



## Review Article

# Application of NLRP3 Inflammasome-related Modulators in Sepsis



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## Abstract

Sepsis is a systemic inflammatory response syndrome that is caused by infection. It is one of the most common critical diseases clinically. Although more anti-inflammatory drugs are available, the treatment options for sepsis remain limited. The nucleotide-binding domain-like receptor protein 3 (NLRP3) inflammasome is a multiprotein complex that has been implicated in the development and evolution of sepsis and other autoimmune inflammatory diseases. Although the activation pathway and biological function of NLRP3 in sepsis are becoming clear, the treatment of sepsis by regulating NLRP3 is being explored. This article will review the status of various NLRP3 modulators that might improve the symptoms of sepsis to provide a basis for further research into the treatment of sepsis.

## Introduction

Sepsis is a life-threatening organ dysfunction that is caused by a host-dysregulated response to infection.<sup>1</sup> Although mortality has declined significantly in recent decades, sepsis remains a leading cause of death in most intensive care units, with mortality rates as high as 10–20%.<sup>2,3</sup> In addition, the incidence of sepsis has increased due to the age of the population, the increase of antibiotic-resistant microorganisms, the extended lives of patients with chronic diseases, and the wide use of immunosuppressants and chemotherapy drugs.<sup>4</sup> The inflammatory response to sepsis has two parts: an excessive inflammatory response that causes chronic or systemic inflammatory diseases of the body and a lower response that causes continual infection with pathogens. This sug-

gests that the precise control of inflammatory status is crucial for the pathogenesis and progression of sepsis.<sup>4,5</sup>

Activation of the inflammasome is a critical step in the inflammatory and innate immune responses, and the cytoplasmic receptors of the nucleotide-binding domain-like receptor (NLR) family are the main components of the inflammasome. Among them, NLR protein 3 (NLRP3) inflammasome activation has been studied and plays a crucial regulatory role in sepsis and its induced multiple organ dysfunction, which includes disorders in the cardiovascular,<sup>6</sup> gastrointestinal,<sup>7</sup> renal,<sup>8</sup> respiratory,<sup>9</sup> and central nervous systems.<sup>10</sup> Mechanically, it can sense pathogen-associated molecular patterns and damage-associated molecular patterns, such as mitochondrial DNA (mtDNA) and ATP.<sup>5,11</sup> When detecting pathogen-associated, or damage-associated molecular patterns, NLRP3 recruits an apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and caspase-1, which generates a complex called NLRP3 inflammasome that could further mediate the activation and maturation of caspase-1 and the secretion of various proinflammatory cytokines such as interleukin (IL)-1 $\beta$  and IL-18. In addition, caspase-7 can be activated, which together triggers lytic death of host cells, for example, pyroptosis.<sup>4,5</sup>

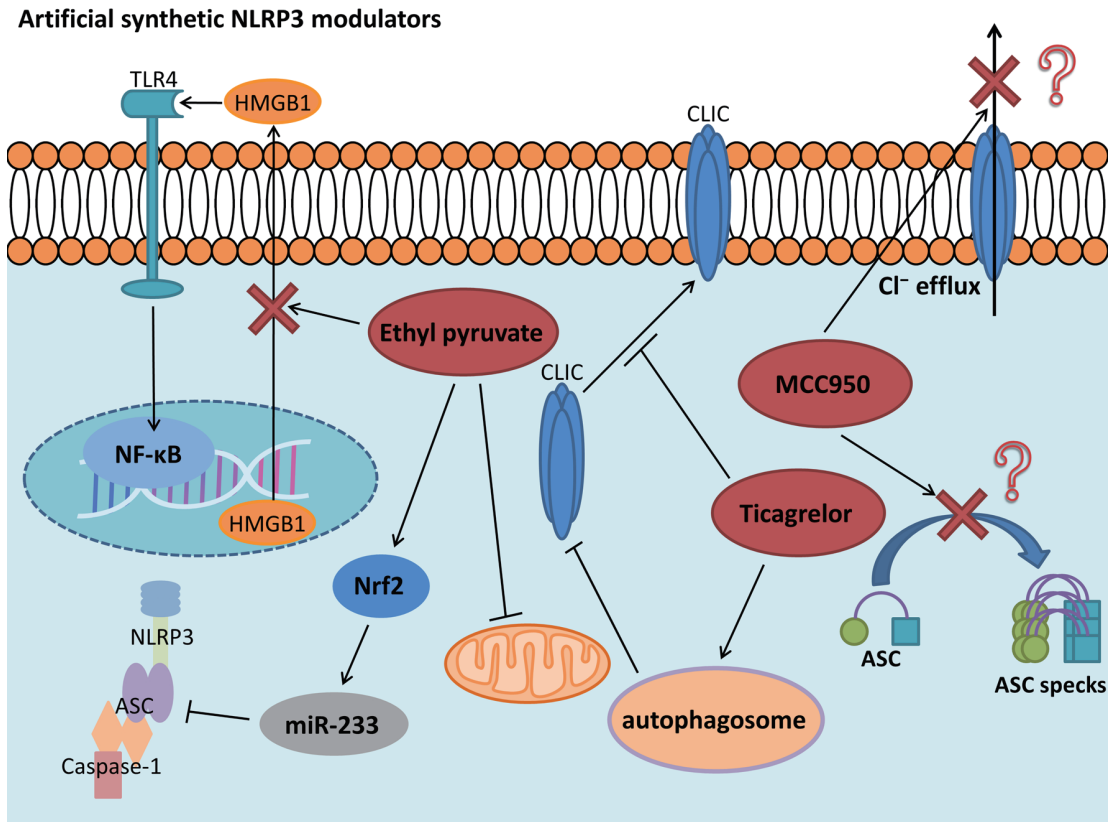
Recently, increasing studies have reported that NLRP3-mediated pyroptosis contributed to the progression of sepsis.<sup>10,12</sup> In addition, the NLRP3 inflammasome was regulated by autophagic proteins to release mtDNA into the cytosol in response to lipopolysaccharide (LPS), which was verified in sepsis mice models.<sup>13</sup> NLRP3 inflammasome is active in all types of inflammation reactions that are caused by sepsis. The abnormal activation of NLRP3 inflammasome is closely related to the onset and progression of

**Keywords:** Sepsis; nucleotide-binding domain-like receptor protein 3 inflammasomes; Modulator.

**Abbreviations:** ACS, acute coronary syndrome; AKI, acute kidney injury; ALI, acute lung injury; Arg, arginine; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; CLICs, chloride intracellular channel proteins; CLP, cecal ligation and puncture; CO, carbon monoxide; CORMs, CO-releasing molecules; EP, ethyl pyruvate; GLA, glaucocalyxin A; H<sub>2</sub>S, hydrogen sulfide; HO-1, heme oxygenase-1; LPS, lipopolysaccharide; MF, Mangiferin; mtDNA, mitochondrial DNA; NLRP3, nucleotide-binding domain-like receptor protein 3; NO, nitric oxide; SO<sub>2</sub>, sulfur dioxide.

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**Fig. 1. Artificial synthetic NLRP3 modulators.** Overall regulatory mechanisms for three artificial synthetic NLRP3 modulators: MCC950, EP, and ticagrelor on the activation of NLRP3 inflammasome. ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; CLICs, chloride intracellular channel proteins; HMGB1, high mobility group protein 1; NF-κB, nuclear factor kappa B; NLRP3, nucleotide-binding domain-like receptor protein 3; Nrf2, nuclear factor E2-related factor; TLR4, toll like receptor 4.

sepsis, which makes it an ideal drug target. Some modulators effectively treat sepsis-related diseases by inhibiting this drug target. In this review, NLRP3 inflammasome-related modulators in applications for sepsis treatment will be introduced.

**Artificially synthetic NLRP3 modulators**

Artificially synthetic modulators have a good target effect on the regulation of NLRP3 in sepsis. Some modulators that have been reported to treat other diseases could be used for sepsis treatment. The overall regulatory mechanisms of three artificially synthetic NLRP3 modulators: MCC950, EP, and ticagrelor on NLRP3 inflammasome are summarized in Figure 1.

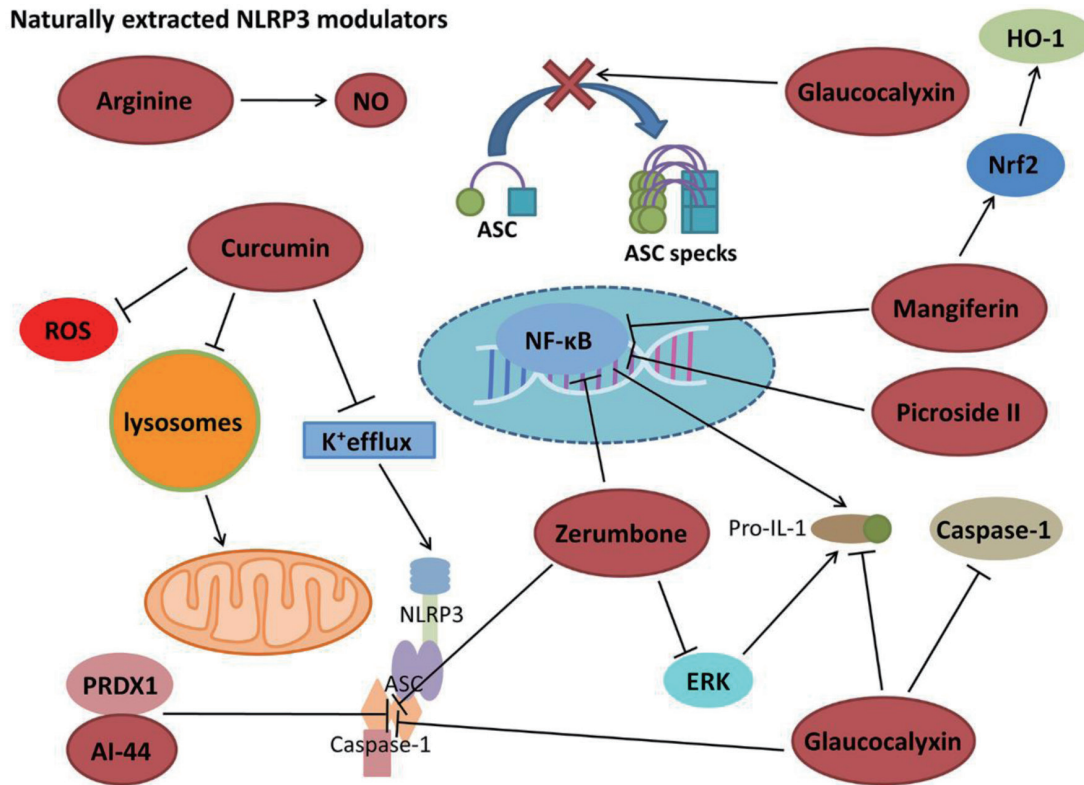
**MCC950**

MCC950 is a compound that contains diarylsulfonylurea, which can specifically inhibit NLRP3 inflammasome activation in canonical and non-canonical manners.<sup>14</sup> MCC950 is closely associated with NLRP3; however, the underlying molecular mechanisms behind this action are unknown. Currently, MCC950 can directly interact with a region of the NLRP3 inflammasome. In addition, it affects the formation of ASC specks by influencing chloride intracellular channel proteins (CLICs).<sup>15,16</sup> Studies have revealed that MCC950 plays a crucial role in several sepsis-related

disorders. Treatment with MCC950 showed dramatically alleviated renal and pulmonary injury and endothelial dysfunctions in the cecal ligation and puncture (CLP) model of sepsis in rats.<sup>17</sup> Moreover, administration of MCC950 could enhance rat survival rate after experimental sepsis by reducing microglial activation and alterations in neurochemistry and behavior.<sup>18</sup> In addition, MCC950 showed protective effects on cardiac function and inhibited apoptosis of cardiomyocytes that were induced by LPS.<sup>19</sup> Of interest, the pharmacological administration of MCC950 reduced sepsis-mediated death in animal models of Parkinson disease.<sup>20</sup> However, although MCC950 has been studied as an NLRP3 inflammasome inhibitor in the regulation of numerous animal models of diseases, its clinical applications are scarce, which should not be ignored.

**Ethyl pyruvate**

Ethyl pyruvate (EP) is a small molecule and an anti-inflammatory food additive.<sup>21</sup> A study found that EP therapy significantly suppressed the activation of NLRP3 inflammasome and IL-1β release into microglia to prevent CLP-induced sepsis-associated encephalopathy in mice, which improved the related cognitive impairment.<sup>22</sup> Another study revealed that the nuclear factor kappa B (NF-κB)/high mobility group protein 1 (HMGB1)/miR-223 axis was the internal mechanism for EP to effectively inhibit NLRP3 inflammasome activation in microglial cells.<sup>23</sup> EP pretreatment



**Fig. 2. Naturally extracted NLRP3 modulators.** Seven naturally extracted modulators that regulate NLRP3 inflammasome activation. ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; ERK, extracellular signal-regulated kinases; HO-1, heme oxygenase-1; NF-κB, nuclear factor kappa B; NLRP3, nucleotide-binding domain-like receptor protein 3; NO, nitric oxide; Nrf2, nuclear factor E2-related factor; PRDX1, peroxiredoxin 1; ROS, reactive oxygen species.

inhibited the activation of NF-κB and prevented the release of HMGB1 from the nucleus. In addition, it could activate the Nrf2 signaling pathway to increase miR-223 levels.<sup>23</sup> Moreover, EP inhibited NLRP3 inflammasome activation by reducing mitochondrial damage, which partially interpreted the mechanism by which it produces anti-inflammatory effects in sepsis.<sup>21</sup> Therefore, EP is an encouraging medication for the elimination of cognitive dysfunction that is induced by sepsis.<sup>22</sup>

**Ticagrelor**

Ticagrelor is a drug used to treat acute coronary syndrome (ACS). Moreover, it reduces mortality from several inflammatory diseases, such as sepsis and infection by hindering the inflammatory activation of NLRP3 in macrophages. Studies have revealed that the underlying mechanism of ticagrelor on NLRP3 activation was independent of the canonical P2Y<sub>12</sub> signaling pathway. Cellular chloride efflux was mediated by chloride intracellular channel proteins (CLICs) through its translocation to the plasma membrane. The administration of ticagrelor induced autophagic effects in LPS-treated macrophages and caused CLIC degradation. In addition, it blocked the migration of CLICs to the plasma membrane. Blockage of chloride efflux to increase cellular chloride ion concentration by ticagrelor might be the internal mechanism by which it suppresses the inflammatory activation of NLRP3.<sup>24</sup> In a Denmark nationwide cohort study, researchers found that compared with clopidogrel, treatment with ticagrelor significantly re-

duced the 1-year risk of sepsis patients.<sup>25</sup> These data suggested that ticagrelor could be a potential therapeutic agent for NLRP3-associated conditions, such as sepsis.

**Naturally extracted NLRP3 modulators**

Natural extraction is a traditional way to discover NLRP3 modulators. Seven naturally extracted modulators that regulate NLRP3 inflammasome activation and could be used in sepsis disorders (Fig. 2) are introduced in the following sections.

**Mangiferin**

Mangiferin (MF) is a xanthone that is found in mango fruits and many other parts of the mango.<sup>26</sup> MF exerted protective effects against sepsis-mediated acute kidney injury (AKI) through inhibition of NLRP3 inflammasome activation and Nrf2 upregulation.<sup>27</sup> In addition, MF protected against sepsis-induced acute lung injury (ALI). MF could hinder the activation of NLRP3 inflammasome via blocking the nuclear translocation of the RelA (P65) and NF-κB1 (P50); therefore, attenuating LPS-induced ALI.<sup>28</sup> Other studies suggested that MF attenuated sepsis-induced ALI by upregulation of heme oxygenase-1 (HO-1), and this effect was possibly achieved via the suppression of NLRP3 inflammasome activation.<sup>29,30</sup> Therefore, an MF-dominant therapeutic strategy could be applied against sepsis.

### Curcumin and curcumin analog

Curcumin has a wide spectrum of biological and pharmacological activities.<sup>31</sup> The administration of curcumin significantly hindered NLRP3-induced secretion of peritoneal IL-1 $\beta$ , alleviated tissue damage, and enhanced the survival rate in the mice models of LPS-induced septic shock. Curcumin showed inhibitory effects on NLRP3 inflammasome activation, and this might be related to the downregulated ERK signaling by hindering potassium (K<sup>+</sup>) efflux, decreased lysosomal disruption, and intracellular reactive oxygen species (ROS) formation.<sup>32</sup> In addition, AI-44, which is a curcumin analog, was studied to be involved in NLRP3 inflammasome inhibition. AI-44 bound to peroxiredoxin 1 and promoted the competitive interaction between peroxiredoxin 1 and ASC with pro-caspase-1, which led to an interrupted assembly of the NLRP3 inflammasome and inhibited caspase-1 activation. This inhibitory effect of AI-44 on NLRP3 inflammasome alleviated LPS-induced endotoxemia in mice. Therefore, AI-44 might be a promising candidate therapeutic compound for applications in sepsis and other NLRP3 inflammasome-driven disease-related treatments.<sup>33</sup>

### Zerumbone

Zerumbone is a natural product, which has a wide range of pharmacological activities and anti-inflammatory effects. A study proved that zerumbone could effectively attenuate the LPS-induced inflammatory response in macrophages, which was shown by the suppression of the activation of the ERK-MAPK and NF- $\kappa$ B signaling pathways and the promotion of pro-inflammatory indicators, such as the IL-1 $\beta$  precursor, from *in vitro* and *ex vivo* experiments. In addition, zerumbone decreased the assembly of ASC and caspase-1; therefore, blocking NLRP3 inflammasome activation. The previous findings showed that zerumbone might exert effects on treatments for sepsis and inflammasome-related diseases.<sup>34,35</sup>

### Piplartine

Piplartine, which is a natural alkaloid, is isolated from *Piper longum* L. Piplartine has anticancer and antibacterial effects. Piplartine could prevent the activation of NF- $\kappa$ B to further hinder the LPS-induced inflammatory response.<sup>36</sup> Administration of piplartine showed reduced mortality of LPS-induced sepsis, which resulted from the piplartine-dominant inhibition of NLRP3, cleaved caspase-1, and pro-IL-1 $\beta$  levels, and repressed IL-1 $\beta$  secretion and decreased the colocalization of caspase-1 and ASC in LPS-activated macrophages.<sup>37</sup> However, studies that investigated the effects of piperine on NLRP3 inflammasome activation are limited, and more research that focuses on the detailed piplartine regulation in sepsis is required.

### Glucocalyxin

Glucocalyxin A (GLA) is a natural substance that is extracted from the herbal medicine *Rabdosia japonica* var. A study suggested that canonical and non-canonical NLRP3 inflammasome activation that was induced by different agonists could be significantly inhibited by GLA. This inhibition was caused by the regulation of ASC oligomerization. However, for upstream signaling of NLRP3 inflammasome activation, GLA did not work. However, the sup-

pression effect of GLA on NLRP3 inflammasome activation alleviated LPS-mediated septic shock and provided a promising drug target for therapeutic strategies in NLRP3-driven diseases.<sup>38</sup>

### Picroside II

Picroside II is an iridoid compound that is isolated from *Picrorhiza* and exhibits a protective effect against CLP-induced sepsis in mice. It alleviates the sepsis-mediated systemic inflammatory response by hindering the activation of NF- $\kappa$ B and NLRP3 inflammasome.<sup>39</sup> The regulation between picroside II and NLRP3 inflammasome has been studied, but the specific target that is involved in the underlying mechanism needs to be explained in future research. Some of the mechanism is based on the reduction of pro-IL-1 $\beta$  and ROS.

### Arginine

Arginine (Arg) is a nonessential amino acid; however, it is regarded as an essential amino acid in sepsis.<sup>40</sup> Studies reported that Arg application improved nitric oxide (NO) production and reduced the expression of proteins associated with NLRP3 inflammasomes, which led to diminished AKI that was induced by sepsis. Since Arg and L-N<sup>6</sup>-(1-iminoethyl)-lysine hydrochloride alleviated kidney injury after CLP, NO-mediated suppression of NLRP3 inflammasome might be why Arg alleviates septic AKI.<sup>41</sup>

### Autosecreted NLRP3 modulators

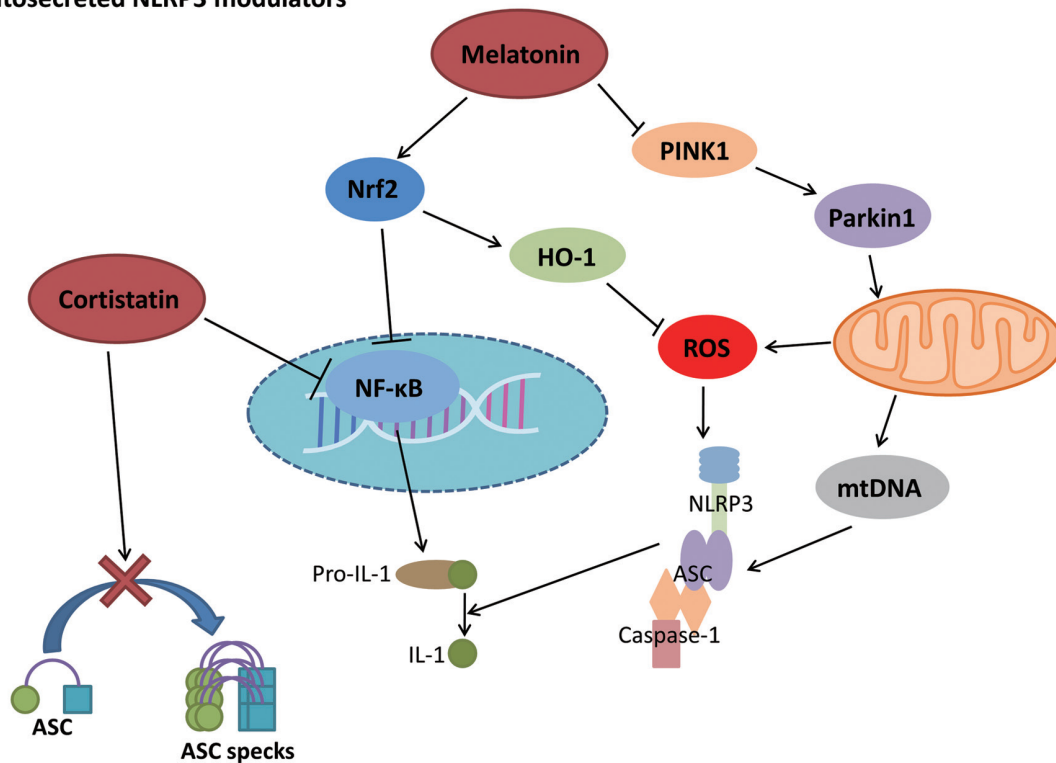
Some hormones that are secreted by the body can act as modulators of NLRP3 activation. [Figure 3](#) shows two autosecreted modulators: melatonin and cortistatin, which have important roles in the regulation of NLRP3 inflammasome.

### Melatonin

Melatonin, an autosecreted hormone, reduces the activity of NLRP3 inflammasomes by a variety of intracellular signaling pathways. The main inhibitory effect of melatonin on NLRP3 inflammatory activation was the prevention of the initiation of NLRP3 inflammatory activation by inhibiting the TLR4/NF- $\kappa$ B signaling pathway and inhibiting NF- $\kappa$ B migration.<sup>42</sup> In addition, melatonin changed the LPS-induced increase in mitochondrial ROS and membrane potential, reduced the release of ROS and oxidative mitochondrial DNA, and indirectly impeded the activation of NLRP3 inflammasome.<sup>43-45</sup> Furthermore, studies indicated that some of the therapeutic effects of melatonin might be through the activation of the Nrf2/HO-1 signaling pathway, the improvement in the Nrf2 signaling pathway, and the decrease in NLRP3 inflammasomes and mitochondrial destruction during sepsis, which significantly reduced septic myocardial injury.<sup>46</sup> In addition, melatonin suppressed NLRP3 expression by inhibiting the PINK1/Parkin1 signaling pathway, and alleviated the activation of inflammatory bodies in sepsis; therefore, preventing kidney damage caused by sepsis.<sup>47</sup> Recent research reported that melatonin protected against sepsis in COVID-19 patients.<sup>48</sup> Clinical trials for septic patient treatment that used melatonin showed a dramatic reduction in patient mortality and hospital stays.<sup>49</sup> Therefore, melatonin application could be a promising therapeutic strategy for sepsis and NLRP3-related disorders.



## Autosecreted NLRP3 modulators



**Fig. 3. Autosecreted NLRP3 modulators.** Two autosecreted modulators: melatonin and cortistatin, have important roles in the regulation of NLRP3 inflammasome. ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; mtDNA, mitochondrial DNA; NF-κB, nuclear factor kappa B; NLRP3, nucleotide-binding domain-like receptor protein 3; Nrf2, nuclear factor E2-related factor; PINK1, protein tyrosine phosphatase induced putative kinase 1; ROS, reactive oxygen species.

### Cortistatin

Cortistatin is a cyclic neuropeptide that has therapeutic effects on septic shock.<sup>50</sup> Preconditioning with cortistatin inhibited NLRP3-intervened ASC pyroptosome formation, caspase-1 activation, and IL- $\beta$  secretion in cardiac fibroblasts after CLP modeling. In addition, cortistatin inhibited the NF- $\kappa$ B signaling pathway and reduced the production of pro-IL-1 $\beta$ . As a novel immune regulator, cortistatin could deactivate the NLRP3 inflammasome activity, and therefore, prevent myocardial injury caused by sepsis. This study gave important implications for designing new strategies for sepsis control.<sup>51</sup>

### Gaseous NLRP3 modulators

Gas is an integral part of the modulators. Many gases exert important effects on the inflammatory response. Figure 4 shows the regulatory mechanisms of several gases in sepsis-induced NLRP3 activation.

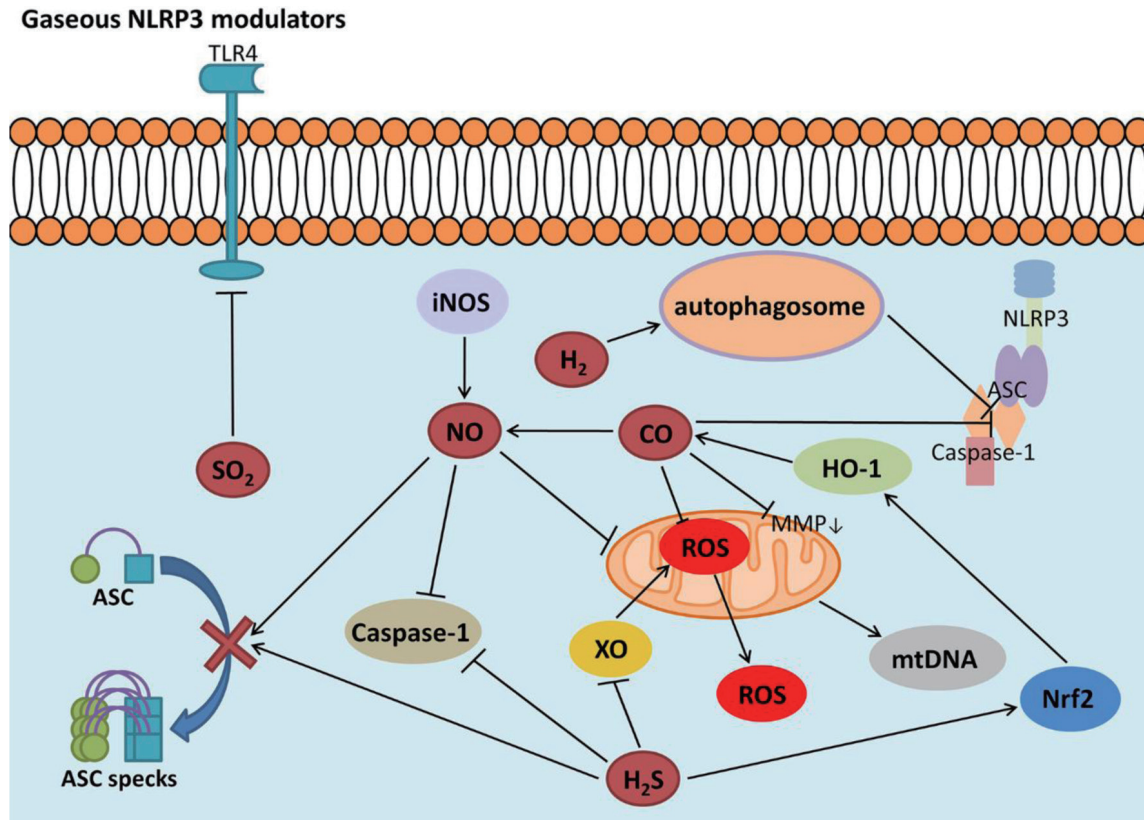
The gas transmitter carbon monoxide (CO) is produced by the stress-responsive enzyme HO-1.<sup>52</sup> A study demonstrated that CO was a negative regulator of NLRP3 inflammasome activation and decreased the release of IL-1 $\beta$  and IL-18 *in vitro* and *in vivo*. CO could inhibit the generation of mitochondrial ROS in response to LPS in macrophages, prevent LPS-induced decrease in the mitochondrial membrane potential and release mtDNA into the cytosol.<sup>53</sup> In addition, CO-releasing molecules (CORMs) have been

widely studied for their anti-inflammatory effects.<sup>54</sup> Treatment with CORM-2 reduced NLRP3 inflammasome activation to protect against sepsis-caused AKI. A study suggested that CO reduced ROS levels, which might be the internal mechanism that inhibits NLRP3 inflammasome activation in sepsis-related AKI. This influence was reflected in increasing NO levels.<sup>55</sup> CORM-3, another CO-releasing molecule, suppressed NLRP3 inflammasome activation by preventing NLRP3 interactions with ASC, which weakened myocardial dysfunction in septic mice.<sup>56</sup> CORMs could be a treatment for sepsis-induced diseases.

Hydrogen (H<sub>2</sub>) exhibited protective effects on organ functions in sepsis and enhanced the survival rate of septic patients. H<sub>2</sub> could decrease the sepsis-induced inflammation and mitochondrial dysfunction through autophagy-mediated inhibition of NLRP3 inflammasome activation.<sup>57</sup> A H<sub>2</sub>-rich solution (i.e., hydrogen-saturated saline) could reduce septic AKI and ALI by inhalation of an aerogel or intrabdominal injection.<sup>58,59</sup>

Hydrogen sulfide (H<sub>2</sub>S) is a metabolite of sulfur-containing amino acids in cells.<sup>60</sup> H<sub>2</sub>S could inhibit NLRP3 inflammasome by reducing xanthine oxidase activity, mitochondrial ROS production, ASC oligomerization, and caspase-1 activity. Meanwhile, H<sub>2</sub>S could activate the Nrf2 signaling pathway, which upregulated HO-1 expression.<sup>61</sup> GYY4137 is a novel and stable H<sub>2</sub>S *in vivo* and *in vitro*. It could inhibit NLRP3 inflammasome and reduce ALI that was caused by sepsis.<sup>62</sup>

NO and sulfur dioxide (SO<sub>2</sub>) have effects on NLRP3 inflammasome. NO inhibited NLRP3 activation through a variety of pathways. It affected ASC pyroptosome formation and caspase-1 activation and reduced ROS and mtDNA that was released by



**Fig. 4. Gaseous NLRP3 modulators.** The regulatory mechanisms of various gases in sepsis-induced NLRP3 activation. ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; CO, carbon monoxide; H<sub>2</sub>, hydrogen; H<sub>2</sub>S, hydrogen sulfide; HO-1, heme oxygenase-1; iNOS, inducible nitric oxide synthase; mtDNA, mitochondrial DNA; NLRP3, nucleotide-binding domain-like receptor protein 3; NO, nitric oxide; Nrf2, nuclear factor E2-related factor; ROS, reactive oxygen species; SO<sub>2</sub>, sulfur dioxide; TLR4, toll like receptor 4; XO, xanthine oxidase.

mitochondria. They protected against sepsis shock by inhibiting the upstream regulatory pathway of NLRP3 and the assembly of NLRP3 inflammasome. Moreover, studies indicated that SO<sub>2</sub> could suppress sepsis-induced myocardial injury by inhibiting the TLR4/NLRP3 inflammasome pathway directly. Both gas molecules have potential applications in sepsis treatment.<sup>63,64</sup>

**Future directions**

Recently, several new NLRP3 inflammasome regulatory pathways have been discovered, which provided ideas for the design or discovery of new therapeutics. There is a long way to go in the treatment of sepsis with NLRP3 inflammasomes. Suitable drugs need to be identified, and relevant strategies need to be developed to optimize their pharmacokinetics, improve their therapeutic potential, and deliver them for clinical applications as soon as possible, which could provide a new method for the treatment of sepsis.

**Conclusions**

As a common critical disease in clinical practice, sepsis harms all organs and tissues in the body; however, there is not a complete system for its treatment in clinical practice. Recently, with the discovery and continuous research into the inflammasome, the treat-

ment of sepsis by the NLRP3 inflammasome regulatory pathway has been gradually recognized. In addition, various modulators for the NLRP3 inflammasome have emerged. NLRP3 modulators used in sepsis applications have been classified. All the modulators have at least been studied at the laboratory level and have demonstrated positive therapeutic effects in animal models. However, most of them have not progressed from the bench to bedside, or into widespread applications. In addition, for some modulators, especially the gas molecules, it is hard to achieve the correct dose, which adds difficulty for clinical applications.

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**Conflict of interest**

The authors have no conflicts of interest related to this publication.

### Author contributions

JX proposed the review aim. MY, CD, and SL collected and organized literature and data. MY drafted the manuscript. CD and SL advised on the structure and content of the manuscript. JX revised the manuscript. All authors have read and approved the manuscript.

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