NLRP3 inflammasome in sepsis (Review)

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Abstract. Sepsis is an imbalanced response to infection that leads to life-threatening organ dysfunction. Although an increasing number of anti-inflammatory drugs are available, the options for treating sepsis remain limited. Therefore, it is imperative to understand the pathogenesis and pathophysiology of sepsis and develop novel therapeutic targets to treat this state. The Nod-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome is a cytoplasmic high-molecular weight protein complex composed of the sensor NLRP3, adapter protein apoptosis-related speck-like protein and pro-caspase-1. It functions by cleaving pro-caspase-1 to become active caspase-1, resulting in the maturation and release of IL-1β and IL-18. Activation of the NLRP3 inflammasome is necessary for innate immune defense and also serves an important role in adaptive immune responses. Studies have shown that the NLRP3 inflammasome is involved in the occurrence and evolution of sepsis and other immune inflammatory diseases. The present paper reviews the activation pathways and biological function of the NLRP3 inflammasome in sepsis, with the aim to provide a basis for further research.

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Abbreviations: NLRP3, Nod-like receptor family pyrin domain-containing 3; ASC, apoptosis-related speck-like protein; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; NLRs, nucleotide binding oligomerization domain and leucine-rich repeat-containing receptors; PYD, pyrin domain; ROS, reactive oxygen species; LPS, lipopolysaccharide; mtROS, mitochondrial ROS; mtDNA, mitochondrial DNA; MAVS, mitochondrial antiviral signaling protein; CLP, cecal ligation and puncture

Key words: NLRP3 inflammasome, activation, ubiquitination, phosphorylation, sepsis

Contents

1. Introduction

Sepsis is a common sequela of severe trauma, burns, infection and major surgery, often secondary to septic shock and multiple organ dysfunction syndrome (1). Despite research on the pathogenesis and treatment of sepsis using a variety of antibiotics and supportive therapies, its incidence and associated mortality is still high, as there are an estimated 48.9 million cases of sepsis and 11 million sepsis-related deaths worldwide (2). An important reason for the high mortality rate of sepsis is the uncontrolled inflammatory response leading to damage to multiple organs (3,4). The pathogenesis of sepsis is complex and involves interaction between infectious microorganisms and the host. In sepsis, pathogens, such as bacteria, fungi and viruses, invade the body and release lipopolysaccharide (LPS), exotoxin and other moieties with pathogen-associated molecular patterns (PAMPs). The organism rapidly senses these PAMPs and a series of events are triggered, culminating in the release of material carrying damage-associated molecular patterns (DAMPs), such as damaged DNA. These PAMPs and DAMPs influence fluid control and immune, inflammatory and other systems, causing complex pathophysiological changes and multi-organ functional damage (5). In the course of infection, the activation of various receptors is essential for the recognition of a variety of microorganisms to regulate innate and adaptive immunity. In sepsis, pattern-recognition receptors, such as Toll-like receptors (TLRs) on the cell membrane and Nod-like receptors, in the cytoplasm recognize PAMPs and DAMPs, leading to the activation of intracellular signaling pathways that result in the transcrip-

tion and release of pro-inflammatory factors, such as TNFα, IL-18 and IL-1β (6).

In sepsis, circulating PAMPs, DAMPs and cytokines activate endothelial cells, cardiac fibroblasts and cardiomyocytes, and increase the production of inflammatory mediators, thereby further activating the expression of inducible nitric oxide synthase and causing myocardial inhibition (7). In the lungs, interstitial and endothelial barriers are broken down, which may lead to an imbalance in the alveolar ventilation/blood flow ratio and decreased lung compliance, resulting in acute respiratory distress syndrome (8). In the gastrointestinal tract, the increased permeability of the inner layer of the mucosa leads to leakage of bacteria from the intestinal tract, which causes gastrointestinal dysfunction (9). In the kidneys, decreased renal perfusion, acute tubular necrosis and microvascular damage contribute to varying degrees of acute injury (10). These endothelial cell changes also disrupt the blood-brain barrier, leading to the entry of toxins, inflammatory cells and cytokines, which in turn cause brain edema, neurotransmitter destruction and oxidative stress, culminating in the development of septic encephalopathy. Proinflammatory cytokines can cause leukocyte activation and proliferation, upregulation of endothelial adhesion molecules and chemokine expression, production of tissue factors and amplification of immune responses, which also leads to host cell and tissue damage. Hence, the ability to treat sepsis may be significantly improved by inhibiting the inflammatory response in order to protect against the multi-organ functional damage caused by this condition (11).

Inflammasomes are multi-protein complexes with a molecular weight of ~700 kDa that are assembled following intracytoplasmic pattern recognition receptor ligation (12). They consist primarily of a sensor, adaptor and pro-caspase-1. Sensors of PAMPs and DAMPs in the cytoplasm include nucleotide-binding oligomerization domain and leucine-rich repeat (LRR)-containing receptors (NLRs), absent in melanoma-2 and pyrin. NLRs include Nod-like receptor family pyrin domain-containing (NLRP)1, NLRP3, NLRP6, NLRP7, NLRP12 and NLRC4, which assemble into their own inflammasomes (13). All members of the NLR protein family contain a central nucleotide-binding domain, and most also have a variable N-terminal domain and a C-terminal LRR domain. Based on the presence of an N-terminal pyrin domain (PYD) or caspase activation and recruitment domain (CARD), the family is further divided into NLRP or NLRC receptors (14). The NLRP3 inflammasome, one of the most well-studied inflammasomes, is composed of NLRP3, adaptor apoptosis-related speck-like protein (ASC) and pro-caspase-1 molecules. When stimulated by infection or other factors, the NLRP3 inflammasome interacts with ASC via the CARD/CARD and PYD/PYD domains to increase expression levels of pro-caspase-1, which is self-catalyzed to cleave into two subunits, p20 and p10 (15). Tetramers of p20 and p10 that constitute active caspase-1, which further cleaves pro-IL-1β and pro-IL-18, thus promoting the activation and release of the caspase-1-dependent inflammatory mediators IL-18 and IL-1β (13). Activated caspase-1 also activates pore-forming gasdermin D to induce a form of cell death called pyroptosis (12). Activation of inflammasomes serves an important role in pathogen defense, stimulating both innate and adaptive immune responses. However, dysregulation of inflammasomes activity has been implicated in numerous human diseases, such as gout, diabetes and atherosclerosis, amongst others (16-18). Thus, inflammasome activation is a tightly regulated process which requires multiple molecular and cellular signals. The present review summarizes the primary regulatory mechanisms of NLRP3 inflammasome activation and discusses the role of this inflammasome in the development of sepsis.

2. NLRP3 inflammasome activation

The activation of the NLRP3 inflammasome takes place in two stages, first priming and then activating. The initial signal (Signal I) is provided by pro-inflammatory cytokines or microbial components, leading to the activation of the transcription factor NF-κB and subsequent upregulation of pro-IL-1β and NLRP3 (13). The expression of NLRP3 and pro-IL-1β is regulated at the transcriptional level during the priming phase. This transcriptional upregulation can be induced via the recognition of various PAMPs or DAMPs that engage pattern recognition receptors (PRRs), such as TLRs or IL-1 receptor, or via cytokines, such as TNF and IL-1β, that lead to NF-κB activation and gene transcription (19). Signal II can be provided by a variety of different stimuli, including ATP, nigericin, particulate matter, pore-forming toxins and RNA viruses (13). Several cellular events, including lysosomal destruction, production of reactive oxygen species (ROS), mitochondrial dysfunction and changes in ion flux, have all been shown to activate the NLRP3 inflammasome (20). A two-signal model for NLRP3 inflammasome activation is presented in Fig. 1.

The efflux of K^+ has long been considered a common ionic event occurring in the activation of NLRP3 inflammasomes. K^+ efflux regulates the maturation and release of IL-1β in neutrophils, mediated by the NLRP3/ASC inflammasome and caspase-1 (21). The two-pore domain K^+ channel family 2 potassium efflux channel in macrophages can activate the NLRP3 inflammasome to mediate inflammatory responses (22). Studies have shown that membrane remodeling induced by saturated fatty acids can destroy plasma membrane Na-K-ATPase, thereby activating the NLRP3 inflammasome in human macrophages (23). ATP-mediated activation of the P2X purinoceptor 7 (P2X7), a member of the ligand-gated ion channel purinergic receptor family, promotes IL-1β maturation via K^+ efflux (24). For this reason, K^+ efflux is regarded as a common trigger for the activation of the NLRP3 inflammasome. In addition, a non-classical inflammatory pathway induced by LPS can result in the activation of caspase-11, which leads to a decrease in intracellular K^+ levels, thereby activating the NLRP3 inflammasome to induce pyroptosis (25). However, K^+ efflux is not required for activation of the alternative NLRP3 inflammasome pathway (25). The decrease of cytoplasmic K^+ can activate the NLRP3 inflammasome independently of an increase of cytoplasmic Ca^{2+} to initiate the inflammatory cascade (26). These findings suggest that K^+ efflux serves an important role in NLRP3 inflammasome activation, but how NLRP3 detects changes in intracellular potassium concentration and whether other proteins are involved in K^+ efflux to regulate the activation of NLRP3 remain to be investigated.

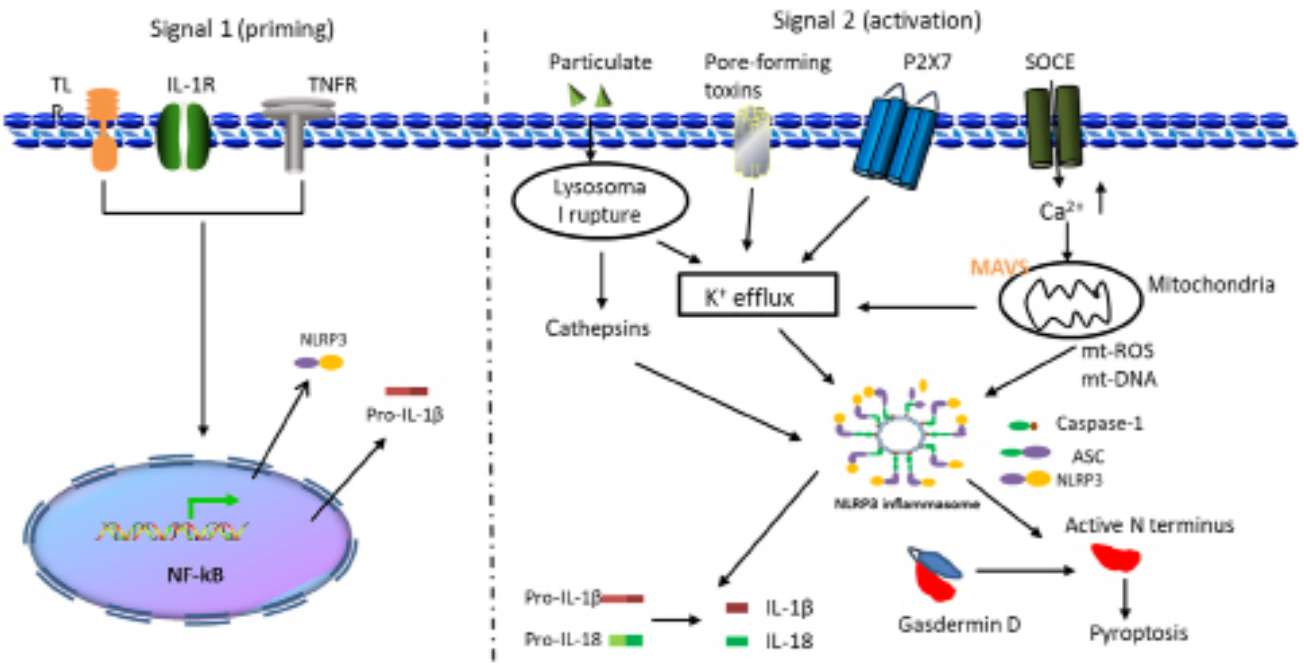

Figure 1. A two-signal model for NLRP3 inflammasome activation. Signal I (priming, left) is provided by microbial molecules or endogenous cytokines and leads to the upregulation of NLRP3 and pro-IL-1β via activation of the transcription factor NF-κB. Signal II (activation, right) is provided by various stimuli, such as ATP, pore-forming toxins and particulates. Numerous signaling events have been proposed as the key mechanism of NLRP3 activation. Most NLRP3 stimuli induce K^+ efflux, Ca^{2+} signaling and mitochondrial dysfunction-derived signals, such as mtROS and oxidized mtDNA, which has been suggested to mediate NLRP3 activation. The mitochondrial adaptor MAVS mediates NLRP3 activation induced by RNA viruses. Particulates activate NLRP3 via lysosomal rupture-induced K^+ efflux and release of cathepsins. NLRP3, Nod-like receptor family pyrin domain-containing 3; mt, mitochondrial; ROS, reactive oxygen species; MAVS, mitochondrial antiviral signaling protein; TLR, Toll-like receptor; IL-1R, IL-1β receptor; TNFR, TNF receptor; SOCE: store-operated Ca^{2+} entry; ASC, apoptosis-related speck-like protein; P2X7, P2X purinoceptor 7.

The role of ROS production and mitochondrial dysfunction in NLRP3 inflammasome activation is widely recognized. ROS may serve as a common signal for NLRP3 inflammasome activation because most NLRP3 inflammasome stimuli mediate ROS production and NADPH oxidase is considered to be one of the main sources of ROS (27). Recent studies have found that orexin contributes to vascular disease by inhibiting NLRP3 inflammasome activation via suppressing the expression of NADPH oxidase 4 in human aortic endothelial cells at high concentrations of glucose (28). Sterol regulatory element-binding protein 2 transactivates NADPH oxidase, thereby activating the NLRP3 inflammasome in vascular endothelial cells and increasing susceptibility to atherosclerosis (29). However, studies have shown that the activation of the NLRP3 inflammasome and the release of IL-1β in human macrophages requires calcium but does not involve NADPH oxidase (30).

The mitochondrial respiratory chain is another pathway for ROS production. A growing body of evidence suggests that mitochondrial dysfunction is involved in the assembly and conformational alteration of the NLRP3 inflammasome via ROS production, which results in its activation (13). Studies have shown that MitoQ can inhibit activation of the NLRP3 inflammasome and release of IL-1β by blocking the production of mitochondrial ROS (mtROS), thereby decreasing tubular injury in diabetic nephropathy (31). Shimada *et al* (32) found that oxidized mitochondrial DNA (mtDNA) is necessary for the activation of the NLRP3 inflammasome. NLRP3 secondary signal activators can induce mitochondrial dysfunction, leading to the release of mtDNA into the cytoplasm, where it can bind to and activate NLRP3 inflammasomes. Zhong *et al* (33) found that TLR-dependent initiation signals induce the synthesis of new mtDNA, which is required for NLRP3 inflammasome activation. Epigallocatechin-3-gallate has been found to inhibit the synthesis of mtDNA and production of ROS in mouse macrophages, thereby inhibiting activation of the NLRP3 inflammasome (34). These findings suggest that mitochondrial dysfunction, mtROS and mtDNA production serve a critical role in NLRP3 inflammasome activation.

Mitochondria can co-localize with NLRP3 inflammasomes, in addition to producing mtROS and mtDNA. Mitochondrial antiviral signaling proteins (MAVS) have been shown to promote recruitment of NLRP3 inflammasomes to mitochondria and may enhance their oligomerization and activation by bringing them into close proximity to mtROS (35). Subramanian *et al* (36) found that the N-terminal of NLRP3 regulates association and mitochondrial recruitment of MAVS, and MAVS promote the production of NLRP3-mediated mature IL-1β by facilitating NLRP3 recruitment to mitochondria. Li *et al* (37) found that NLRX1 decreases the inflammatory response and apoptosis of ischemic myocardial cells by inhibiting the activation of MAVS-dependent NLRP3 inflammasomes. Iyer *et al* (38) found that mitochondria-specific lipidocardiol can directly bind to the LRR domain of NLRP3, which not only serves as a docking station for the co-localization of NLRP3 and its activated ligands, but also provides activation signals to the NLRP3 inflammasome itself. Studies have shown that both NLRP3 and caspase-1 interact with mitochondrial lipids (34,35). After receiving appropriate activation signals, cardiolipin eversion into the

outer membrane of mitochondria results in the formation of a calcium-dependent association between ASC and mitochondria, thus leading to the assembly and activation of NLRP3 inflammasomes (39). Following infection by RNA viruses, NLRP3 inflammasome activation is associated with the presence of mitochondrial protein mitofusin 2 (40). Taken together, the aforementioned findings suggest that mitochondria may activate inflammasomes by participating in the assembly of the NLRP3 complex. In addition, it has been found that phosphatidylinositol 4,5-bisphosphate on the scattered trans-Golgi network can be used as a scaffold for NLRP3 inflammasome activation (41). Zhang *et al* (42) also found that Golgi can activate NLRP3 inflammasomes via protein kinase D on the mitochondrial-associated endoplasmic reticulum membrane.

Particulates, such as cholesterol crystals, silica, and monosodium urate, phagocytosed by macrophages can destroy lysosomes and cause the lysosomal contents to be released into the cytoplasm to activate NLRP3 inflammasomes (13). Previous studies have shown that particle activators induce lysosomal rupture and release of material into the cytoplasm, which alters plasma membrane permeability and releases ATP and purine, which in turn activate the NLRP3 inflammasome (43). Jessop *et al* (44) found that inhaling particles that cause lysosomal membrane permeability can activate the NLRP3 inflammasome, and that lysosomal acidification is a prerequisite for particle-induced lysosomal membrane permeability. Similarly, NLRP3-deficient macrophages show a considerable decrease in ATP depletion and mitochondrial function, but maintain lysosomal acidity, suggesting that LMP is NLRP3-dependent (45).

Previous studies have reported that phagocytosed particles can destroy lysosomes and release cathepsin B into the cytoplasm to trigger the activation of the NLRP3 inflammasome, and that the cathepsin B inhibitor CA-074 Me blocks this response (46). However, cathepsin B-knockdown in macrophages does not prevent inflammasome-mediated cell death, which may be due to off-target effects; alternatively, CA-074 Me may also act on other members of the cathepsin family (47). It has been reported that cathepsins B had redundant effects on the activation of the NLRP3 inflammasome by particulates, while cathepsin X has a non-redundant effect on the activation of NLRP3 inflammasomes by non-particulates (48). Cathepsin B is required for ASC spot formation, IL-1β production and caspase-1 activation in response to different types of NLRP3 activators (49). Tang *et al* (50) found that hydroxychloroquine inhibits cathepsin B, thereby redistributing lysosomal bulk, inhibiting the activation of the NLRP3 inflammasome and decreasing renal injury. Oxidative stress activates NLRP3 inflammasomes in microglia by upregulating the activity of cathepsin B, thereby promoting the development of neurodegenerative disease (51). Taken together, the aforementioned studies documented that cathepsin B can activate NLRP3 inflammasomes, but the mechanism still needs further study.

3. Ubiquitination modification of the NLRP3 inflammasome

The ubiquitin system is a complex post-translational modification system, which primarily mediates the addition of ubiquitin to its substrates via sequential activation of E1-E2-E3 enzymes (52). E3 ubiquitin ligase may be involved in NLRP3 inflammasome activation by targeting either NLRP3 or other components of the inflammasome. E3 ubiquitin ligase regulates NLRP3 expression via autophagy or proteasomal degradation (33). It has been reported that the E3 ubiquitin ligase tripartite motif-containing protein (TRIM)31 binds directly to NLRP3, promotes polyubiquitination of K48 junctions and proteasomal degradation of NLRP3, and thereby inhibits NLRP3 inflammasome activation (53). Silencing by small interfering RNA of the deubiquitinase BRCC36 in macrophages treated with the proteasome inhibitor MG132 prevented oxidized low-density lipoprotein-induced NLRP3 inflammasome activation and IL-1β secretion (54). E3 ubiquitin ligase also inhibits NLRP3 inflammasome activation by maintaining NLRP3 in an inactive state not associated with degradation. Following inflammasome priming, Cullin1 mediates ubiquitination of NLRP3 causing it to form an inactive inflammasome. Upon exposure to inflammatory stimuli, Cullin1 dissociates from NLRP3, allowing it to return to an active state (55). Ariadne homolog 2 interacts with the NACHT domain of NLRP3 and induces ubiquitination of K48 and K63, thereby inhibiting NLRP3 inflammasome activation (56). E3 ubiquitin ligase also positively regulates the activation of the NLRP3 inflammasome. A recent study suggested that the E3 ligase Pellino2 serves a dual role in the regulation of NLRP3. It can interact with NLRP3 during LPS priming to promote the polyubiquitination of NLRP3 K63 and thus inhibit the activation of the NLRP3 inflammasome (57). Pellino2 also ubiquitinates IL-1 receptor-associated kinase 1 (IRAK1) and prevents its interaction with NLRP3, thus limiting the inhibitory effect of IRAK1 on NLRP3 and also promoting the activation of NLRP3 inflammasomes (57). Xing *et al* (58) found that lack of TNF receptor-associated factor 6 (TRAF6) prevents activation of the NLRP3 inflammasome, which is mediated by the E3 ubiquitin ligase function of TRAF6. In addition, double-stranded RNA in the cytoplasm activates the NLRP3 inflammasome, mediated by the interaction of DHX33, cytoplasmic RNA sensors and NLRP3; this interaction requires TRIM33-mediated K63 polyubiquitination of DHX33 (59).

Ubiquitination of inflammasome-binding protein ASC also controls the activation of the NLRP3 inflammasome. Following viral infection, MAVS-mediated E3 ubiquitin ligase TRAF3 recruitment leads to K63 polyubiquitination of ASC via autophagy, leading to its degradation (60). Far infrared can cause TRAF6-mediated ASC polyubiquitination via autophagy degradation in macrophages and has been used in the treatment of burn wounds (61). The linear ubiquitin assembly complex regulates the activation of NLRP3 inflammasomes by linear polyubiquitination of ASC. Furthermore, HOIL-1-deficient macrophages exhibit decreased IL-1β secretion following LPS stimulation (62).

E3 ubiquitin ligase can also mediate the ubiquitination of caspase-1 to regulate the activation of NLRP3 inflammasomes. Inhibitor of apoptosis proteins (IAPs) activate the inflammasome by inducing the polyubiquitination of caspase-1 K63; accordingly, the activation of caspase-1 is decreased in cellular (c)IAP1/2 or X-linked (X)IAP-deficient mice (63). cIAP1/2 and XIAP are depleted when caspase-1 is activated, and the absence of E3 ligase leads to the production of receptor interacting protein kinase 3-dependent ROS, which

is sufficient to activate the NLRP3 inflammasome (64). The ubiquitination system serves positive and negative roles in the activation of inflammasomes by acting on various components of the NLRP3 inflammasome, depending on cell location, the nature of the substrate and the different ubiquitin chains that modify it.

4. Phosphorylation modification of the NLRP3 inflammasome

Phosphorylation is a common mechanism for post-translational modification of proteins and is involved in the signal transduction pathway of NLRP3 inflammasome activation. Basak *et al* (65) reported that PYD of NLRP3 is dephosphorylated by phosphatase 2A at the ser5 site to activate the NLRP3 inflammasome, and inhibition or knockdown of phosphatase 2A decreases NLRP3 activation. NLRP3 activators induce mitochondria-associated endoplasmic reticulum membrane translocation to the adjacent Golgi to increase diacylglycerol, which recruits protein kinase D to phosphorylate NLRP3 at ser295, facilitating the assembly of the NLRP3 inflammasome (42). Li *et al* (66) found that protein kinase A (PKA) inhibitor H89 blocks baicalin and induces phosphorylation of NLRP3 on PKA-specific sites and thus inhibit the activation of the NLRP3 inflammasome. However, it is not clear why NLRP3 phosphorylation at the same site has the opposite effect on the activation of NLRP3 inflammasomes. Bile acids activate the TGR5 receptor pathway, leading to an increase in cAMP and subsequent PKA activation. PKA phosphorylates the NOD domain of NLRP3 at ser291, and NLRP3 phosphorylation promotes polyubiquitination of K48 and K63 and degradation (67). The protein tyrosine phosphatase non-receptor 22 dephosphorylates NLRP3 at tyrosine residues Tyr861, thereby promoting activation of the NLRP3 inflammasome (68). Martin *et al* (69) found that, during the activation of NLRP3 inflammasomes, ASC is phosphorylated by IκB kinase (IKK)i at s58 and promotes the migration of ASC from the nucleus to the perinuclear region; ASC is also phosphorylated by IKKα at s16 and s193 and interacts with IKKα. However, Signal II for NLRP3 inflammasome activation inhibits IKKα kinase activity by recruiting protein phosphatase 2A, thus enabling ASC to participate in the assembly of NLRP3 inflammasomes (69). Studies have shown that caspase-1 is phosphorylated and activated by PI-3K/Rac1/p21-activated kinase at s376, thus participating in the activation of inflammatory cortisone (65). Therefore, these findings suggest that the NLRP3 inflammasome serves a key role in the development of innate immunity and immune inflammatory disease, while post-translational modification of NLRP3 inflammasomes, including ubiquitination and phosphorylation, can precisely regulate their activation, providing the host with immune protection against tissue damage.

5. NLRP3 activation in sepsis

Effects on the central nervous system. In sepsis-induced brain injury, recombinant club cell protein protects the hippocampus from injury by inhibiting p38 protein and the ERK signaling pathway to inhibit the NLRP3 inflammasome (70). The NLRP3 inhibitor MC950 and caspase-1 inhibitor Ac-YVAD-CMK ameliorate cognitive impairment caused by sepsis-associated encephalopathy via inhibiting NLRP3/caspase-1 pathway-mediated pyroptosis (71). Melatonin improves spinal cord injury and protects motor neurons in rats by inhibiting the activation of the NLRP3 inflammasome (72). Similarly, melatonin-mediated mitochondrial autophagy prevents early brain damage following subarachnoid hemorrhage by inhibiting the activation of NLRP3 inflammasomes (73).

Effects on the cardiovascular system. Studies have shown that the NLRP3 inflammasome is activated in cardiac fibroblasts during sepsis, which induces the maturation and release of inflammatory factors such as IL-1β. Inhibiting the activation of the NLRP3 inflammasome in cardiac fibroblasts can alleviate LPS-induced myocardial dysfunction and improve the survival of mice with septic peritonitis (74). Carbon monoxide-releasing molecule treatment inhibits activation of the NLRP3 inflammasome by blocking interactions between the NLRP3 inflammasome and adaptor protein ASC and alleviates myocardial dysfunction in septic mice (75). In addition, Tanuseputero *et al* (76) found that by blocking the NLRP3 pathway, LPS-induced inflammatory responses and cell apoptosis could be alleviated and the function of damaged myocardial tissue could be restored.

Effects on the respiratory system. Wang *et al* (77) reported that dihydromyricetin significantly inhibits the activation of the NLRP3 inflammasome in cecal ligation and puncture (CLP) sepsis model mice, and also inhibits the expression levels of pyrodeath-associated proteins in lung cells, thus protecting against CLP-induced acute lung injury. In sepsis-induced acute respiratory distress syndrome, activation of the NLRP3 inflammasome pathway in bronchial epithelial cells leads to secretion of excessive amounts of mucins and inflammatory cytokines, promoting the expression levels of chemokines and cell adhesion molecules (78). Vasoactive intestinal peptide attenuates LPS-induced acute lung injury by inhibiting the activation of the NLRP3 inflammasome in mouse primary peritoneal macrophages (79). Ying *et al* (80) found that overexpressed microRNA (miRNA)-495 decreases levels of inflammatory alveolar macrophages, infiltration of neutrophils and activation of NLRP3 inflammasomes in LPS-mediated acute lung injury, while methylation of the miRNA-495 promoter region aggravates LPS-mediated lung injury.

Effects on the gastrointestinal system. Zhang *et al* (81) found that NLRP3 blockade downregulates the IL-1β response in LPS-stimulated liver macrophages infected with HIV-1, indicating that NLRP3/Caspase-1 inflammatory signaling pathways are involved in the IL-1β response of liver macrophages to HIV-1-infection. NIMA-related kinase 7 is a significant component of the NLRP3 inflammasome in macrophages; studies have shown that NIMA-related kinase 7 interacts with NLRP3 to regulate the activation of the NLRP3 inflammasome in LPS stimulation to mediate pyroptosis in inflammatory bowel disease (82). Inhibiting the thioredoxin-interacting protein/NLRP3 axis restores intestinal barrier function in non-alcoholic steatohepatitis by decreasing LPS-mediated myeloperoxidase activity and oxidative stress (83). Studies have shown that autophagy induced by AXL receptor tyrosine kinase binding to its ligand growth arrest specific 6 in macrophages can prevent the

maturation of caspase-1-dependent IL-1β and IL-18. Therefore, AXL-mediated autophagy can protect against LPS-mediated acute liver injury by inhibiting the activation of the NLRP3 inflammasome (84).

Effects on the renal system. Arginine can protect against acute kidney injury in sepsis by inhibiting NO-mediated activation of the NLRP3 inflammasome (76). Yang *et al* (85) found that transfected renal tubular epithelial cells over-expressing CD39 exhibit decreased production of LPS-mediated pro-inflammatory cytokines and activated NLRP3. Hydrogen sulfide inhibits NLRP3 inflammasome activation via the TLR4/NLRP3 signaling pathway to protect against LPS-induced sepsis-associated acute kidney injury (86). In LPS-induced acute kidney injury, dexmedetomidine inhibits mRNA and protein expression levels of TLR4, NADPH oxidase-4 and NLRP3, and alleviates LPS-mediated acute kidney injury by modulating the TLR4/NADPH oxidase-4/NLRP3 pathway to inhibit the activation of NLRP3 inflammasomes and decrease oxidative stress damage (87). Sepsis-induced activation of NLRP3 inflammasome in activated platelets has been shown to be associated with organ damage in septicemic CLP rat models. Treatment with MCC950, a specific inhibitor of NLRP3, significantly decreases sepsis-induced platelet activation and prevents kidney damage and endothelial dysfunction in CLP (88).

6. Conclusion

The innate immune system is the first line of host defense. Pattern recognition receptors are activated in response to harmful stimuli, such as various pathogenic microorganisms (which contain PAMPs and result in the release of DAMPs), and trigger downstream inflammatory responses to eliminate infection and repair damaged tissue (5). NLRP3 stimulation induces multiple signaling pathways and cellular events, resulting from NLRP3 inflammasome activation. Among these, the major activating agents are potassium efflux, ROS production, mitochondrial dysfunction, lysosomal damage and protein post-translational modifications (13). However, a unified mechanism of NLRP3 inflammasome activation has not yet been discerned, and further studies are needed to clarify this.

Sepsis is a disorder in the host response to infection, resulting in life-threatening organ dysfunction. This definition emphasizes that infection leads to homeostasis imbalances in the host and a potentially fatal risk (89). The assembly and activation of the NLRP3 inflammasome leads to varying degrees of damage to different systems during sepsis (5,6). So far, a number of studies have shown that inhibiting the activation of the inflammasome can decrease the inflammatory response in sepsis (16-18). Nevertheless, sepsis can cause organ dysfunction, suggesting that its pathophysiological mechanisms are complex. Further studies are necessary to elucidate the specific effects of NLRP3 inflammasomes on the pathophysiological mechanisms of sepsis so that novel diagnostic and therapeutic measures can be developed.

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Authors' contributions

XYS drafted the manuscript. XYS and SPT conceived and designed the framework of this article. XYS and SCT collected and analyzed the literature. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Kim M and Li G: Postoperative complications affecting survival after cardiac arrest in general surgery patients. Anesth Analg 126: 858-864, 2018.
2. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, *et al*: Global, regional, and national sepsis incidence and mortality, 1990-2017: Analysis for the Global Burden of Disease Study. Lancet 395: 200-211, 2020.
3. Davis FM, Schaller MA, Dendekker A, Joshi AD, Kimball AS, Evanoff H, Wilke C, Obi AT, Melvin WJ, Cavassani K, *et al*: Sepsis Induces Prolonged Epigenetic Modifications in Bone Marrow and Peripheral Macrophages Impairing Inflammation and Wound Healing. Arterioscler Thromb Vasc Biol 39: 2353-2366, 2019.
4. Xu S, Zhou Z, Li H, Liu Z, Pan X, Wang F, Huang Y, Li X, Xiao Y, Pan J, *et al*: BMSCs ameliorate septic coagulopathy by suppressing inflammation in cecal ligation and puncture-induced sepsis. J Cell Sci 131: 131, 2018.
5. Gruda MC, Ruggeberg KG, O'Sullivan P, Guliashvili T, Scheirer AR, Golobish TD, Capponi VJ and Chan PP: Broad adsorption of sepsis-related PAMP and DAMP molecules, mycotoxins, and cytokines from whole blood using CytoSorb® sorbent porous polymer beads. PLoS One 13: e0191676, 2018.
6. Salomão R, Ferreira BL, Salomão MC, Santos SS, Azevedo LCP and Brunialti MKC: Sepsis: Evolving concepts and challenges. Braz J Med Biol Res 52: e8595, 2019.
7. Lv X and Wang H: Pathophysiology of sepsis-induced myocardial dysfunction. Mil Med Res 3: 30, 2016.
8. Nieman GF, Andrews P, Satalin J, Wilcox K, Kollisch-Singule M, Madden M, Aiash H, Blair SJ, Gatto LA and Habashi NM: Acute lung injury: How to stabilize a broken lung. Crit Care 22: 136, 2018.
9. Strate LL and Morris AM: Epidemiology, pathophysiology, and treatment of diverticulitis. Gastroenterology 156: 1282-1298.e1, 2019.

10. Zarbock A, Gomez H and Kellum JA: Sepsis-induced acute kidney injury revisited: Pathophysiology, prevention and future therapies. Curr Opin Crit Care 20: 588-595, 2014.
11. Varatharaj A and Galea I: The blood-brain barrier in systemic inflammation. Brain Behav Immun 60: 1-12, 2017.
12. Abderrazak A, Syrovets T, Couchie D, El Hadri K, Friguet B, Simmet T and Rouis M: NLRP3 inflammasome: From a danger signal sensor to a regulatory node of oxidative stress and inflammatory diseases. Redox Biol 4: 296-307, 2015.
13. Swanson KV, Deng M and Ting JP: The NLRP3 inflammasome: Molecular activation and regulation to therapeutics. Nat Rev Immunol 19: 477-489, 2019.
14. Lu A and Wu H: Structural mechanisms of inflammasome assembly. FEBS J 282: 435-444, 2015.
15. Stutz A, Kolbe CC, Stahl R, Horvath GL, Franklin BS, van Ray O, Brinkschulte R, Geyer M, Meissner F and Latz E: NLRP3 inflammasome assembly is regulated by phosphorylation of the pyrin domain. J Exp Med 214: 1725-1736, 2017.
16. Kim SR, Lee SG, Kim SH, Kim JH, Choi E, Cho W, Rim JH, Hwang I, Lee CJ, Lee M, *et al*: SGLT2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease. Nat Commun 11: 2127, 2020.
17. Tumurkhuu G, Shimada K, Dagvadorj J, Crother TR, Zhang W, Luthringer D, Gottlieb RA, Chen S and Arditi M: Ogg1-Dependent DNA Repair Regulates NLRP3 Inflammasome and Prevents Atherosclerosis. Circ Res 119: e76-e90, 2016.
18. Renaudin F, Orliaguet L, Castelli F, Fenaille F, Prignon A, Alzaid F, Combes C, Delvaux A, Adimy Y, Cohen-Solal M, *et al*: Gout and pseudo-gout-related crystals promote GLUT1-mediated glycolysis that governs NLRP3 and interleukin-1β activation on macrophages. Ann Rheum Dis 79: 1506-1514, 2020.
19. Afonina IS and Zhong Z: Karin M and Beyaert R: Limiting inflammation-the negative regulation of NF-κB and the NLRP3 inflammasome. Nat Immunol 18: 861-869, 2017.
20. He Y, Hara H and Núñez G: Mechanism and regulation of NLRP3 inflammasome activation. Trends Biochem Sci 41: 1012-1021, 2016.
21. Karmakar M, Katsnelson M, Malak HA, Greene NG, Howell SJ, Hise AG, Camilli A, Kadioglu A, Dubyak GR and Pearlman E: Neutrophil IL-1β processing induced by pneumolysin is mediated by the NLRP3/ASC inflammasome and caspase-1 activation and is dependent on K^+ efflux. J Immunol 194: 1763-1775, 2015.
22. Di A, Xiong S, Ye Z, Malireddi RKS, Kometani S, Zhong M, Mittal M, Hong Z, Kanneganti T-D, Rehman J, *et al*: The TWIK2 potassium efflux channel in macrophages mediates NLRP3 inflammasome-induced inflammation. Immunity 49: 56-65.e4, 2018.
23. Gianfrancesco MA, Dehairs J, L'homme L, Herinckx G, Esser N, Jansen O, Habraken Y, Lassence C, Swinnen JV, Rider MH, *et al*: Saturated fatty acids induce NLRP3 activation in human macrophages through K^+ efflux resulting from phospholipid saturation and Na, K-ATPase disruption. Biochim Biophys Acta Mol Cell Biol Lipids 1864: 1017-1030, 2019.
24. Wang W, Hu D, Feng Y, Wu C, Song Y, Liu W, Li A, Wang Y, Chen K, Tian M, *et al*: Paxillin mediates ATP-induced activation of P2X7 receptor and NLRP3 inflammasome. BMC Biol 18: 182, 2020.
25. Rühl S and Broz P: Caspase-11 activates a canonical NLRP3 inflammasome by promoting K(+) efflux. Eur J Immunol 45: 2927-2936, 2015.
26. Katsnelson MA, Rucker LG, Russo HM and Dubyak GR: K^+ efflux agonists induce NLRP3 inflammasome activation independently of Ca^{2+} signaling. J Immunol 194: 3937-3952, 2015.
27. Abais JM, Xia M, Zhang Y, Boini KM and Li PL: Redox regulation of NLRP3 inflammasomes: ROS as trigger or effector? Antioxid Redox Signal 22: 1111-1129, 2015.
28. Zhang C, Abdukerim M, Abilailieti M, Tang L, Ling Y and Pan S: The protective effects of orexin a against high glucose-induced activation of NLRP3 inflammasome in human vascular endothelial cells. Arch Biochem Biophys 672: 108052, 2019.
29. Xiao H, Lu M, Lin TY, Chen Z, Chen G, Wang W-C, Marin T, Shentu TP, Wen L, Gongol B, *et al*: Sterol regulatory element binding protein 2 activation of NLRP3 inflammasome in endothelium mediates hemodynamic-induced atherosclerosis susceptibility. Circulation 128: 632-642, 2013.
30. Rada B, Park JJ, Sil P, Geiszt M and Leto TL: NLRP3 inflammasome activation and interleukin-1β release in macrophages require calcium but are independent of calcium-activated NADPH oxidases. Inflamm Res 63: 821-830, 2014.
31. Han Y, Xu X, Tang C, Gao P, Chen X, Xiong X, Yang M, Yang S, Zhu X, Yuan S, *et al*: Reactive oxygen species promote tubular injury in diabetic nephropathy: The role of the mitochondrial ros-txnip-nlrp3 biological axis. Redox Biol 16: 32-46, 2018.
32. Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S, Ramanujan VK, Wolf AJ, Vergnes L, Ojcius DM, *et al*: Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. Immunity 36: 401-414, 2012.
33. Zhong B, Liu X, Wang X, Liu X, Li H, Darnay BG, Lin X, Sun SC and Dong C: Ubiquitin-specific protease 25 regulates TLR4-dependent innate immune responses through deubiquitination of the adaptor protein TRAF3. Sci Signal 6: ra35, 2013.
34. Lee HE, Yang G, Park YB, Kang HC, Cho YY, Lee HS and Lee JY: Epigallocatechin-3-gallate prevents acute gout by suppressing NLRP3 inflammasome activation and mitochondrial DNA synthesis. Molecules 24: 2138, 2019.
35. Park S, Juliana C, Hong S, Datta P, Hwang I, Fernandes-Alnemri T, Yu JW and Alnemri ES: The mitochondrial antiviral protein MAVS associates with NLRP3 and regulates its inflammasome activity. J Immunol 191: 4358-4366, 2013.
36. Subramanian N, Natarajan K, Clatworthy MR, Wang Z and Germain RN: The adaptor MAVS promotes NLRP3 mitochondrial localization and inflammasome activation. Cell 153: 348-361, 2013.
37. Li H, Zhang S, Li F and Qin L: NLRX1 attenuates apoptosis and inflammatory responses in myocardial ischemia by inhibiting MAVS-dependent NLRP3 inflammasome activation. Mol Immunol 76: 90-97, 2016.
38. Iyer SS, He Q, Janczy JR, Elliott EI, Zhong Z, Olivier AK, Sadler JJ, Knepper-Adrian V, Han R, Qiao L, *et al*: Mitochondrial cardiolipin is required for Nlrp3 inflammasome activation. Immunity 39: 311-323, 2013.
39. Elliott EI, Miller AN, Banoth B, Iyer SS, Stotland A, Weiss JP, Gottlieb RA, Sutterwala FS and Cassel SL: Cutting edge: Mitochondrial assembly of the NLRP3 inflammasome complex is initiated at priming. J Immunol 200: 3047-3052, 2018.
40. Ichinohe T, Yamazaki T, Koshiba T and Yanagi Y: Mitochondrial protein mitofusin 2 is required for NLRP3 inflammasome activation after RNA virus infection. Proc Natl Acad Sci USA 110: 17963-17968, 2013.
41. Chen J and Chen ZJ: PtdIns4P on dispersed trans-Golgi network mediates NLRP3 inflammasome activation. Nature 564: 71-76, 2018.
42. Zhang Z, Meszaros G, He WT, Xu Y, de Fatima Magliarelli H, Mailly L, Mihlan M, Liu Y, Puig Gámez M, Goginashvili A, *et al*: Protein kinase D at the Golgi controls NLRP3 inflammasome activation. J Exp Med 214: 2671-2693, 2017.
43. Riteau N, Baron L, Villeret B, Guillou N, Savigny F, Ryffel B, Rassendren F, Le Bert M, Gombault A and Couillin I: ATP release and purinergic signaling: A common pathway for particle-mediated inflammasome activation. Cell Death Dis 3: e403, 2012.
44. Jessop F, Hamilton RF Jr, Rhoderick JF, Fletcher P and Holian A: Phagolysosome acidification is required for silica and engineered nanoparticle-induced lysosome membrane permeabilization and resultant NLRP3 inflammasome activity. Toxicol Appl Pharmacol 318: 58-68, 2017.
45. Heid ME, Keyel PA, Kamga C, Shiva S, Watkins SC and Salter RD: Mitochondrial reactive oxygen species induces NLRP3-dependent lysosomal damage and inflammasome activation. J Immunol 191: 5230-5238, 2013.
46. Liu A, Gao X, Zhang Q and Cui L: Cathepsin B inhibition attenuates cardiac dysfunction and remodeling following myocardial infarction by inhibiting the NLRP3 pathway. Mol Med Rep 8: 361-366, 2013.
47. Newman ZL, Leppla SH and Moayeri M: CA-074Me protection against anthrax lethal toxin. Infect Immun 77: 4327-4336, 2009.
48. Orlowski GM, Colbert JD, Sharma S, Bogyo M, Robertson SA and Rock KL: Multiple cathepsins promote Pro-IL-1β synthesis and NLRP3-mediated IL-1β activation. J Immunol 195: 1685-1697, 2015.
49. Chevriaux A, Pilot T, Derangère V, Simonin H, Martine P, Chalmin F, Ghiringhelli F and Rébé C: Cathepsin B is required for NLRP3 inflammasome activation in macrophages, through NLRP3 interaction. Front Cell Dev Biol 8: 167, 2020.
50. Tang TT, Lv LL, Pan MM, Wen Y, Wang B, Li ZL, Wu M, Wang FM, Crowley SD and Liu BC: Hydroxychloroquine attenuates renal ischemia/reperfusion injury by inhibiting cathepsin mediated NLRP3 inflammasome activation. Cell Death Dis 9: 351, 2018.
51. Bai H, Yang B, Yu W, Xiao Y, Yu D and Zhang Q: Cathepsin B links oxidative stress to the activation of NLRP3 inflammasome. Exp Cell Res 362: 180-187, 2018.
52. Wang D, Bu F and Zhang W: The role of ubiquitination in regulating embryonic stem cell maintenance and cancer development. Int J Mol Sci 20: 2667, 2019.

53. Song H, Liu B, Huai W, Yu Z, Wang W, Zhao J, Han L, Jiang G, Zhang L, Gao C, *et al*: The E3 ubiquitin ligase TRIM31 attenuates NLRP3 inflammasome activation by promoting proteasomal degradation of NLRP3. Nat Commun 7: 13727, 2016.
54. Singh M, Kumari B and Yadav UCS: Regulation of oxidized LDL-induced inflammatory process through NLRP3 inflammasome activation by the deubiquitinating enzyme BRCC36. Inflamm Res 68: 999-1010, 2019.
55. Zhuo Y, Li D, Cui L, Li C, Zhang S, Zhang Q, Zhang L, Wang X and Yang L: Treatment with 3,4-dihydroxyphenylethyl alcohol glycoside ameliorates sepsis-induced ALI in mice by reducing inflammation and regulating M1 polarization. Biomed Pharmacother 116: 109012, 2019.
56. Kawashima A, Karasawa T, Tago K, Kimura H, Kamata R, Usui-Kawanishi F, Watanabe S, Ohta S, Funakoshi-Tago M, Yanagisawa K, *et al*: ARIH2 ubiquitinates NLRP3 and negatively regulates NLRP3 inflammasome activation in macrophages. J Immunol 199: 3614-3622, 2017.
57. Humphries F, Bergin R, Jackson R, Delagic N, Wang B, Yang S, Dubois AV, Ingram RJ and Moynagh PN: The E3 ubiquitin ligase Pellino2 mediates priming of the NLRP3 inflammasome. Nat Commun 9: 1560, 2018.
58. Xing Y, Yao X, Li H, Xue G, Guo Q, Yang G, An L, Zhang Y and Meng G: Cutting edge: TRAF6 mediates TLR/IL-1R signaling-induced nontranscriptional priming of the NLRP3 inflammasome. J Immunol 199: 1561-1566, 2017.
59. Weng L, Mitoma H, Trichot C, Bao M, Liu Y, Zhang Z and Liu YJ: The E3 ubiquitin ligase tripartite motif 33 is essential for cytosolic RNA-induced NLRP3 inflammasome activation. J Immunol 193: 3676-3682, 2014.
60. Guan K, Wei C, Zheng Z, Song T, Wu F, Zhang Y, Cao Y, Ma S, Chen W, Xu Q, *et al*: MAVS promotes inflammasome activation by targeting ASC for K63-linked ubiquitination via the E3 ligase TRAF3. J Immunol 194: 4880-4890, 2015.
61. Chiu HW, Chen CH, Chang JN, Chen CH and Hsu YH: Far-infrared promotes burn wound healing by suppressing NLRP3 inflammasome caused by enhanced autophagy. J Mol Med (Berl) 94: 809-819, 2016.
62. Rodgers MA, Bowman JW, Fujita H, Orazio N, Shi M, Liang Q, Amatya R, Kelly TJ, Iwai K, Ting J, *et al*: The linear ubiquitin assembly complex (LUBAC) is essential for NLRP3 inflammasome activation. J Exp Med 211: 1333-1347, 2014.
63. Labbé K, McIntire CR, Doiron K, Leblanc PM and Saleh M: Cellular inhibitors of apoptosis proteins cIAP1 and cIAP2 are required for efficient caspase-1 activation by the inflammasome. Immunity 35: 897-907, 2011.
64. Vince JE, Wong WW-L, Gentle I, Lawlor KE, Allam R, O'Reilly L, Mason K, Gross O, Ma S, Guarda G, *et al*: Inhibitor of apoptosis proteins limit RIP3 kinase-dependent interleukin-1 activation. Immunity 36: 215-227, 2012.
65. Basak C, Pathak SK, Bhattacharyya A, Mandal D, Pathak S and Kundu M: NF-kappaB- and C/EBPbeta-driven interleukin-1beta gene expression and PAK1-mediated caspase-1 activation play essential roles in interleukin-1beta release from *Helicobacter pylori* lipopolysaccharide-stimulated macrophages. J Biol Chem 280: 4279-4288, 2005.
66. Li C-G, Yan L, Mai F-Y, Shi Z-J, Xu L-H, Jing Y-Y, Zha Q-B, Ouyang D-Y and He X-H: Baicalin inhibits NOD-like receptor family, pyrin containing domain 3 inflammasome activation in murine macrophages by augmenting protein kinase A signaling. Front Immunol 8: 1409, 2017.
67. Guo C, Xie S, Chi Z, Zhang J, Liu Y, Zhang L, Zheng M, Zhang X, Xia D, Ke Y, *et al*: Bile acids control inflammation and metabolic disorder through inhibition of NLRP3 inflammasome. Immunity 45: 802-816, 2016.
68. Spalinger MR, Kasper S, Gottier C, Lang S, Atrott K, Vavricka SR, Scharl S, Raselli T, Frey-Wagner I, Gutte PM, *et al*: NLRP3 tyrosine phosphorylation is controlled by protein tyrosine phosphatase PTPN22. J Clin Invest 126: 1783-1800, 2016.
69. Martin BN, Wang C, Willette-Brown J, Herjan T, Gulen MF, Zhou H, Bulek K, Franchi L, Sato T, Alnemri ES, *et al*: IKKα negatively regulates ASC-dependent inflammasome activation. Nat Commun 5: 4977, 2014.
70. Zhou R, Yang X, Li X, Qu Y, Huang Q, Sun X and Mu D: Recombinant CC16 inhibits NLRP3/caspase-1-induced pyroptosis through p38 MAPK and ERK signaling pathways in the brain of a neonatal rat model with sepsis. J Neuroinflammation 16: 239, 2019.
71. Fu Q, Wu J, Zhou XY, Ji MH, Mao QH, Li Q, Zong MM, Zhou ZQ and Yang JJ: NLRP3/Caspase-1 Pathway-induced pyroptosis mediated cognitive deficits in a mouse model of sepsis-associated encephalopathy. Inflammation 42: 306-318, 2019.
72. Xu G, Shi D, Zhi Z, Ao R and Yu B: Melatonin ameliorates spinal cord injury by suppressing the activation of inflammasomes in rats. J Cell Biochem 120: 5183-5192, 2019.
73. Cao S, Shrestha S, Li J, Yu X, Chen J, Yan F, Ying G, Gu C, Wang L and Chen G: Melatonin-mediated mitophagy protects against early brain injury after subarachnoid hemorrhage through inhibition of NLRP3 inflammasome activation. Sci Rep 7: 2417, 2017.
74. Tong Z, Jiang B, Zhang L, Liu Y, Gao M, Jiang Y, Li Y, Lu Q, Yao Y and Xiao X: HSF-1 is involved in attenuating the release of inflammatory cytokines induced by LPS through regulating autophagy. Shock 41: 449-453, 2014.
75. Zhang W, Tao A, Lan T, Cepinskas G, Kao R, Martin CM and Rui T: Carbon monoxide releasing molecule-3 improves myocardial function in mice with sepsis by inhibiting NLRP3 inflammasome activation in cardiac fibroblasts. Basic Res Cardiol 112: 16, 2017.
76. Tanuseputero SA, Lin MT, Yeh SL and Yeh CL: Intravenous arginine administration downregulates NLRP3 inflammasome activity and attenuates acute kidney injury in mice with polymicrobial sepsis. Mediators Inflamm 2020: 3201635, 2020.
77. Wang YC, Liu QX, Zheng Q, Liu T, Xu XE, Liu XH, Gao W, Bai XJ and Li ZF: Dihydromyricetin alleviates sepsis-induced acute lung injury through inhibiting NLRP3 inflammasome-dependent pyroptosis in mice model. Inflammation 42: 1301-1310, 2019.
78. Lyubasyuk V, Ouyang H, Yu FX, Guan KL and Zhang K: YAP inhibition blocks uveal melanogenesis driven by GNAQ or GNA11 mutations. Mol Cell Oncol 2: e970957, 2014.
79. Zhou Y, Zhang CY, Duan JX, Li Q, Yang HH, Sun CC, Zhang J, Luo XQ and Liu SK: Vasoactive intestinal peptide suppresses the NLRP3 inflammasome activation in lipopolysaccharide-induced acute lung injury mice and macrophages. Biomed Pharmacother 121: 109596, 2020.
80. Ying Y, Mao Y and Yao M: NLRP3 inflammasome activation by microRNA-495 promoter methylation may contribute to the progression of acute lung injury. Mol Ther Nucleic Acids 18: 801-814, 2019.
81. Zhang L, Mosoian A, Schwartz ME, Florman SS, Gunasekaran G, Schiano T, Fiel MI, Jiang W, Shen Q, Branch AD, *et al*: HIV infection modulates IL-1β response to LPS stimulation through a TLR4-NLRP3 pathway in human liver macrophages. J Leukoc Biol 105: 783-795, 2019.
82. Chen X, Liu G, Yuan Y, Wu G, Wang S and Yuan L: NEK7 interacts with NLRP3 to modulate the pyroptosis in inflammatory bowel disease via NF-κB signaling. Cell Death Dis 10: 906, 2019.
83. Bai RX, Xu YY, Qin G, Chen YM, Wang HF, Wang M and Du SY: Repression of TXNIP-NLRP3 axis restores intestinal barrier function via inhibition of myeloperoxidase activity and oxidative stress in nonalcoholic steatohepatitis. J Cell Physiol 234: 7524-7538, 2019.
84. Han J, Bae J, Choi CY, Choi SP, Kang HS, Jo EK, Park J, Lee YS, Moon HS, Park CG, *et al*: Autophagy induced by AXL receptor tyrosine kinase alleviates acute liver injury via inhibition of NLRP3 inflammasome activation in mice. Autophagy 12: 2326-2343, 2016.
85. Yang M, Lu L, Kang Z, Ma T and Wang Y: Overexpressed CD39 mitigates sepsis-induced kidney epithelial cell injury via suppressing the activation of NLR family pyrin domain containing 3. Int J Mol Med 44: 1707-1718, 2019.
86. Chen Y, Jin S, Teng X, Hu Z, Zhang Z and Qiu X, Tian D and Wu Y: Hydrogen sulfide attenuates LPS-induced acute kidney injury by inhibiting inflammation and oxidative stress. Oxid Med Cell Longev 2018: 6717212, 2018.
87. Yao Y, Hu X, Feng X, Zhao Y, Song M, Wang C and Fan H: Dexmedetomidine alleviates lipopolysaccharide-induced acute kidney injury by inhibiting the NLRP3 inflammasome activation via regulating the TLR4/NOX4/NF-κB pathway. J Cell Biochem 120: 18509-18523, 2019.
88. Cornelius DC, Travis OK, Tramel RW, Borges-Rodriguez M, Baik CH, Greer M, Giachelli CA, Tardo GA and Williams JM: NLRP3 inflammasome inhibition attenuates sepsis-induced platelet activation and prevents multi-organ injury in cecal-ligation puncture. PLoS One 15: e0234039, 2020.
89. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, *et al*: The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315: 801-810, 2016.