Review Article

NLRP3 Inflammasome and Inflammatory Diseases

Zheng Wang [ID],[1] Simei Zhang [ID],[1] Ying Xiao [ID],[1] Wunai Zhang [ID],[1] Shuai Wu [ID],[1] Tao Qin [ID],[1] Yangyang Yue [ID],[1] Weikun Qian [ID],[1] and Li Li [ID][2]

[1]*Department of Hepatobiliary Surgery, First Affiliated Hospital, Xi'an Jiaotong University, Xi'an 710061, China*
[2]*Department of Ophthalmology, First Affiliated Hospital, Xi'an Jiaotong University, Xi'an 710061, China*

Correspondence should be addressed to Li Li; eyelili2010@xjtu.edu.cn

Almost all human diseases are strongly associated with inflammation, and a deep understanding of the exact mechanism is helpful for treatment. The NLRP3 inflammasome composed of the NLRP3 protein, procaspase-1, and ASC plays a vital role in regulating inflammation. In this review, NLRP3 regulation and activation, its proinflammatory role in inflammatory diseases, interactions with autophagy, and targeted therapeutic approaches in inflammatory diseases will be summarized.

1. Introduction

Inflammasomes, first identified by Martinon and coworkers in 2002 [1–3], are a class of cytosolic complexes of proteins that mediate the activation of potent inflammatory mediators. They are integral parts of the innate immune response against invading pathogens and are activated upon cellular infections or stressors that promote the expression, maturation, and release of a multitude of proinflammatory cytokines, triggering a cascade of inflammatory responses [4, 5]. The nucleotide-binding oligomerization- (NOD-) like receptors (NLRs), a newly identified type of pattern recognition receptors (PRRs), which include Toll-like receptors (TLRs), C-type lectins (CTLs), and galectins, mediate the innate immune response to detect pathogenic microbes and other endogenous or exogenous pathogens [6, 7] and are important components of inflammasomes; they are located within the cytoplasm and recognize pathogen/damage-associated molecular patterns (PAMPs/DAMPs) [8–10]. The NLRs comprise 22 human genes and more mouse genes, and their family members are characterized by the presence of a tripartite structure: a central NOD, which is commonly flanked by C-terminal leucine-rich repeats (LRRs) and a N-terminal caspase recruitment domain (CARD) or pyrin domains (PYDs) [4, 11].

There are 4 known inflammasomes (NLRP1, NLRP3, NLRP4, and Aim2 inflammasomes), and they all contain a PRR that belongs to the NLR family [12, 13]. Among these inflammasomes, the NLRP3 inflammasome plays a pivotal role both in shaping immune responses and regulating the integrity of intestinal homeostasis in many common inflammatory diseases [14, 15]. NLRP3, a multiprotein complex consisting of an NLRP3 scaffold, an adaptor apoptosis speck-like protein (ASC) and the effector procaspase-1, initiates the formation of the inflammasome by interacting with ASC, which recruits and activates procaspase-1 to generate active caspase-1 and then converts the cytokine precursors pro-IL-1β and pro-IL-18 into mature and biologically active IL-1β and IL-18, respectively. Once activated, the active IL-1β and IL-18 will trigger a series of inflammatory responses and pyroptotic cell death [10, 16–18].

The NLRP3 inflammasome is produced by bone marrow-derived macrophages (after stimulation by microbial and nonmicrobial factors such as bacterial toxins, particulate matter, and lipopolysaccharide (LPS)) [8, 19]. The mechanism of NLRP3 activation remains elusive. Several molecular and cellular events have been proposed to describe to be involved in inflammasome activation, including K^+ efflux, Ca^{2+} signaling, mitochondrial dysfunction, and reactive oxygen species (ROS) production [9]. For example, particulate matter activates the NLRP3 inflammasome by inducing endocytosis and damage to the lysosome membrane, resulting in the release of cathepsin B into the cytosol [20]. Interestingly, the role of ROS and mitochondrial

perturbation in NLRP3 inflammasome activation remains controversial and requires further investigation [21–24].

NLRP3 has also been implicated in the pathogenesis of a number of complex diseases, notably including metabolic disorders such as type 2 diabetes [25], atherosclerosis [11, 26–29], obesity, and gout [30]. A role for NLRP3 in diseases of the central nervous system is emerging, including Alzheimer's disease and Parkinson's disease [31, 32]. Abnormal activation of the NLRP3 inflammasome might contribute to intestinal cancer, inflammatory diseases, and autoinflammatory diseases such as keratitis/conjunctivitis [16, 33–36]. In this review, NLRP3 regulation and activation, its proinflammatory role in inflammatory diseases, interactions with autophagy, and targeted therapeutic approaches in inflammatory diseases will be summarized.

2. The Role of NLRP3 in Inflammation

Inflammasomes are multiprotein complexes located in macrophages, dendritic cells, and some other immune cells and control the activation of the proteolytic enzyme caspase-1. Caspase-1 then regulates the maturation of IL-1β and IL-18 and the subsequent pyroptosis [37]. The NLRP3 inflammasome is composed of the NLRP3 protein, procaspase-1, and ASC [38]. Procaspase-1 is the effector in the NLRP3 inflammasome with a CARD domain. ASC is a bipartite complex containing a PYD and a CARD, which makes it a bridge connecting the sensor NLRP3 and the effector procaspase-1. NLRP3 inflammasome activation is a self-defending mechanism against invading factors and stress. Upon infection and/or injury, inflammasome components assemble and oligomerize, leading to the autocleavage of procaspase-1 to its active form. Activated caspase-1 transforms proinflammatory cytokines into their mature forms, which then participate in the following inflammatory response [39].

The NLRP3 response to stimuli occurs in the trans-Golgi network [40]. The activation of NLRP3 begins with the recognition of the danger or stressor by the sensor PRRs [41]. PAMPs (including microbial nucleic acids, bacterial secretion systems, and components of microbial cell walls) can be sensed by PPRs [42]. In addition, DAMPs (such as ATP and uric acid crystals) can also trigger PPRs [43]. The activation of the NLRP3 inflammasome is a two-stage process. The first stage is the sensing and producing stage, which begins with the recognition of PAMPs and DAMPs by TLRs. In this stage, TLRs recognize various stress factors and activate NF-κB signaling, resulting in elevated production of precursor proteins, including the NLRP3 protein, pro-IL-1β, and pro-IL-18 [44]. The second stage is the assembly and effector stage, which begins with the assembly of the NLRP3 inflammasome. The NLRP3 protein, ASC, and procaspase-1 assemble into the mature complex, which then transforms the immature forms of IL-1β and IL-18 into their mature forms [45]. IL-1β and IL-18 participate in the subsequent inflammatory effect.

NLRP3 is commonly involved in the immune response to bacteria, viruses, fungi, and parasites [42]. In most cases, the recognition of pathogens in the immune response is indirect. TLRs recognize the particular components of the invader and then induce the NLRP3 inflammasome components to be transcribed and assembled. Microbial stimuli, including Bacterial Muramyl Dipeptide (MDP) [46], bacterial RNA [47], and LPS [47], can activate the NLRP3 inflammasome in a TLR-dependent manner, while living microbes, rather than dead microbes, can induce a particular immune response via the Toll/interleukin-1 receptor domain-containing adaptor-inducing interferon-β- (TRIF-) dependent recognition by the NLRP3 inflammasome [48].

In addition, various danger signals unrelated to infection can trigger the NLRP3 inflammasome, including ROS, Ca^{2+}, nitric oxide (NO), and mitochondrial dysfunction (MtD). The production of ROS in cell has two origins: mitochondria-derived ROS (mtROS) and the cytosolic ROS. The mtROS can act as the second messenger to trigger the activation of inflammasomes after the recognition of PAMPs from microbes or DAMPs [49]. In a research about the muscle wasting, the researchers found that angiotensin II can promote the mtROS production as well as MtD, which further activated NLRP3 inflammasome [50].

The proper function of mitochondria is also crucial for NLRP3 inflammasome activation. Several factors including NO [51] and Ca^{2+} [52] can lead to MtD, which may also trigger the NLRP3 inflammasome activation via the release of oxidized mitochondrial DNA (mtDNA) following the engagement of TLRs [21]. MtD induced by the NLRP3 secondary signal activators can lead to the release of oxidized mtDNA into the cytosol, and then NLRP3 inflammasome is activated by the bondage of mtDNA [53]. Mitophagy, a crucial procedure involved in mitochondrial dynamics, has been reported to has an influence on excessive inflammasome activation. Mitophagy clears damaged mitochondria through a variety of mechanisms, including the activation of the PINK/PARKIN pathway [54], p62 aggregation [55], and SESN2 activation [56].

The endocytosis of silica and asbestos by pulmonary macrophages may activate the NLRP3 inflammasome and ROS signaling, which further leads to silicosis and asbestosis [20]. Similarly, the accumulation of monosodium urate during gout can activate the NLRP3 inflammasome in macrophages [46]. In osteoarthritis, hydroxyapatite crystals are able to activate IL-1β and elevate its production through the NLRP3 inflammasome, thus mediating inflammation and joint diseases [57]. In atherosclerosis, the NLRP3 inflammasome drives IL-1β release, thus contributing to the progression of atherosclerosis [58]. Similarly, the inhibition of caspase-1 and IL-1β activation induced by bone marrow-derived mesenchymal stem cells can suppress the generation of mitochondrial ROS and then inhibit the NLRP3 inflammasome activation [59]. Systemic inflammation has been reported to be related to an overproduction of IL-1β and IL-18 [60]. In a mouse model focusing on systemic inflammatory response syndrome, the researchers found that NLRP3 activates the adaptive immune response in mice during acute pancreatitis. This response depends on IL-1β and IL-18, but not IL-12 [60]. Similar results have also been observed to support the NLRP3 active effect of IL-18 in an engineered mouse model [61]. However, the exact mechanism by which NLRP3 recognizes DAMPs remains

unclear. Studies have reported that K^+ efflux and Ca^{2+} signaling participate in the activation of the NLRP3 inflammasome [62–66]. Among the reported upstream mechanisms involved in the NLRP3 inflammasome, the generation of mitochondrial ROS is an important one [67]. During ischemia and reperfusion, ethanol, obesity (saturated fatty acids), and ROS can induce NLRP3 inflammasome activation [68–70].

In a research about the HBV infection, researchers found that HBeAg could inhibit the NF-κB pathway and ROS production. This effect prevents LPS from inducing NLRP3 inflammasome activation, without interrupting the intracellular calcium concentration and lysosomal rupture [71]. In addition, in a study of RNA viruses, the production of ROS induced by the RIP1-RIP3 complex activated the NLRP3 inflammasome [72]. NADPH oxidase can produce cytosolic ROS, which is responsible for the activation of the NLRP3 inflammasome [73]; nevertheless, proof to the contrary showed that macrophages lacking NADPH oxidase can exhibit normal activation of the NLRP3 inflammasome [74]. Hence, the importance of ROS in NLRP3 inflammasome function has been widely acknowledged, but the exact mechanism remains to be explored.

3. The Crosstalk between NLRP3 and Autophagy

Autophagy is a physiological process that maintains the normal metabolic function and survival of cells. The formation of autophagosome is a feature of autophagy. The first step in autophagosome formation is initiation. The ULK1-Atg13-FIP200 complex is activated and localizes in the endoplasmic reticulum and some other areas. This is followed by a nucleation step driven by class III phosphoinositide 3-kinase complex (consisting of VPS34, VPS15, Beclin 1, ATG14L, and NRBF2) which is activated by ULK1. After the phagophore has almost wrapped the shipment to be degraded, the phagophore stretch and seal the shipment. The elongation step was performed with an Atg5-Atg 12-Atg16L and LC3II-PE conjugate. Then, autophagosome fuses to lysosomes to form autophagolysosomes [75].

Autophagy recycles cellular proteins and damaged organelles to obtain metabolic energy during starvation or stress to modulate cell survival in many diseases. In normoxia, autophagy is essential for maintaining corneal epithelium physiology and cell survival [76]. Additionally, autophagy serves as an essential process in resisting infection by degrading pathogens. In keratitis, the innate immune response, including autophagy, is activated when pathogens adhere to the ocular surface [77]. Interestingly, some viruses (such as HSV1) inhibit autophagy (by binding of the virus protein ICP34.5 to the host protein Beclin 113) and reduce damage [78]. In addition, excessive or abnormal autophagy can lead to cell death. The autophagy of dendritic cells enhanced the activation of CD^{4+} T cells and pathological keratitis, which significantly promoted the occurrence of herpes simplex keratitis [79]. Interfering with autophagy may be able to intervene in this incurable infectious blindness.

Normally, activation of the inflammasome, including NLRP3, triggers an antiviral inflammatory response that clears the virus and cures the inflamed tissue. NLRP3-knockout mice with keratitis induced by HSV1 developed more severe disease than infected wild-type animals, with stromal keratitis lesions occurring earlier and having more angiogenesis; this result may be related to the nuclear translocation of the NLRP3-IRF4 complex in Th2 cells, which promotes the expression of the IL-4, IL-5, and IL-13 genes to fight the HSV1 infection [80, 81]. In addition, the NLRP3/caspase-1/IL-1β pathway plays an important role in leukocyte aggregation and fighting infection during Aspergillus fumigatus infection [36]. However, the abnormal activation of the inflammasome will lead to harmful overwhelming inflammation, which may damage the infected tissue. Persistent and abnormal NLRP3 signaling is the basis of many chronic and degenerative diseases, including Stargardt disease type 1 [82], Alzheimer's disease [83], atherosclerosis [84], atrial fibrillation [85], osteoarthritis [86], and cancer [87] (Table 1).

The relationship between autophagy and NLRP3 is complex. Some studies have shown that autophagy could inhibit priming and assembly stages of the NLRP3 inflammasome [88]. In autophagy-deficient cells, including autophagic protein depletion [89], activation of the inflammatory NLRP3 complex is enhanced due to mitochondrial dysfunction such as excessive mitochondrial ROS production and changes in mitochondrial membrane permeability [90], contributed to IL-1β and IL-18 secretion. Loss of autophagy/mitophagy can lead to a buildup of cytosolic reactive oxygen species and mitochondrial DNA, which can, in turn, activate immune signaling pathways that ultimately lead to the releases of inflammatory cytokines, including IL-1α, IL-1β, and IL-18 [91]. In addition, mitophagy can clear damage mitochondria through a variety of mechanisms, including activation of the PINK/PARKIN pathway [91], p62 aggregation [92], and SESN2 activation [91], thereby preventing excessive inflammation activation. Research has shown that resveratrol inhibits NLRP3 activation in macrophages by inhibiting mitochondrial damage and enhancing autophagy [93]. Studies have also shown that autophagosomes can directly encapsulate and degrade inflammasome components, including the linker molecules ASC, NLRP3, and pro-IL-1β [94]. However, some studies have also shown that autophagy promotes NLRP3 activation. Zearalenone increases autophagy and triggers NLRP3 resonance activation by promoting NF-κB activation and nuclear translocation, ultimately resulting in cell pyroptosis [95]. In turn, NLRP3 has an effect on autophagy activation. The induction of NLRP3 inflammasomes in macrophages triggers the activation of the G-protein RalB and then the activation of autophagy, which tempers inflammation by eliminating active inflammasomes to prevent a cascade of amplified inflammatory responses [93]. Nevertheless, the inflammation induced by the NLRP3 inflammasome can also inhibit autophagy. In neuritis, the neuroinflammation promoted by NLRP3 inflammatory complexes may be amplified and regulated by a glia maturation factor, thus inhibiting the clearance of the protein aggregates that formed as a result of the

TABLE 1: Role of NLRP3 inflammasome in disease.

Disease	Responsible factor	Effect	Ref
Aspergillus fumigatus keratitis	NLRP3, caspase-1, and IL-1β	Pannexin 1 channels play important roles in the regulation of progression and leucocyte aggregation during corneal A. fumigatus infection via the NLRP3/caspase-1/IL-1β pathway.	[36]
Stargardt disease type 1	NLRP3, ROS, IL-1β, and IL-18	Aberrant buildup of atRAL promotes the death of RPE cells via NLRP3 inflammasome activation.	[82]
Alzheimer's disease	NLRP3, caspase-1, and IL-1β	Strongly enhanced the active NLRP3/caspase-1 axis in human mild cognitive impairment and brains with Alzheimer's disease.	[83]
Atherosclerosis	NLRP3	NLRP3 was overexpressed in aorta of patients with coronary atherosclerosis.	[84]
Atrial fibrillation	NLRP3	The inhibition of NLRP3 as a potential novel AF therapy approach.	[85]
Osteoarthritis	NLRP3, caspase-1, and IL-1β	Inhibition to the release of inflammasome NLRP3 exerts protection on osteoarthritis leading to the downregulation of inflammatory cytokines.	[85]
Cancer	NLRP3, caspase-1, IL-1β, and IL-18	Dysregulation of NLRP3 inflammasome activation is involved in tumor pathogenesis.	[87]

autophagic pathway [96]. In nonalcoholic steatohepatitis, NLRP3 and caspase-1 can inhibit autophagy by regulating the PINK/PARKIN pathway [91]. Additionally, the NLRP3 inflammasome inhibitor MCC950 can activate autophagy and PPARα through mTOR inhibition [97]. In conclusion, the complex relationship between NLRP3 and autophagy needs more research to provide new ideas for clinical treatment.

4. The Therapeutic Prospect of NLRP3 on Related Diseases

In clinical settings, the NLRP3 inflammasome is upregulated in myocardial fibroblasts mainly during acute myocardial infarction (AMI) [98]. van Hout et al. [99] also proved that the inflammasome can be inhibited by MCC950 in large animal AMI models. In addition, the immune complexes in systemic lupus erythematosus (SLE) patients can trigger the NLRP3 inflammasome, activate macrophages, and cause cell and tissue damage [100]. A recent study [101] has shown that citral can inhibit the expression of pro-IL-1β mediated by endotoxin and the activation of the NLRP3 inflammasome mediated by ATP, which is intriguing for the treatment of SLE. Moreover, activation of the NLRP3 inflammasome also plays an important role in the nonspecific inflammation of inflammatory bowel disease (IBD). It is noteworthy that Villani et al. [102] found that the SNP rs10733113 in the NLRP3 gene region is a Crohn's disease susceptibility gene. Subsequently, Lewis et al. [103] also reported that men carrying the c10x motif in card8, Q705k in NLRP3, and wild-type NOD2 showed susceptibility to Crohn's disease. In addition, a recent study [104] has shown that dysfunctional CARD8 mutations can also activate the NLRP3 inflammasome and contribute to the occurrence of Crohn's disease. Clarification of the exact physiological mechanism of the NLRP3 inflam-

masome will undoubtedly guide the development of effective treatments for IBD in the future.

NLRP3 inflammasomes are of great importance to therapies targeting inflammation due to their critical role in regulating inflammation. In many bacterial infections, pathogens activate NLRP3-based inflammation through the secretion of pore-forming toxins by Staphylococcus aureus [105]. Vibrio cholerae secretes toxins to activate NLRP3 similar to Staphylococcus aureus. In vivo, mice lacking inflammatory components showed that caspase-1 and ASC had protective effects against Vibrio cholerae infection [106]. NLRP3 was beneficial for mice during pneumonia caused by Streptococcus pneumoniae, and NLRP3$^{-/-}$ mice had higher bacterial load and higher mortality than wild-type mice [107]. The NLRP3 inflammasome can also be activated by viruses, such as influenza A, through the recognition of viral RNA [108]. Recent studies [109, 110] have shown that the NLRP3 inflammasome can be activated by superficial fungi such as T. schoenleinii and M. canis or their components through direct or indirect pathways to produce active inflammatory factors, which play an important role in host immunity. Currently, it has been found that the mechanisms against infection of nonsuperficial fungi may be related to the NLRP3 inflammasome [111–113]. NLRP3 can recognize Candida albicans, activate the NLRP3 inflammation complex, and induce pro-IL-1β processing, maturation, and secretion [114, 115]. The mortality rate of NLRP3 or ASC gene-deficient mice after infection with Cryptococcus neoformans was higher than that of wild-type mice, and the bacterial load in the lung tissues of NLRP3-deficient mice was significantly higher than that of wild-type mice [116]. These results showed that the NLRP3 inflammasome plays an important role in the host response to cryptococcal infection.

In eye diseases, the NLRP3 inflammasome has been shown to contribute to diabetic retinopathy [117], acute

TABLE 2: Inhibitors of NLRP3 pathways as well as their effects in cell cultures, animal models, or patients of inflammatory diseases.

Inhibitors	Molecular mechanism	Cell/animal model/patients	Ref
MCC950	Block the ATPase domain of NLRP3 and inhibit the activation of typical and atypical NLRP3 inflammasome	Autoimmune encephalomyelitis Cryopyrin-associated periodic syndrome Muckle-Wells syndrome	[124]
MNS	Bind to the LRR and NACHT domains and suppress ATPase activity of NLRP3	Bone marrow-derived macrophages	[91]
CY-09	Inhibit NLRP3 ATPase activity	Cryopyrin-associated autoinflammatory syndrome Type 2 diabetes Synovial fluid cells from gout patients	[137]
OLT1177	Inhibit NLRP3 ATPase activity and block canonical and noncanonical activation of NLRP3 inflammasome	Human blood-derived macrophages Human blood neutrophils Monocytes isolated from patients with cryopyrin-associated periodic syndrome Spleen cells from mice	[128]
Glyburide	Inhibit ATP-sensitive K^+ channels, act as downstream of the P2X7 receptor, and inhibit ASC aggregation	Bone marrow-derived macrophages Familial cold-associated autoinflammatory syndrome patients	[129]
16673-34-0	Interfere the downstream of NLRP3 conformational changes and bind to ASC	Acute myocardial infarction	[138]
JC124	Block ASC aggregation, caspase-1 activation, and IL-1β secretion	Acute myocardial infarction Alzheimer's disease	[139] [140]
BHB	Inhibit K^+ efflux and block ASC aggregation	Muckle-Wells syndrome Familial cold autoinflammatory syndrome Urate crystal-induced peritonitis	[70]
Parthenolide	Inhibit caspase-1 activation and NLRP3 ATPase activity	Bone marrow-derived macrophages Cystic fibrosis	[131] [141]
Bay 11-7082	Alkylation of cysteine residues of the NLRP3 ATPase region	Psoriasis-like dermatitis Diabetic nephropathy	[142] [143]

glaucoma [118], age-related macular degeneration [119], Behcet's syndrome, and dry eye disease [120]. In addition, in a mouse model of Pseudomonas aeruginosa keratitis, the inhibition of caspase-1 and the killing of bacteria by ciprofloxacin reduced the severity of corneal inflammation [121]. Another study showed that in a mouse model of keratitis, the level of IL-1 increased starting at 4 h after infection [122]. Treatment with the IL-1 receptor antagonist anakinra has also proven successful in the treatment of scleritis and episcleritis in the context of different rheumatic conditions [123].

To treat NLRP3-related diseases, researchers have found several inhibitors of NLRP3 or IL-1β, including direct inhibitors of NLRP3 proteins such as MCC950 [124, 125], 3,4-methylenedioxy-β-nitrostyrene (MNS) [126], CY-09 [127], and OLT1177 [128], indirect inhibitors such as glyburide [129], 16673-34-0, and JC124 [130], and inhibitors of components of the complex such as β-hydroxybutyrate (BHB) [70], parthenolide, and bay 11-7082 [131] (Table 2). The NLRP3 inflammasome can also produce IL-18, which leads to physical disorders [132]. Compared to blocking IL-1β, specific targeting with NLRP3 inhibitors may be a good choice for related diseases [133]. However, the Food and Drug Administration (FDA) does not currently approve

these drugs. Future research should focus on the development of structure-oriented direct inhibitors to improve the specificity and effectiveness.

5. Discussion

NLRP3 plays a vital role in various inflammatory diseases by altering immune responses or regulating the integrity of intestinal homeostasis. ROS, K^+ efflux, and Ca^{2+} signaling have been suggested to activate NLRP3 [9], but the specific mechanism remains unclear. Particularly, the role of ROS in NLRP3 inflammasome activation remains controversial, and it has been revealed that the cytosolic ROS induced by NADPH is responsible for the activation of the NLRP3 inflammasome [73]. However, other studies have shown that macrophages lacking NADPH oxidase exhibit normal activation of the NLRP3 inflammasome [74]. Therefore, we can conclude that the function of ROS is undetermined in the NLRP3 inflammasome, and more precise research about the mechanism is necessary.

The NLRP3 inflammasome is composed of the NLRP3 protein, procaspase-1, and ASC [134] and can generate active caspase-1 and then convert the cytokine precursors
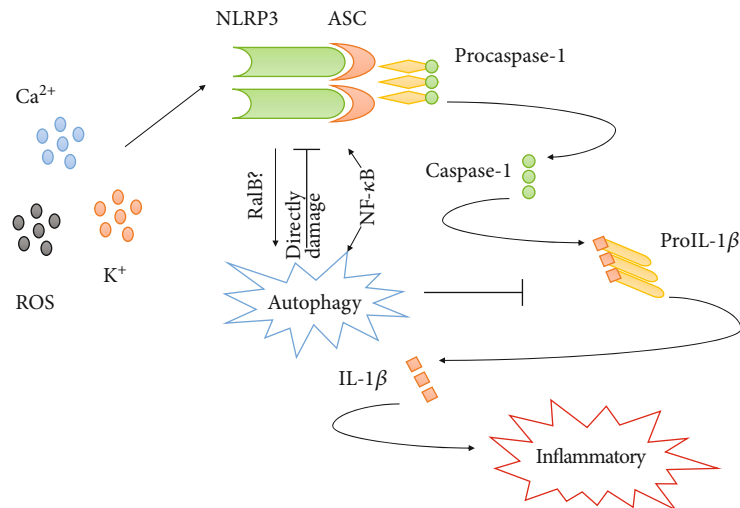
Figure 1: NLRP3 inflammasome-mediated inflammation and autophagy have complex and bidirectional regulatory effects. After being stimulated by Ca^{2+}, K^+, or ROS, the NLRP3 inflammasome is activated and recruits and activates procaspase-1 to generate active caspase-1, which then converts the cytokine precursor pro-IL-1β or other proinflammatory cytokines into mature and biologically active forms and triggers a series of inflammatory responses and pyroptotic cell death. However, this process can be regulated and interrupted by autophagy via damage of NLRP3 inflammasome; however, NLRP3 can promote cell autophagy via activation of the G-protein RalB. Interestingly, the relationship between NLRP3 and autophagy is not definitively understood, and there have also been reports that contradict the above statement such as NF-κB activation can modulate the NLRP3 and autophagy in same direction.

pro-IL-1β and pro-IL-18 into mature and biologically active IL-1β and IL-18, respectively. Ultimately, active IL-1β and IL-18 trigger a series of inflammatory responses and pyroptotic cell death [17, 18, 135]. As an important physiological process, autophagy is also strongly associated with the NLRP3 inflammasome. Many studies have shown that autophagosomes can directly encapsulate and degrade inflammasome components, including the linker molecules ASC, NLRP3, and pro-IL-1β [90, 93, 94]. Nevertheless, other researchers have demonstrated that autophagy can promote the activation of the NLRP3 inflammasome and that NLRP3 also triggers autophagy by activating the G-protein RalB in turn [95–97]. NLRP3 and autophagy have a complex relationship, and an exploration of this relationship will be helpful for understanding the mechanism of inflammation (Figure 1).

The NLRP3 inflammasome is considered a promising target for the treatment of many diseases associated with inflammation. In AMI, SLE, IBD, Crohn's disease, bacterial infections, eye diseases, etc., the NLRP3 inflammasome plays a critical role in regulating pathological processes [98, 100, 102–105, 119, 136]. Although several inhibitors of the NLRP3 inflammasome have been developed, they have not been approved by the FDA and more basic and clinical research to confirm the curative effects is necessary. With in-depth research on the mechanism of the NLRP3 inflammasome, we believe that a more exact mechanism of the NLRP3 inflammasome itself and its relationship with autophagy will be uncovered and that more specific and effective inhibitors will be exploited.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

References

[1] S. R. Ali, M. Karin, and V. Nizet, "Signaling cascades and inflammasome activation in microbial infections," *Inflammasome*, vol. 2, no. 1, 2016.

[2] L. F. Gentile, A. L. Cuenca, A. G. Cuenca et al., "Improved emergency myelopoiesis and survival in neonatal sepsis by caspase-1/11 ablation," *Immunology*, vol. 145, no. 2, pp. 300–311, 2015.

[3] I. Jorgensen and E. A. Miao, "Pyroptotic cell death defends against intracellular pathogens," *Immunological Reviews*, vol. 265, no. 1, pp. 130–142, 2015.

[4] K. Schroder and J. Tschopp, "The inflammasomes," *Cell*, vol. 140, no. 6, pp. 821–832, 2010.

[5] H. Yaribeygi, N. Katsiki, A. E. Butler, and A. Sahebkar, "Effects of antidiabetic drugs on NLRP3 inflammasome activity, with a focus on diabetic kidneys," *Drug Discovery Today*, vol. 24, no. 1, pp. 256–262, 2019.

[6] C. Bourgeois and K. Kuchler, "Fungal pathogens—a sweet and sour treat for *toll*-like receptors," *Frontiers in Cellular and Infection Microbiology*, vol. 2, p. 142, 2012.

[7] B. Z. Shao, Z. Q. Xu, B. Z. Han, D. F. Su, and C. Liu, "NLRP3 inflammasome and its inhibitors: a review," *Frontiers in Pharmacology*, vol. 6, p. 262, 2015.

[8] G. Y. Chen and G. Nunez, "Inflammasomes in intestinal inflammation and cancer," *Gastroenterology*, vol. 141, no. 6, pp. 1986–1999, 2011.

[9] Y. He, H. Hara, and G. Nunez, "Mechanism and regulation of NLRP3 inflammasome activation," *Trends in Biochemical Sciences*, vol. 41, no. 12, pp. 1012–1021, 2016.

[10] T. Prochnicki and E. Latz, "Inflammasomes on the crossroads of innate immune recognition and metabolic control," *Cell Metabolism*, vol. 26, no. 1, pp. 71–93, 2017.

[11] A. Grebe, F. Hoss, and E. Latz, "NLRP3 inflammasome and the IL-1 pathway in atherosclerosis," *Circulation Research*, vol. 122, no. 12, pp. 1722–1740, 2018.

[12] M. Lamkanfi and V. M. Dixit, "Mechanisms and functions of inflammasomes," *Cell*, vol. 157, no. 5, pp. 1013–1022, 2014.

[13] F. Lu, Z. Lan, Z. Xin et al., "Emerging insights into molecular mechanisms underlying pyroptosis and functions of inflammasomes in diseases," *Journal of Cellular Physiology*, vol. 235, no. 4, pp. 3207–3221, 2019.

[14] C. Pellegrini, L. Antonioli, G. Lopez-Castejon, C. Blandizzi, and M. Fornai, "Canonical and non-canonical activation of NLRP3 inflammasome at the crossroad between immune tolerance and intestinal inflammation," *Frontiers in Immunology*, vol. 8, p. 36, 2017.

[15] E. Elinav, J. Henao-Mejia, and R. A. Flavell, "Integrative inflammasome activity in the regulation of intestinal mucosal immune responses," *Mucosal Immunol*, vol. 6, no. 1, pp. 4–13, 2013.

[16] M. S. J. Mangan, E. J. Olhava, W. R. Roush, H. M. Seidel, G. D. Glick, and E. Latz, "Erratum: Targeting the NLRP3 inflammasome in inflammatory diseases," *Nature Reviews Drug Discovery*, vol. 17, no. 9, p. 688, 2018.

[17] A. Liston and S. L. Masters, "Homeostasis-altering molecular processes as mechanisms of inflammasome activation," *Nature Reviews Immunology*, vol. 17, no. 3, pp. 208–214, 2017.

[18] A. Lu, V. G. Magupalli, J. Ruan et al., "Unified polymerization mechanism for the assembly of ASC-dependent inflammasomes," *Cell*, vol. 156, no. 6, pp. 1193–1206, 2014.

[19] F. Martinon, V. Petrilli, A. Mayor, A. Tardivel, and J. Tschopp, "Gout-associated uric acid crystals activate the NALP3 inflammasome," *Nature*, vol. 440, no. 7081, pp. 237–241, 2006.

[20] V. Hornung, F. Bauernfeind, A. Halle et al., "Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization," *Nature Immunology*, vol. 9, no. 8, pp. 847–856, 2008.

[21] Z. Zhong, S. Liang, E. Sanchez-Lopez et al., "New mitochondrial DNA synthesis enables NLRP3 inflammasome activation," *Nature*, vol. 560, no. 7717, pp. 198–203, 2018.

[22] N. Subramanian, K. Natarajan, M. R. Clatworthy, Z. Wang, and R. N. Germain, "The adaptor MAVS promotes NLRP3 mitochondrial localization and inflammasome activation," *Cell*, vol. 153, no. 2, pp. 348–361, 2013.

[23] R. Allam, K. E. Lawlor, E. C. W. Yu et al., "Mitochondrial apoptosis is dispensable for NLRP3 inflammasome activation but non-apoptotic caspase-8 is required for inflammasome priming," *EMBO Reports*, vol. 15, no. 9, pp. 982–990, 2014.

[24] E. I. Elliott and F. S. Sutterwala, "Initiation and perpetuation of NLRP3 inflammasome activation and assembly," *Immunological Reviews*, vol. 265, no. 1, pp. 35–52, 2015.

[25] H. Yaribeygi, M. T. Mohammadi, R. Rezaee, and A. Sahebkar, "Fenofibrate improves renal function by amelioration of NOX-4, IL-18, and p53 expression in an experimental model of diabetic nephropathy," *Journal of Cellular Biochemistry*, vol. 119, no. 9, pp. 7458–7469, 2018.

[26] H. Wen, J. P. Y. Ting, and L. A. J. O'Neill, "A role for the NLRP3 inflammasome in metabolic diseases—did Warburg miss inflammation?," *Nature Immunology*, vol. 13, no. 4, pp. 352–357, 2012.

[27] H. Zhang, X. Gong, S. Ni, Y. Wang, L. Zhu, and N. Ji, "C1q/TNF-related protein-9 attenuates atherosclerosis through AMPK-NLRP3 inflammasome singling pathway," *International Immunopharmacology*, vol. 77, 2019.

[28] B. A. Ference, H. N. Ginsberg, I. Graham et al., "Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel," *European Heart Journal*, vol. 38, no. 32, pp. 2459–2472, 2017.

[29] Z. Hoseini, F. Sepahvand, B. Rashidi, A. Sahebkar, A. Masoudifar, and H. Mirzaei, "NLRP3 inflammasome: its regulation and involvement in atherosclerosis," *Journal of Cellular Physiology*, vol. 233, no. 3, pp. 2116–2132, 2018.

[30] H. Y. Kim, H. J. Lee, Y. J. Chang et al., "Interleukin-17-producing innate lymphoid cells and the NLRP3 inflammasome facilitate obesity-associated airway hyperreactivity," *Nature Medicine*, vol. 20, no. 1, pp. 54–61, 2014.

[31] C. Ising, C. Venegas, S. Zhang et al., "NLRP3 inflammasome activation drives tau pathology," *Nature*, vol. 575, no. 7784, pp. 669–673, 2019.

[32] S. Wang, Y. H. Yuan, N. H. Chen, and H. B. Wang, "The mechanisms of NLRP3 inflammasome/pyroptosis activation and their role in Parkinson's disease," *International Immunopharmacology*, vol. 67, pp. 458–464, 2019.

[33] E. Tourkochristou, I. Aggeletopoulou, C. Konstantakis, and C. Triantos, "Role of NLRP3 inflammasome in inflammatory bowel diseases," *World Journal of Gastroenterology*, vol. 25, no. 33, pp. 4796–4804, 2019.

[34] L. Liu, Y. Dong, M. Ye et al., "The pathogenic role of NLRP3 inflammasome activation in inflammatory bowel diseases of both mice and humans," *Journal of Crohn's and Colitis*, vol. 11, no. 6, pp. 737–750, 2017.

[35] C. de Torre-Minguela, P. Mesa Del Castillo, and P. Pelegrin, "The NLRP3 and pyrin inflammasomes: implications in the pathophysiology of autoinflammatory diseases," *Frontiers in Immunology*, vol. 8, p. 43, 2017.

[36] X. Yang, G. Zhao, J. Yan et al., "Pannexin 1 channels contribute to IL-1β expression via NLRP3/caspase-1 inflammasome inAspergillus FumigatusKeratitis," *Current Eye Research*, vol. 44, no. 7, pp. 716–725, 2019.

[37] J. Liu and X. Cao, "Cellular and molecular regulation of innate inflammatory responses," *Cellular & Molecular Immunology*, vol. 13, no. 6, pp. 711–721, 2016.

[38] A. Lu and H. Wu, "Structural mechanisms of inflammasome assembly," *FEBS Journal*, vol. 282, no. 3, pp. 435–444, 2015.

[39] R. C. Rai, "Host inflammatory responses to intracellular invaders: review study," *Life Sciences*, vol. 240, p. 117084, 2020.

[40] Y. Zhen and H. Zhang, "NLRP3 inflammasome and inflammatory bowel disease," *Frontiers in Immunology*, vol. 10, p. 276, 2019.

[41] P. Broz and V. M. Dixit, "Inflammasomes: mechanism of assembly, regulation and signalling," *Nature Reviews Immunology*, vol. 16, no. 7, pp. 407–420, 2016.

[42] L. Franchi, R. Munoz-Planillo, and G. Nunez, "Sensing and reacting to microbes through the inflammasomes," *Nature Immunology*, vol. 13, no. 4, pp. 325–332, 2012.

[43] E. Latz and P. Duewell, "NLRP3 inflammasome activation in inflammaging," *Seminars in Immunology*, vol. 40, pp. 61–73, 2018.

[44] B. Z. Shao, S. L. Wang, P. Pan et al., "Targeting NLRP3 inflammasome in inflammatory bowel disease: putting out the fire of inflammation," *Inflammation*, vol. 42, no. 4, pp. 1147–1159, 2019.

[45] K. V. Swanson, M. Deng, and J. P. Y. Ting, "The NLRP3 inflammasome: molecular activation and regulation to therapeutics," *Nature Reviews Immunology*, vol. 19, no. 8, pp. 477–489, 2019.

[46] F. Martinon, L. Agostini, E. Meylan, and J. Tschopp, "Identification of bacterial muramyl dipeptide as activator of the NALP3/cryopyrin inflammasome," *Current Biology*, vol. 14, no. 21, pp. 1929–1934, 2004.

[47] T. D. Kanneganti, N. Ozören, M. Body-Malapel et al., "Bacterial RNA and small antiviral compounds activate caspase-1 through cryopyrin/Nalp3," *Nature*, vol. 440, no. 7081, pp. 233–236, 2006.

[48] L. E. Sander, M. J. Davis, M. V. Boekschoten et al., "Detection of prokaryotic mRNA signifies microbial viability and promotes immunity," *Nature*, vol. 474, no. 7351, pp. 385–389, 2011.

[49] Y. Yang, A. V. Bazhin, J. Werner, and S. Karakhanova, "Reactive oxygen species in the immune system," *International Reviews of Immunology*, vol. 32, no. 3, pp. 249–270, 2013.

[50] Y. Liu, X. Bi, Y. Zhang, Y. Wang, and W. Ding, "Mitochondrial dysfunction/NLRP3 inflammasome axis contributes to angiotensin II-induced skeletal muscle wasting via PPAR-γ," *Laboratory Investigation*, 2019.

[51] E. Caballano-Infantes, J. Terron-Bautista, A. Beltrán-Povea et al., "Regulation of mitochondrial function and endoplasmic reticulum stress by nitric oxide in pluripotent stem cells," *World Journal of Stem Cells*, vol. 9, no. 2, pp. 26–36, 2017.

[52] C. Giorgi, S. Marchi, and P. Pinton, "The machineries, regulation and cellular functions of mitochondrial calcium," *Nature Reviews Molecular Cell Biology*, vol. 19, no. 11, pp. 713–730, 2018.

[53] K. Shimada, T. R. Crother, J. Karlin et al., "Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis," *Immunity*, vol. 36, no. 3, pp. 401–414, 2012.

[54] A. Nardin, E. Schrepfer, and E. Ziviani, "Counteracting PINK/parkin deficiency in the activation of mitophagy: a potential therapeutic intervention for Parkinson's disease," *Current Neuropharmacology*, vol. 14, no. 3, pp. 250–259, 2016.

[55] A. L. Bujak, J. D. Crane, J. S. Lally et al., "AMPK activation of muscle autophagy prevents fasting-induced hypoglycemia and myopathy during aging," *Cell Metabolism*, vol. 21, no. 6, pp. 883–890, 2015.

[56] M.-J. Kim, S. H. Bae, J.-C. Ryu et al., "SESN2/sestrin2 suppresses sepsis by inducing mitophagy and inhibiting NLRP3 activation in macrophages," *Autophagy*, vol. 12, no. 8, pp. 1272–1291, 2016.

[57] C. Jin, P. Frayssinet, R. Pelker et al., "NLRP3 inflammasome plays a critical role in the pathogenesis of hydroxyapatite-associated arthropathy," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 36, pp. 14867–14872, 2011.

[58] T. Karasawa and M. Takahashi, "Role of NLRP3 inflammasomes in atherosclerosis," *Journal of Atherosclerosis and Thrombosis*, vol. 24, no. 5, pp. 443–451, 2017.

[59] S. Li, H. Wu, D. Han et al., "A novel mechanism of mesenchymal stromal cell-mediated protection against sepsis: restricting inflammasome activation in macrophages by increasing mitophagy and decreasing mitochondrial ROS," *Oxidative Medicine and Cellular Longevity*, vol. 2018, Article ID 3537609, 15 pages, 2018.

[60] M. Sendler, C. van den Brandt, J. Glaubitz et al., "NLRP3 Inflammasome Regulates Development of Systemic Inflammatory Response and Compensatory Anti-Inflammatory Response Syndromes in Mice With Acute Pancreatitis," *Gastroenterology*, vol. 158, no. 1, pp. 253–269.e14, 2020.

[61] E. S. Weiss, C. Girard-Guyonvarc'h, D. Holzinger et al., "Interleukin-18 diagnostically distinguishes and pathogenically promotes human and murine macrophage activation syndrome," *Blood*, vol. 131, no. 13, pp. 1442–1455, 2018.

[62] L. Franchi, T. D. Kanneganti, G. R. Dubyak, and G. Nunez, "Differential requirement of P2X7 receptor and intracellular K^+ for caspase-1 activation induced by intracellular and extracellular bacteria," *Journal of Biological Chemistry*, vol. 282, no. 26, pp. 18810–18818, 2007.

[63] V. Petrilli, S. Papin, C. Dostert, A. Mayor, F. Martinon, and J. Tschopp, "Activation of the NALP3 inflammasome is triggered by low intracellular potassium concentration," *Cell Death & Differentiation*, vol. 14, no. 9, pp. 1583–1589, 2007.

[64] G. S. Lee, N. Subramanian, A. I. Kim et al., "The calcium-sensing receptor regulates the NLRP3 inflammasome through Ca^{2+} and cAMP," *Nature*, vol. 492, no. 7427, pp. 123–127, 2012.

[65] M. Rossol, M. Pierer, N. Raulien et al., "Extracellular Ca^{2+} is a danger signal activating the NLRP3 inflammasome through G protein-coupled calcium sensing receptors," *Nature Communications*, vol. 3, no. 1, 2012.

[66] T. Murakami, J. Ockinger, J. Yu et al., "Critical role for calcium mobilization in activation of the NLRP3 inflammasome," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 109, no. 28, pp. 11282–11287, 2012.

[67] L. Minutoli, D. Puzzolo, M. Rinaldi et al., "ROS-mediated NLRP3 inflammasome activation in brain, heart, kidney, and testis ischemia/reperfusion injury," *Oxidative Medicine and Cellular Longevity*, vol. 2016, Article ID 2183026, 10 pages, 2016.

[68] Y. Wang, Y. Wu, J. Chen, S. Zhao, and H. Li, "Pirfenidone attenuates cardiac fibrosis in a mouse model of TAC-induced left ventricular remodeling by suppressing NLRP3 inflammasome formation," *Cardiology*, vol. 126, no. 1, pp. 1–11, 2013.

[69] S. Alfonso-Loeches, J. R. Urena-Peralta, M. J. Morillo-Bargues, J. Oliver-De La Cruz, and C. Guerri, "Role of mitochondria ROS generation in ethanol-induced NLRP3 inflammasome activation and cell death in astroglial cells," *Frontiers in Cellular Neuroscience*, vol. 8, p. 8, 2014.

[70] Y. H. Youm, K. Y. Nguyen, R. W. Grant et al., "The ketone metabolite β-hydroxybutyrate blocks NLRP3

inflammasome-mediated inflammatory disease," *Nature Medicine*, vol. 21, no. 3, pp. 263–269, 2015.

[71] X. Yu, P. Lan, X. Hou et al., "HBV inhibits LPS-induced NLRP3 inflammasome activation and IL-1β production via suppressing the NF-κB pathway and ROS production," *Journal of Hepatology*, vol. 66, no. 4, pp. 693–702, 2017.

[72] X. Wang, W. Jiang, Y. Yan et al., "RNA viruses promote activation of the NLRP3 inflammasome through a RIP1-RIP3-DRP1 signaling pathway," *Nature Immunology*, vol. 15, no. 12, pp. 1126–1133, 2014.

[73] C. Dostert, V. Pétrilli, R. Van Bruggen, C. Steele, B. T. Mossman, and J. Tschopp, "Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica," *Science*, vol. 320, no. 5876, pp. 674–677, 2008.

[74] R. van Bruggen, M. Y. Köker, M. Jansen et al., "Human NLRP3 inflammasome activation is Nox1-4 independent," *Blood*, vol. 115, no. 26, pp. 5398–5400, 2010.

[75] M. Y. Wu and J. H. Lu, "Autophagy and macrophage functions: inflammatory response and phagocytosis," *Cells*, vol. 9, no. 1, p. 70, 2020.

[76] G. Wang, Y. Xue, Y. Wang et al., "The role of autophagy in the pathogenesis of exposure keratitis," *Journal of Cellular and Molecular Medicine*, vol. 23, no. 6, pp. 4217–4228, 2019.

[77] T. P. O'Brien, "Management of bacterial keratitis: beyond exorcism towards consideration of organism and host factors," *Eye*, vol. 17, no. 8, pp. 957–974, 2003.

[78] A. M. Yakoub and D. Shukla, "Autophagy stimulation abrogates herpes simplex virus-1 infection," *Scientific Reports*, vol. 5, no. 1, 2015.

[79] Y. Jiang, X. Yin, P. M. Stuart, and D. A. Leib, "Dendritic cell autophagy contributes to herpes simplex virus-driven stromal keratitis and immunopathology," *mBio*, vol. 6, no. 6, 2015.

[80] F. Gimenez, S. Bhela, P. Dogra et al., "The inflammasome NLRP3 plays a protective role against a viral immunopathological lesion," *Journal of Leukocyte Biology*, vol. 99, no. 5, pp. 647–657, 2016.

[81] M. Bruchard, C. Rebe, V. Derangere et al., "The receptor NLRP3 is a transcriptional regulator of T_H2 differentiation," *Nature Immunology*, vol. 16, no. 8, pp. 859–870, 2015.

[82] Y. Liao, H. Zhang, D. He et al., "Retinal pigment epithelium cell death is associated with NLRP3 inflammasome activation by All-transRetinal," *Investigative Opthalmology & Visual Science*, vol. 60, no. 8, pp. 3034–3045, 2019.

[83] M. T. Heneka, M. P. Kummer, A. Stutz et al., "NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice," *Nature*, vol. 493, no. 7434, pp. 674–678, 2013.

[84] F. Zheng, S. Xing, Z. Gong, and Q. Xing, "NLRP3 inflammasomes show high expression in aorta of patients with atherosclerosis," *Heart, Lung and Circulation*, vol. 22, no. 9, pp. 746–750, 2013.

[85] C. Yao, T. Veleva, L. Scott Jr. et al., "Enhanced cardiomyocyte NLRP3 inflammasome signaling promotes atrial fibrillation," *Circulation*, vol. 138, no. 20, pp. 2227–2242, 2018.

[86] Y. Sun, W. Liu, H. Zhang et al., "Curcumin prevents osteoarthritis by inhibiting the activation of inflammasome NLRP3," *Journal of Interferon & Cytokine Research*, vol. 37, no. 10, pp. 449–455, 2017.

[87] M. Moossavi, N. Parsamanesh, A. Bahrami, S. L. Atkin, and A. Sahebkar, "Role of the NLRP3 inflammasome in cancer," *Molecular Cancer*, vol. 17, no. 1, p. 158, 2018.

[88] X. Qu, H. Gao, L. Tao et al., "Autophagy inhibition-enhanced assembly of the NLRP3 inflammasome is associated with cisplatin-induced acute injury to the liver and kidneys in rats," *Journal of Biochemical and Molecular Toxicology*, vol. 33, no. 1, p. e22208, 2019.

[89] K. Nakahira, J. A. Haspel, V. A. K. Rathinam et al., "Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome," *Nature Immunology*, vol. 12, no. 3, pp. 222–230, 2011.

[90] A. Salminen, K. Kaarniranta, and A. Kauppinen, "Inflammaging: disturbed interplay between autophagy and inflammasomes," *Aging*, vol. 4, no. 3, pp. 166–175, 2012.

[91] J. Harris, N. Deen, S. Zamani, and M. A. Hasnat, "Mitophagy and the release of inflammatory cytokines," *Mitochondrion*, vol. 41, pp. 2–8, 2018.

[92] Z. Zhong, A. Umemura, E. Sanchez-Lopez et al., "NF-κB Restricts Inflammasome Activation via Elimination of Damaged Mitochondria," *Cell*, vol. 164, no. 5, pp. 896–910, 2016.

[93] Y. P. Chang, S. M. Ka, W. H. Hsu et al., "Resveratrol inhibits NLRP3 inflammasome activation by preserving mitochondrial integrity and augmenting autophagy," *Journal of Cellular Physiology*, vol. 230, no. 7, pp. 1567–1579, 2015.

[94] C. S. Shi, K. Shenderov, N. N. Huang et al., "Activation of autophagy by inflammatory signals limits IL-1β production by targeting ubiquitinated inflammasomes for destruction," *Nature Immunology*, vol. 13, no. 3, pp. 255–263, 2012.

[95] X. Wang, L. Jiang, L. Shi et al., "Zearalenone induces NLRP3-dependent pyroptosis via activation of NF-κB modulated by autophagy in INS-1 cells," *Toxicology*, vol. 428, p. 152304, 2019.

[96] M. E. Ahmed, S. Iyer, R. Thangavel et al., "Co-localization of glia maturation factor with NLRP3 inflammasome and autophagosome markers in human Alzheimer's disease brain," *Journal of Alzheimer's Disease*, vol. 60, no. 3, pp. 1143–1160, 2017.

[97] F. Marin-Aguilar, B. Castejon-Vega, E. Alcocer-Gomez et al., "NLRP3 inflammasome inhibition by MCC950 in aged mice improves health via enhanced autophagy and PPARα activity," *The Journals of Gerontology: Series A*, 2019.

[98] O. Sandanger, T. Ranheim, L. E. Vinge et al., "The NLRP3 inflammasome is up-regulated in cardiac fibroblasts and mediates myocardial ischaemia-reperfusion injury," *Cardiovascular Research*, vol. 99, no. 1, pp. 164–174, 2013.

[99] G. P. J. van Hout, L. Bosch, G. H. J. M. Ellenbroek et al., "The selective NLRP3-inflammasome inhibitor MCC950 reduces infarct size and preserves cardiac function in a pig model of myocardial infarction," *European Heart Journal*, vol. 38, no. 11, pp. ehw247–ehw836, 2017.

[100] J. Zhao, H. Wang, Y. Huang et al., "Lupus nephritis: glycogen synthase kinase 3β promotion of renal damage through activation of the NLRP3 inflammasome in lupus-prone mice," *Arthritis & Rheumatology*, vol. 67, no. 4, pp. 1036–1044, 2015.

[101] S. M. Ka, J. C. Lin, T. J. Lin et al., "Citral alleviates an accelerated and severe lupus nephritis model by inhibiting the activation signal of NLRP3 inflammasome and enhancing Nrf2 activation," *Arthritis Research & Therapy*, vol. 17, no. 1, 2015.

[102] A. C. Villani, M. Lemire, G. Fortin et al., "Common variants in the *NLRP3* region contribute to Crohn's disease susceptibility," *Nature Genetics*, vol. 41, no. 1, pp. 71–76, 2009.

[103] G. J. Lewis, D. C. O. Massey, H. Zhang et al., "Genetic association between NLRP3 variants and Crohn's disease does not replicate in a large UK panel," *Inflammatory Bowel Diseases*, vol. 17, no. 6, pp. 1387–1391, 2011.

[104] L. Mao, A. Kitani, M. Similuk et al., "Loss-of-function CARD8 mutation causes NLRP3 inflammasome activation and Crohn's disease," *Journal of Clinical Investigation*, vol. 128, no. 5, pp. 1793–1806, 2018.

[105] R. Munoz-Planillo, L. Franchi, L. S. Miller, and G. Nunez, "A critical role for hemolysins and bacterial lipoproteins in Staphylococcus aureus-induced activation of the Nlrp3 inflammasome," *The Journal of Immunology*, vol. 183, no. 6, pp. 3942–3948, 2009.

[106] C. Toma, N. Higa, Y. Koizumi et al., "Pathogenic Vibrio activate NLRP3 inflammasome via cytotoxins and TLR/nucleotide-binding oligomerization domain-mediated NF-κB signaling," *Journal of Immunology*, vol. 184, no. 9, pp. 5287–5297, 2010.

[107] M. Witzenrath, F. Pache, D. Lorenz et al., "The NLRP3 inflammasome is differentially activated by pneumolysin variants and contributes to host defense in pneumococcal pneumonia," *Journal of Immunology*, vol. 187, no. 1, pp. 434–440, 2011.

[108] I. C. Allen, M. A. Scull, C. B. Moore et al., "The NLRP3 inflammasome mediates in vivo innate immunity to influenza A virus through recognition of viral RNA," *Immunity*, vol. 30, no. 4, pp. 556–565, 2009.

[109] S. L. Cassel, S. Joly, and F. S. Sutterwala, "The NLRP3 inflammasome: a sensor of immune danger signals," *Seminars in Immunology*, vol. 21, no. 4, pp. 194–198, 2009.

[110] H. Li, S. Wu, L. Mao et al., "Human pathogenic fungus Trichophyton schoenleinii activates the NLRP3 inflammasome," *Protein & Cell*, vol. 4, no. 7, pp. 529–538, 2013.

[111] S. Joly and F. S. Sutterwala, "Fungal pathogen recognition by the NLRP3 inflammasome," *Virulence*, vol. 1, no. 4, pp. 276–280, 2010.

[112] P. Lee, D. J. Lee, C. Chan, S. W. Chen, I. Ch'en, and C. Jamora, "Dynamic expression of epidermal caspase 8 simulates a wound healing response," *Nature*, vol. 458, no. 7237, pp. 519–523, 2009.

[113] E. J. Robertson, J. M. Wolf, and A. Casadevall, "EDTA inhibits biofilm formation, extracellular vesicular secretion, and shedding of the capsular polysaccharide glucuronoxylomannan by Cryptococcus neoformans," *Applied and Environmental Microbiology*, vol. 78, no. 22, pp. 7977–7984, 2012.

[114] N. C. Silva, J. M. Nery, and A. L. T. Dias, "Aspartic proteinases of Candida spp.: role in pathogenicity and antifungal resistance," *Mycoses*, vol. 57, no. 1, pp. 1–11, 2014.

[115] L. A. Braga-Silva and A. L. S. Santos, "Aspartic protease inhibitors as potential anti-Candida albicans drugs: impacts on fungal biology, virulence and pathogenesis," *Current Medicinal Chemistry*, vol. 18, no. 16, pp. 2401–2419, 2011.

[116] K. Nakamura, A. Miyazato, G. Xiao et al., "Deoxynucleic acids from Cryptococcus neoformans activate myeloid dendritic cells via a TLR9-dependent pathway," *Journal of Immunology*, vol. 180, no. 6, pp. 4067–4074, 2008.

[117] L. Perrone, T. S. Devi, K. I. Hosoya, T. Terasaki, and L. P. Singh, "Thioredoxin interacting protein (TXNIP) induces inflammation through chromatin modification in retinal capillary endothelial cells under diabetic conditions," *Journal of Cellular Physiology*, vol. 221, no. 1, pp. 262–272, 2009.

[118] W. Chi, F. Li, H. Chen et al., "Caspase-8 promotes NLRP1/NLRP3 inflammasome activation and IL-1β production in acute glaucoma," *Proceedings of the National Academy of Sciences*, vol. 111, no. 30, pp. 11181–11186, 2014.

[119] W. A. Tseng, T. Thein, K. Kinnunen et al., "NLRP3 inflammasome activation in retinal pigment epithelial cells by lysosomal destabilization: implications for age-related macular degeneration," *Investigative Opthalmology & Visual Science*, vol. 54, no. 1, pp. 110–120, 2013.

[120] Q. Zheng, Y. Ren, P. S. Reinach et al., "Reactive oxygen species activated NLRP3 inflammasomes initiate inflammation in hyperosmolarity stressed human corneal epithelial cells and environment- induced dry eye patients," *Experimental Eye Research*, vol. 134, pp. 133–140, 2015.

[121] A. Thakur, R. P. Barrett, J. A. Hobden, and L. D. Hazlett, "Caspase-1 inhibitor reduces severity of Pseudomonas aeruginosa Keratitis in mice," *Investigative Opthalmology & Visual Science*, vol. 45, no. 9, pp. 3177–3184, 2004.

[122] N. Cole, E. B. H. Hume, S. Khan, L. Garthwaite, T. C. R. Conibear, and M. D. P. Willcox, "The role of CXC chemokine receptor 2 in Staphylococcus aureus keratitis," *Experimental Eye Research*, vol. 127, pp. 184–189, 2014.

[123] C. Fabiani, J. Sota, G. M. Tosi et al., "The emerging role of interleukin (IL)-1 in the pathogenesis and treatment of inflammatory and degenerative eye diseases," *Clinical Rheumatology*, vol. 36, no. 10, pp. 2307–2318, 2017.

[124] R. C. Coll, A. A. B. Robertson, J. J. Chae et al., "A small-molecule inhibitor of the NLRP3 inflammasome for the treatment of inflammatory diseases," *Nature Medicine*, vol. 21, no. 3, pp. 248–255, 2015.

[125] R. C. Coll, J. R. Hill, C. J. Day et al., "MCC950 directly targets the NLRP3 ATP-hydrolysis motif for inflammasome inhibition," *Nature Chemical Biology*, vol. 15, no. 6, pp. 556–559, 2019.

[126] Y. He, S. Varadarajan, R. Munoz-Planillo, A. Burberry, Y. Nakamura, and G. Nunez, "3,4-Methylenedioxy-β-nitrostyrene inhibits NLRP3 inflammasome activation by blocking assembly of the inflammasome," *Journal of Biological Chemistry*, vol. 289, no. 2, pp. 1142–1150, 2014.

[127] Y. Huang, H. Jiang, Y. Chen et al., "Tranilast directly targets NLRP3 to treat inflammasome-driven diseases," *EMBO Molecular Medicine*, vol. 10, no. 4, 2018.

[128] C. Marchetti, B. Swartzwelter, F. Gamboni et al., "OLT1177, a β-sulfonyl nitrile compound, safe in humans, inhibits the NLRP3 inflammasome and reverses the metabolic cost of inflammation," *Proceedings of the National Academy of Sciences*, vol. 115, no. 7, pp. E1530–E1539, 2018.

[129] M. Lamkanfi, J. L. Mueller, A. C. Vitari et al., "Glyburide inhibits the Cryopyrin/Nalp3 inflammasome," *The Journal of Cell Biology*, vol. 187, no. 1, pp. 61–70, 2009.

[130] R. Kuwar, A. Rolfe, L. Di et al., "A novel small molecular NLRP3 inflammasome inhibitor alleviates neuroinflammatory response following traumatic brain injury," *Journal of Neuroinflammation*, vol. 16, no. 1, p. 81, 2019.

[131] C. Juliana, T. Fernandes-Alnemri, J. Wu et al., "Anti-inflammatory compounds parthenolide and Bay 11-7082 are direct inhibitors of the inflammasome," *Journal of Biological Chemistry*, vol. 285, no. 13, pp. 9792–9802, 2010.

[132] R. Nowarski, R. Jackson, N. Gagliani et al., "Epithelial IL-18 equilibrium controls barrier function in colitis," *Cell*, vol. 163, no. 6, pp. 1444–1456, 2015.

[133] A. Zahid, B. Li, A. J. K. Kombe, T. Jin, and J. Tao, "Pharmacological inhibitors of the NLRP3 inflammasome," *Frontiers in Immunology*, vol. 10, p. 2538, 2019.

[134] Z. Hu and J. Chai, "Structural mechanisms in NLR inflammasome assembly and signaling," *Current Topics in Microbiology and Immunology*, vol. 397, pp. 23–42, 2016.

[135] M. S. J. Mangan, E. J. Olhava, W. R. Roush, H. M. Seidel, G. D. Glick, and E. Latz, "Targeting the NLRP3 inflammasome in inflammatory diseases," *Nature Reviews Drug Discovery*, vol. 17, no. 8, pp. 588–606, 2018.

[136] W. Chi, F. Li, H. Chen et al., "Caspase-8 promotes NLRP1/NLRP3 inflammasome activation and IL-1 production in acute glaucoma," *Proceedings of the National Academy of Sciences*, vol. 111, no. 30, pp. 11181–11186, 2014.

[137] H. Jiang, H. He, Y. Chen et al., "Identification of a selective and direct NLRP3 inhibitor to treat inflammatory disorders," *The Journal of Experimental Medicine*, vol. 214, no. 11, pp. 3219–3238, 2017.

[138] C. Marchetti, S. Toldo, J. Chojnacki et al., "Pharmacologic inhibition of the NLRP3 inflammasome preserves cardiac function after ischemic and nonischemic injury in the mouse," *Journal of Cardiovascular Pharmacology*, vol. 66, no. 1, pp. 1–8, 2015.

[139] J. Fulp, L. He, S. Toldo et al., "Structural insights of benzenesulfonamide analogues as NLRP3 inflammasome inhibitors: design, synthesis, and biological characterization," *Journal of Medicinal Chemistry*, vol. 61, no. 12, pp. 5412–5423, 2017.

[140] J. Yin, F. Zhao, J. E. Chojnacki et al., "NLRP3 inflammasome inhibitor ameliorates amyloid pathology in a mouse model of Alzheimer's disease," *Molecular Neurobiology*, vol. 55, no. 3, pp. 1977–1987, 2018.

[141] A. Saadane, S. Masters, J. DiDonato, J. Li, and M. Berger, "Parthenolide inhibits IκB Kinase, NF-κB activation, and inflammatory response in cystic fibrosis cells and mice," *American Journal of Respiratory Cell and Molecular Biology*, vol. 36, no. 6, pp. 728–736, 2007.

[142] N. Irrera, M. Vaccaro, A. Bitto et al., "BAY 11-7082 inhibits the NF-κB and NLRP3 inflammasome pathways and protects against IMQ-induced psoriasis," *Clinical Science*, vol. 131, no. 6, pp. 487–498, 2017.

[143] S. R. Kolati, E. R. Kasala, L. N. Bodduluru et al., "BAY 11-7082 ameliorates diabetic nephropathy by attenuating hyperglycemia- mediated oxidative stress and renal inflammation via NF-κB pathway," *Environmental Toxicology and Pharmacology*, vol. 39, no. 2, pp. 690–699, 2015.