inflammatory disorders. Inhibition of inflammasome activation has been shown to reduce inflammation and improve disease outcomes in animal model and may represent a promising approach for the treatment of these diseases [23].

Role of inflammasomes in infectious diseases

Here are some examples of the role of inflammasomes in infectious diseases:

1. **Bacterial infections:** NLRP3 inflammasome has been shown to play a critical role in the host defense against various bacterial pathogens, such as Salmonella and Legionella [24]. While NLRP3 inflammasome has also been implicated in the host response to Staph. aureus and Strept. Pneumoniae infections [23].

2. **Viral infections:** The role of inflammasomes in the host response to viral infections is complex and depends on the virus and the host response. NLRP3 inflammasome has been shown to be activated in response to several viral infections, including influenza virus, respiratory syncytial virus (RSV), and hepatitis C virus (HCV) [25]. However, in some cases, inflammasome activation can also promote viral replication and exacerbate disease severity [25].

3. **Fungal infections:** NLRP3 inflammasome has been shown to play a critical role in the host defense against fungal pathogens, such as Candida albicans and Aspergillus fumigatus [24].

4. **Parasitic infections:** The role of inflammasomes in the host response to parasitic infections is not well understood, but some studies suggest that inflammasome activation may be involved in the host response to certain parasitic pathogens such as Plasmodium falciparum [26].

Involvement of inflammasomes in autoimmune diseases

Here are some examples of the involvement of inflammasomes in autoimmune diseases:

1. **Rheumatoid Arthritis (RA):** NLRP3 inflammasome has been shown to be activated in the synovial fluid and tissue of patients with RA. IL-1 β and IL-18, which are activated by NLRP3 inflammasome, are also elevated in the serum and synovial fluid of patients with RA [27]. Inhibiting inflammasome activation has been shown to reduce joint damage in animal models of RA [27].

2. **Systemic Lupus Erythematosus (SLE):** Inflammasomes activation, particularly NLRP3, have been implicated in the pathogenesis of SLE, and can lead to the production of autoantibodies, which contribute to the development of SLE [27,28].

3. **Inflammatory Bowel Disease (IBD):** NLRP3 inflammasome activation in intestinal epithelial cells and immune cells has been implicated in the pathogenesis of IBD, and can lead to the production of IL-1 β and IL-18, which contribute to the development of intestinal inflammation, tissue damage and chronic inflammatory response [29].

4. **Type 1 diabetes:** The activation of inflammasomes can lead to the production of IL-1 β , which contributes to the destruction of pancreatic beta cells. Inhibition of inflammasome activation has been shown to improve pancreatic beta cell survival in animal models of type 1 diabetes [30].

Link between inflammasome activation and metabolic disorders

Dysregulated inflammasome activation can lead to chronic inflammation, which is the hallmark of metabolic disorders such as obesity, type 2 diabetes, and metabolic syndrome and leads to the development of insulin resistance and other metabolic abnormalities [31]. Here are some examples of the link between inflammasome activation and metabolic disorders:

1. **Obesity:** NLRP3 inflammasome has been implicated in the development of obesity-related inflammation. Adipose tissue from obese individuals has been shown to have increased NLRP3 inflammasome activation, which contributes to the production of pro-inflammatory cytokines as IL-1 β and IL-18 [32].

2. **Type 2 diabetes:** NLRP3 inflammasome activation in adipose tissue macrophages can lead to the production of IL-1 β , which contributes to the development of insulin resistance, impaired glucose homeostasis, and beta cell dysfunction. Inhibition of inflammasome activation has been shown to improve glucose tolerance and insulin sensitivity in animal models of type 2 diabetes [31].

3. **Metabolic syndrome:** Inflammasome activation can contribute to the development of insulin resistance and other metabolic abnormalities [30].

Relation between inflammasomes and cancer

There is growing evidence that inflammasomes play a role in the development and progression of cancer [31]. Inflammasomes are activated in response to various types of cellular damage, including DNA damage and oxidative stress, both of which are known to be involved in cancer development, and can lead to the production of pro-inflammatory cytokines such as IL-1 β and IL-18 which can promote tumorigenesis by stimulating proliferation and survival of cancer cells [31,33]. However, inflammasomes can also have a protective role in the immune response to cancer by activating cytotoxic T cells to recognize and kill cancer cells, which can help to prevent tumor growth [34].

Association between inflammasome activation and COVID-19 severity

COVID-19 is caused by the SARS-CoV-2 virus, which can trigger an inflammatory response in the body. Dysregulated inflammasome activation can contribute to the excessive inflammation associated with severe COVID-19 disease [35]. Here are some examples of the association between inflammasome activation and COVID-19 severity:

1. **NLRP3 inflammasome activation:** Studies have shown that patients with severe COVID-19 have increased NLRP3 in-

flammasome activation, which contributes to the production of pro-inflammatory cytokines such as IL-1 β and IL-18 [36].

2. **Pyroptosis:** Pyroptotic cell death can contribute to tissue damage and the release of pro-inflammatory cytokines, which can further exacerbate the hyperinflammatory response observed in severe COVID-19 [36].

3. **Therapeutic targeting:** Several clinical trials are investigating the efficacy of inflammasome inhibitors in reducing the severity of COVID-19 through reducing the hyperinflammatory response [35].

Regulation of inflammasome activation

Negative regulators of inflammasome activation

Inflammasome activation is a tightly regulated process, and several negative regulators have been identified that play a critical role in controlling the magnitude and duration of the inflammasome response [37]. These negative regulators act at various levels of the inflammasome pathway, and their dysregulation can lead to excessive inflammation and contribute to the pathogenesis of inflammatory diseases [37]. Understanding the mechanisms of inflammasome regulation and identifying new negative regulators may provide novel therapeutic targets for the treatment of inflammatory diseases. Negative regulators of inflammasome activation include:

o **Pyrin domain-only protein 2 (POP2)**, also known as ASC-associated speck-like protein containing a CARD (CARDINAL): inhibits the oligomerization and activation of caspase-1 by binding to the ASC adaptor protein, which is required for inflammasome assembly. The expression of POP2 is induced by inflammatory stimuli and serves as a negative feedback mechanism to limit the inflammasome response [38].

o **Caspase Recruitment Domain Family Member 8 (CARD8):** Interacts with the NLRP3 inflammasome and inhibits its activation by preventing the recruitment of ASC and caspase-1. Several genetic variants in CARD8 have been associated with increased susceptibility to inflammatory diseases, as Crohn's disease and RA [39].

o **Protein Kinase R (PKR):** Is activated by ds-RNA and inhibits the activation of the NLRP3 inflammasome by phosphorylating its downstream targets, including caspase-1 and ASC. PKR deficiency has been shown to exacerbate the inflammatory response in several disease models, including colitis and sepsis [40].

o **NLR Family Member X1 (NLRX1):** Inhibits the activation of the NLRP3 and NLRC4 inflammasomes by interfering with the assembly of their signaling complexes [39].

o **Tripartite Motif-Containing Protein 30 (TRIM30):** Inhibits the activation of the AIM2 inflammasome by promoting its degradation [40].

o **Cytokine-Inducible SH2-Containing Protein (CISH):** Is induced by cytokine stimulation and inhibits the activation of the NLRP3 inflammasome by interacting with its adaptor protein ASC [41].

Anti-inflammatory cytokines that suppress inflammasome activation

Several anti-inflammatory cytokines and molecules have been identified that can suppress inflammasome activation and

mitigate the inflammatory response:

o **Interleukin-10 (IL-10):** Exerts its anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines, including IL-1 β and IL-18, which are downstream targets of inflammasome activation. IL-10 can also directly suppress inflammasome activation by inhibiting the expression of inflammasome components and the activity of caspase-1 [22].

o **Transforming Growth Factor-Beta (TGF- β):** Regulates immune cell function and tissue repair. TGF- β can inhibit inflammasome activation by suppressing the expression of NLRP3 and other inflammasome components, as well as the activity of caspase-1. TGF- β can also promote the differentiation of regulatory T cells, which can suppress the inflammatory response and prevent excessive inflammasome activation [42].

o **IL-37:** A member of the IL-1 family. It is an anti-inflammatory cytokine and an antagonist for IL-1 receptor (IL-1Ra), which competitively inhibits the binding of IL-1 to its receptor [22].

o **Cyclic AMP (cAMP):** Inhibits NLRP3 inflammasome activation by activating PKA and promoting the degradation of NLRP3 [43].

Inflammasomes future and prospective

Development of small molecule inhibitors of inflammasome activation

Several small molecule inhibitors have been identified that target different components of the inflammasome pathway such as MCC950 and CY-09 [44].

Preclinical studies have provided evidence for the efficacy of inflammasome inhibitors in various inflammatory diseases:

1. **Gout:** MCC950 targets the NLRP3 inflammasome, and has been shown to block IL-1 β production, and reduce joint swelling and inflammation, as well as serum levels of IL-1 β and uric acid, and improve disease outcomes in animal models of gout [17,26].

2. **Alzheimer's disease:** MCC950 has been shown to reduce neuroinflammation, reduce the number of activated microglia and astrocytes, as well as levels of IL-1 β and IL-18 in the brain and improve cognitive function in a mouse model of Alzheimer's disease [45].

3. **Multiple sclerosis (MS):** In a mouse model, MCC950 treatment reduced disease severity and demyelination, as well as levels of IL-1 β and IL-18 in the spinal cord. This suggests that NLRP3 inflammasome inhibition may be a potential therapeutic strategy for MS [46].

4. **Inflammatory bowel disease:** In a mouse model of colitis, treatment with MCC950 or CY-09 reduced inflammation and disease severity, as well as levels of IL-1 β and IL-18 in the colon, and improved disease outcomes [45].

5. **Sepsis:** The AIM2 inflammasome has been implicated in the pathogenesis of sepsis [44]. CY-09 targets the AIM2 inflammasome, and has been shown to reduce levels of IL-1 β and IL-18, as well as inflammatory cytokines and chemokines in the blood and organs of septic mice which reduce inflammation and improve survival in a mouse model of sepsis [44].

Therapeutic targeting of inflammasomes

In addition to small molecule inhibitors, other approaches for targeting inflammasomes include:

1. **Monoclonal antibodies:** Neutralize inflammasome-related cytokines, as IL-1 β and IL-18, have been approved for the treatment of certain inflammatory diseases such as RA and CAPS [1].

2. **Gene therapy:** For modulating inflammasome activation is a promising approach for the treatment of inflammatory diseases. For example, the overexpression of negative regulators of inflammasome activation, such as NLRP12, has been shown to inhibit inflammasome activation and reduce inflammation in animal models [47].

3. **Cell-based therapies:** Such as mesenchymal stem cells and regulatory T cells, has shown promise in preclinical studies for the treatment of various inflammatory diseases [48].

4. **Natural compounds:** Such as curcumin and resveratrol have been shown to inhibit inflammasome activation and reduce inflammation in animal models [49].

While these approaches show promise, there are also potential limitations and challenges in developing effective inflammasome inhibitors such as:

- The potential for off-target effects, as inflammasomes play important roles in the immune response and other physiological processes.
- There may be differences in inflammasome activation and regulation among different tissues and disease states, which may require different targeting strategies [50].

Conclusion

Inflammasomes are key players in the innate immune response by detecting and responding to various danger signals, including pathogens and host-derived molecules. They function by activating the production of pro-inflammatory cytokines and promoting pyroptotic cell death. However, dysregulation of inflammasomes can lead to the development of chronic inflammatory diseases such as diabetes, Alzheimer's, and cancer. As such, targeting inflammasomes has emerged as a promising therapeutic strategy for these conditions. Further research is needed to fully understand the mechanisms underlying inflammasome activation and regulation, and to develop more effective treatments for inflammatory diseases.

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