

# Non-Coding RNAs: Master Regulators of Inflammasomes in Inflammatory Diseases

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**Abstract:** Emerging data indicates that non-coding RNAs (ncRNAs) represent more than just “junk sequences” of the genome and have been found to be involved in multiple diseases by regulating various biological process, including the activation of inflammasomes. As an important aspect of innate immunity, inflammasomes are large immune multiprotein complexes that tightly regulate the production of pro-inflammatory cytokines and mediate pyroptosis; the activation of the inflammasomes is a vital biological process in inflammatory diseases. Recent studies have emphasized the function of ncRNAs in the fine control of inflammasomes activation either by directly targeting components of the inflammasomes or by controlling the activity of various factors that control the activation of inflammasomes; consequently, ncRNAs may represent potential therapeutic targets for inflammatory diseases. Understanding the precise role of ncRNAs in controlling the activation of inflammasomes will help us to design targeted therapies for multiple inflammatory diseases. In this review, we summarize the regulatory role and therapeutic potential of ncRNAs in the activation of inflammasomes by focusing on a range of inflammatory diseases, including microbial infection, sterile inflammatory diseases, and fibrosis-related diseases. Our goal is to provide new ideas and perspectives for future research.

**Keywords:** ncRNAs, inflammasomes, infection, immune, inflammation, fibrosis

## Introduction

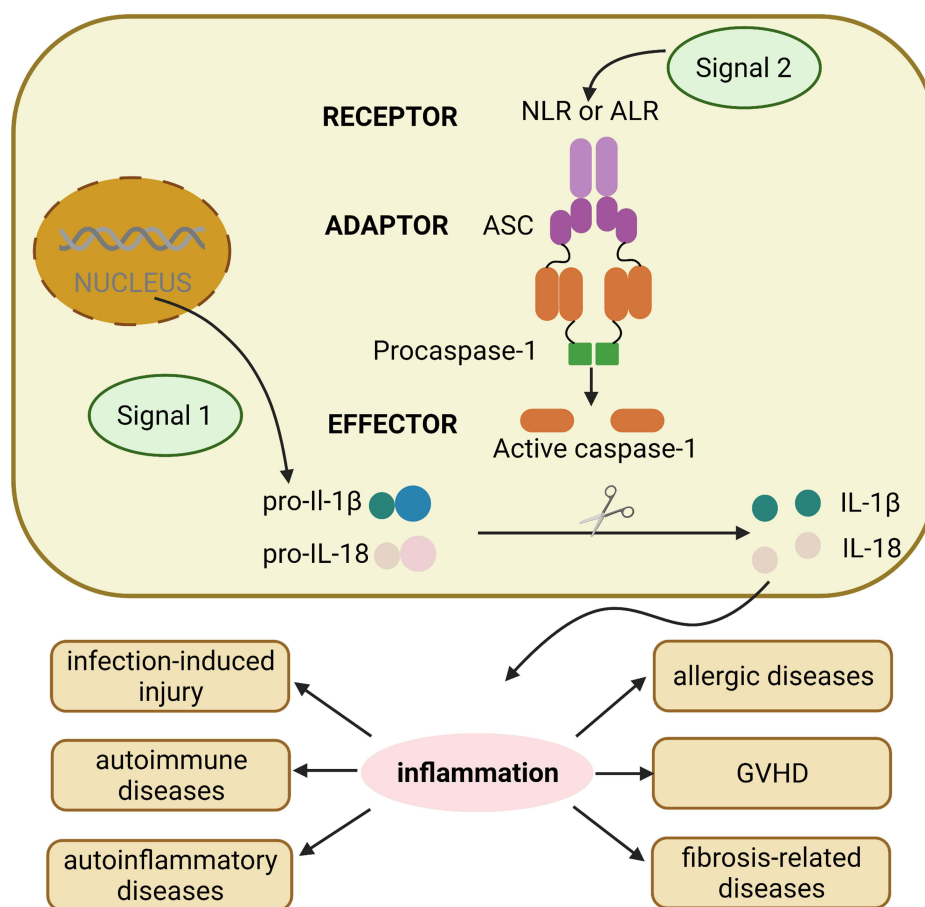
For decades, the miniscule protein-coding portion of the genome was the primary focus of medical research.<sup>1</sup> However, numerous ncRNAs have been discovered over the past 10 years and have been demonstrated to play important roles in various diseases, including inflammatory diseases.<sup>2</sup> Normally, inflammation is a defense response of the body to stimuli which is beneficial; however, disorders of inflammation can cause many diseases, including sepsis and autoimmune diseases.<sup>3</sup> Therefore, orchestrating an effective inflammatory response without harmful immunopathology is an important issue. Exciting research has demonstrated that ncRNAs play a regulatory role in the inflammatory response and are therefore involved in inflammatory diseases.<sup>2</sup> As an important part of innate immunity,<sup>4</sup> the activation of the inflammasomes plays a critical role in the regulation of the inflammatory response; imbalance in such regulation can lead to the occurrence of a variety of diseases. Notably, numerous studies emphasize the function of ncRNAs in the fine control of the inflammasomes activation either by directly targeting components of the inflammasomes or by controlling the activity of various regulators of inflammasomes activation, thus representing potential therapeutic targets for inflammatory diseases.<sup>5</sup>

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The inflammasomes are critical components of the innate immune system.<sup>4</sup> These differ significantly from membrane-bound pattern recognition receptors (PRRs). Rather, inflammasomes are multimeric protein complexes that are formed from cytoplasmic PRRs, including members of the evolutionary conserved NOD-like receptors (NLRs), together with absent in melanoma 2 (AIM2)-like receptors (ALRs) and pyrin. These complexes can feature NLRP1, NLRP3, NLRC4, AIM2, and pyrin and can sense microbial pathogens or detect danger associated molecular patterns (DAMPs) and mediate the activation of proinflammatory cytokines as part of the innate immune response.<sup>6</sup> The assembly and function of inflammasomes involves two different steps: the first initiation step upregulates the expression levels of inflammasomes components while the second activation step induces oligomerization of the inflammasomes complex.<sup>7</sup> The

specific process is shown in Figure 1. The activation of inflammasomes plays a critical role in defense against pathogens and helps to remove damaged and transformed host cells and stimulates an adaptive immune response. Conversely, the aberrant activation of inflammasomes has been linked to some inflammatory diseases.

A firm understanding of the regulation of inflammasomes activation may allow us to induce alterations in this process and improve the prognosis of inflammatory diseases. A substantial number of studies have investigated the regulatory process underlying the activation of inflammasomes from the perspective of ncRNAs in an effort to provide new insights into the regulatory mechanisms associated with inflammatory diseases.<sup>5</sup> For instance, two studies identified miR-223-3p as the first human miRNA that directly targeted NLRP3.<sup>8,9</sup> Subsequent studies found that miR-223 could



**Figure 1** The general process of activation of different inflammasomes. The assembly and function of inflammasomes involves two different steps: signal 1 including various PAMPs and DAMPs turns on the first initiation step, which upregulates the expression levels of inflammasomes components such as pro-IL-1 $\beta$ , pro-IL-18. Then, signal 2 triggers the second activation step, which induces oligomerization of the inflammasome complex including receptor NLRs and ALRs, adaptor ASC, and effector pro-caspase -1, the assembled pro-caspase-1 becomes caspase-1, then cutting pro-IL to activated IL, inducing inflammation response, which plays vital role in inflammation-related diseases including infection-induced injury, autoimmune diseases, autoinflammatory diseases, allergic diseases, GVHD and fibrosis-related diseases.

**Abbreviations:** PAMPs, pathogen-associated molecular patterns; DAMPs, damage associated molecular patterns; IL, interleukin; NLRs, NOD-like receptors; ALRs, absent in melanoma 2-like receptors; ASC, apoptosis-associated speck-like protein containing caspase recruitment domain; GVHD, graft-versus-host disease.

participate in different diseases by targeting NLRP3. Long non-coding RNAs (lncRNAs) are non-coding RNAs (ncRNAs) longer than 200 nucleotides. Notably, another study showed that lncRNA could be used as a scaffold to participate in the assembly of inflammasomes. Zhang et al showed that the Neat 1 lncRNA could promote the assembly of inflammasomes, including NLRC4, AIM2, and NLRP3 inflammasomes, thus facilitating the recruitment, maturation, and stabilization of caspase-1 in activated macrophages.<sup>10</sup> Furthermore, Neat1 deficiency significantly reduced inflammatory responses by reducing the activation of inflammasomes in mouse models of peritonitis and pneumonia.<sup>10</sup> Lian et al demonstrated that circHIPK3 could sponge miR-192 and miR-561, and subsequently promote the expression levels of the target genes for miR-192 and miR-561 (Toll-like receptor 4 (TLR4) and NLRP3), thus promoting an inflammatory response; these authors also found that the knockdown of circHIPK3 could suppress gouty arthritis.<sup>11</sup> These results showed that ncRNAs played an important regulatory role in the activation of inflammasomes.

Herein, we summarize the role and therapeutic potential of ncRNAs in inflammatory diseases by regulating inflammasomes pathways with a particular emphasis on microbial infection and sterile inflammatory diseases, including microbial infection, infection or sepsis-induced multiple organ failure, autoimmune diseases, autoinflammatory diseases, allergic diseases, graft-versus-host disease (GVHD), and fibrosis related diseases.

## Regulatory Mechanisms of ncRNAs

The ncRNAs can be divided into different classes, broadly based upon their size. Small ncRNAs include miRNAs, transfer RNA (tRNA)-derived small RNAs (tsRNAs), and PIWI-interacting RNAs (piRNAs). At the opposite end of the size spectrum are the lncRNAs; these are defined as untranslated RNAs that are greater than 200 nucleotides (nts) in length, and include a number of subclasses, including pseudogenes and circular RNAs (circRNAs).<sup>12</sup> At present, the most commonly studied ncRNAs that regulate inflammasomes in the context of inflammatory diseases are miRNAs, lncRNAs, and circRNAs. Therefore, in this review, we focus specifically on these three forms of ncRNAs (Figure 2).

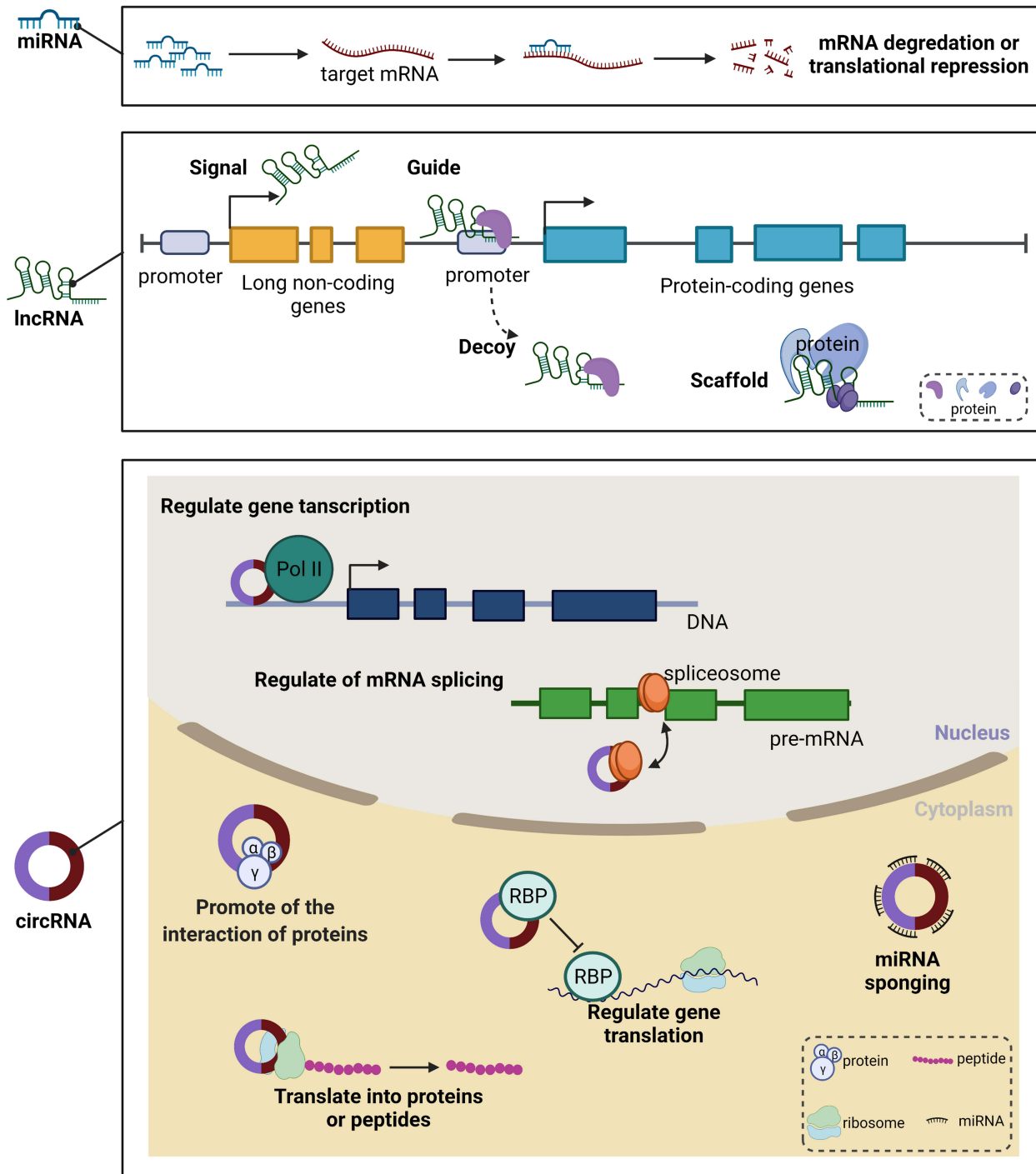
## Regulatory Mechanism of miRNAs

The miRNAs are a form of ncRNAs that are approximately 22nt in length and constitute almost 1% of all predicted genes in nematodes, flies and mammals.<sup>13</sup> Due to their capability to

modulate gene expression at the post-transcriptional level either by inhibiting the translation of messenger RNA (mRNA) or by promoting the degradation of mRNA.<sup>14</sup> The miRNAs have also been shown to be involved in the pathogenesis of many diseases, including neurodegenerative diseases, cardiovascular diseases, and cancer.<sup>15–17</sup> Mechanistically, miRNAs mediate the post-transcriptional gene silencing of target genes by targeting the 3'-untranslated region of mRNA; the seed region (nucleotides 2–7) at the 5'-end of miRNA is considered to be the crucial sequence. In addition, a single miRNA can target hundreds of mRNAs and influence the expression of many genes that are often involved in a functional interacting pathway.<sup>13</sup> The miRNA mimics and miRNA inhibitors are currently in pre-clinical development and have shown promise as novel therapeutic agents. Moreover, several miRNA-targeted therapeutics have reached the clinical development phase, including a mimic of the tumor suppressor miRNA miR-34; this reached Phase I clinical trials for the treatment of cancer. Another example is anti-miRs, which targets miR-122 and reached Phase II trials for the treatment of hepatitis.<sup>18</sup> An increasing number of studies have demonstrated that miRNAs hold huge potential as diagnostic and prognostic biomarkers, and as predictors of drug response. Regarding the regulation of the inflammasomes pathways by miRNAs, miRNAs could not only directly target the inflammasomes components, such as miR-223 targeting NLRP3,<sup>8,9</sup> miR-142 targeting apoptosis-associated speck-like protein containing caspase recruitment domain (ASC),<sup>19</sup> miR-446 targeting pro-interleukin1 $\beta$  (pro-IL-1 $\beta$ ),<sup>20</sup> and miR-379-5p targeting GSDMD,<sup>21</sup> but also could regulate the upstream pathways of the activation of inflammasomes, such as miR-146a,<sup>22</sup> miR-96,<sup>23</sup> and et al regulating NF- $\kappa$ B pathway, miR-33 regulating reactive oxygen species (ROS),<sup>24</sup> and miR-17,<sup>25</sup> miR-20a,<sup>26</sup> targeting thioredoxin-interacting protein (TXNIP).<sup>27</sup> (Figure 3) These miRNAs also play an important role in inflammatory diseases, which will be discussed in detail below.

## Regulatory Mechanisms of lncRNAs

Studies have estimated that the number of lncRNA genes (> 200 nt in length) in humans ranges from less than 20,000 to over 100,000.<sup>28</sup> Research has shown that lncRNAs play essential roles in the regulation of gene expression despite the fact that they do not code proteins.<sup>29</sup> Depending on their regulatory patterns, lncRNAs can be further classified into those that act in cis, thus influencing the expression and/or chromatin status

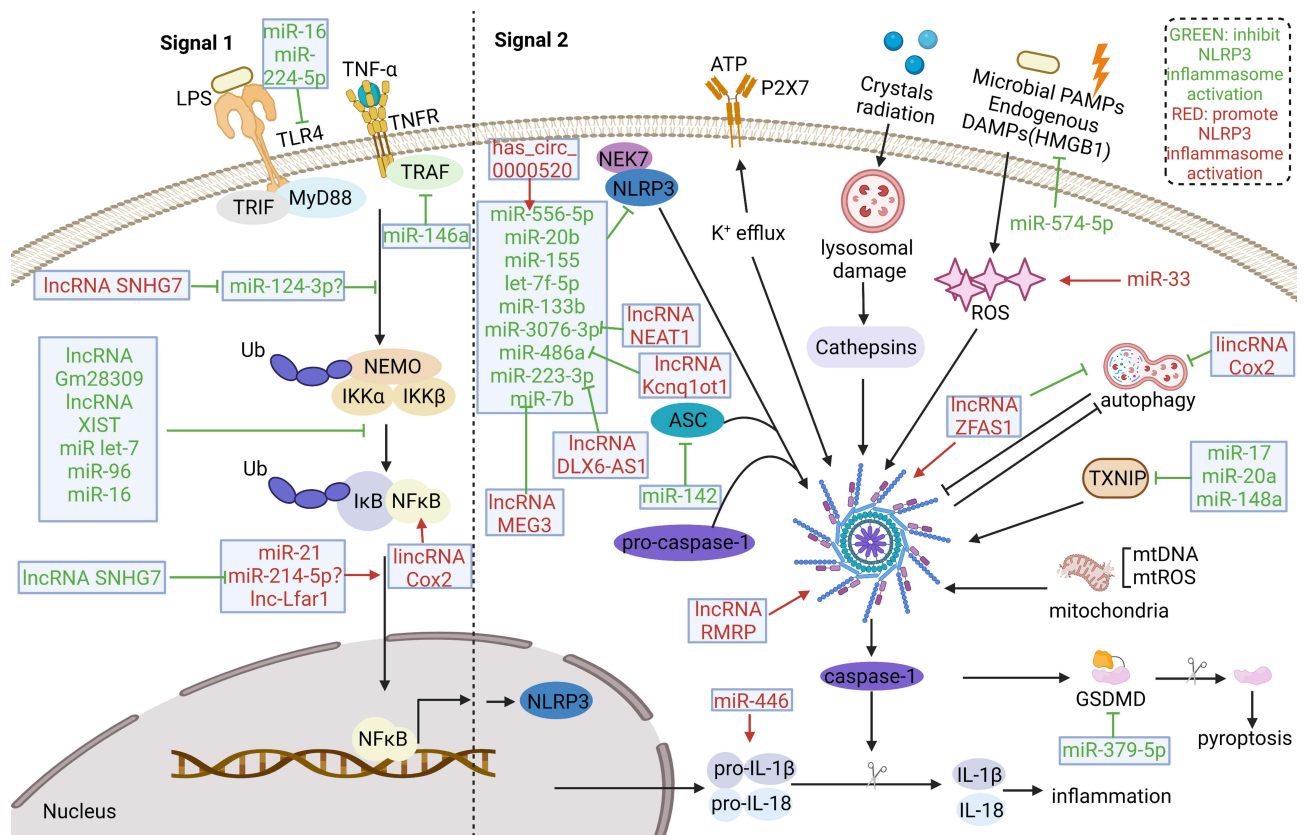


**Figure 2** The general regulatory mechanisms of ncRNAs. miRNAs modulate gene expression at the post-transcriptional level either by inhibiting the translation of mRNA or by promoting the degradation of mRNA. lncRNAs can regulate gene expression as signal, guide, decoy and scaffold. circRNAs can exert function at nucleus and cytoplasm. At nucleus, circRNAs can regulate gene transcription and mRNA splicing. At cytoplasm, circRNAs can promote the interaction of proteins, regulate gene translation, be as miRNAs sponging and translate into proteins or peptides.

**Abbreviations:** mRNA, messenger RNA; miRNAs, micro RNAs; lncRNAs, long non-coding RNAs; circRNAs, circular RNAs; RBP, RNA binding protein.

of nearby genes, and those that execute an array of functions throughout the cell in trans.<sup>28</sup> According to their genomic position relative to nearby protein-coding genes,

lncRNA can be categorized as intergenic, intronic, bidirectional, sense, antisense, and enhancer lncRNAs.<sup>30</sup> Notably, antisense transcripts often interact the



**Figure 3** ncRNAs involved in activation of NLRP3 inflammasomes in inflammatory diseases. ncRNAs can regulate both of the two signal for the activation of NLRP3. In the signal 1 step, multiple molecules or inflammatory cytokines activate NF- $\kappa$ B pathway to up-regulate NLRP3, pro-IL-1 $\beta$ , pro-IL-18. Various miRNAs could regulate NF- $\kappa$ B pathway or target components of NF- $\kappa$ B pathway. Several lncRNAs was found to regulate NF- $\kappa$ B pathway as miRNAs' sponge. The signal 2 is motivated by various endogenous and exogenous stimuli, including ATP, crystals radiation, microbial PAMPs and endogenous DAMPs. These stimuli can induce the activation of diverse molecular and cellular signaling pathways, including K<sup>+</sup> efflux, lysosomal damage, ROS generation and mitochondrial dysfunction, which are involved in the activation of the NLRP3 inflammasome. In addition, autophagy has interaction with inflammasomes activation. Various miRNAs, several lncRNAs and circRNAs were found to target components or activation signals of NLRP3 inflammasome pathways.

**Abbreviations:** IL, interleukin; NF- $\kappa$ B, nuclear factor-kappa B; ATP, adenosine triphosphatase; PAMPs, pathogen-associated molecular patterns; DAMPs, damage associated molecular patterns; ROS, reactive oxygen species.

corresponding sense transcripts encoded from the opposing gene, thereby interfering with post-transcriptional control by promoting transcript degradation or disrupting translation. Recently, Brocker et al showed that lncRNA Gm15441 could suppress its antisense transcript, encoding thioredoxin interacting protein (TXNIP), thereby inhibiting NLRP3 inflammasome activation.<sup>31</sup> Interestingly, some lncRNAs have been found to encode small peptides, thus escalating their complexity.<sup>32</sup> Recently, the study performed by Bhatta et al identified lncRNA 1810058I24Rik, which was downregulated in both human and murine myeloid cells exposed to LPS as well as other Toll-like receptor ligands and inflammatory cytokines and could produce a 47 aa micropeptide, named mitochondrial micropeptide-47 (Mm47), then demonstrated that *Mm47*-deficient or knockdown cells were compromised for NLR3 inflammasome responses.<sup>33</sup> During

the transcriptional regulation of target genes, lncRNAs repress or activate genes by functioning as either scaffolds or decoys.<sup>34,35</sup> Intriguingly, Lin et al demonstrated that lncRNA Platr4 could function to inactivate NLRP3 inflammasome via intercepting NF- $\kappa$ B signaling. Mechanistically, lncRNA Platr4 could prevent binding of the NF- $\kappa$ B/Rxra complex to the  $\kappa$ B sites via a physical interaction, thereby inhibiting the transactivation of NLRP3 and ASC by NF- $\kappa$ B.<sup>36</sup> In addition, during the activation of inflammasomes, lncRNA Neat1 could be used as a scaffold to participate in the assembly of inflammasomes including NLR4, AIM2, and NLRP3 inflammasome, thus facilitating the recruitment, maturation, and stabilization of caspase-1 in activated macrophages.<sup>10</sup> lncRNAs can also recruit proteins to chromatin to participate in histone modification and affect gene transcription as guides. For instance, Wang et al uncovered a novel



lncRNA named Lnc-UC, which could promote expression of Rev-erba (a known dual NF- $\kappa$ B/Nlrp3 repressor) to inactive NF- $\kappa$ B signaling and NLRP3 inflammasome in macrophages. In the molecular level, Lnc-UC could interact with chromobox 1 to reduce H3K9me3 at Rev-erba promoter and to induce Rev-erba transcription and expression.<sup>37</sup> Conversely, Cai et al showed that lncRNA MALAT1 could promote neuroinflammation by recruiting enhancer of zeste homologue 2 to the promoter of nuclear factor erythroid 2-related factor 2 (Nrf2), suppressing Nrf2 expression epigenetically, thereby inducing inflammasomes activation in parkinson's diseases mouse and microglial cell models.<sup>38</sup> LncRNAs can also regulate gene transcription as enhancers.<sup>39–41</sup> They can also co-transcriptionally regulate mRNA transcripts by altering their splicing patterns.<sup>42</sup> At the post-transcriptional level, lncRNAs function as miRNAs sponges, which can indirectly represses the expression of an mRNA that would be targeted by miRNAs.<sup>43</sup> Several studies have showed that lncRNAs could regulate the expression of components of inflammasome-related pathways via miRNAs sponges. For instance, Chi et al demonstrated that lncRNA HOTAIR could promote renal inflammatory response in hyperuricemia mice by competitively binding miR-22 to regulate NLRP3 expression.<sup>44</sup> In addition, the study conducted by Zhou et al showed that overexpression of lncRNA TUG1 could promote NLRP3 inflammasome-mediated cardiomyocyte pyroptosis through targeting miR-186-5p/X-Linked inhibitor of apoptosis axis in coronary microembolization-induced myocardial damage.<sup>45</sup> Moreover, lncRNAs can affect the stability of mRNA transcripts,<sup>46</sup> and modulate mRNA translation by binding to ribosomes or mRNA transcripts during translation.<sup>47</sup> Furthermore, lncRNA could regulate protein nucleoplasmic shuttle. For example, lincRNA-Cox2 could bind NF- $\kappa$ B p65 and promote its nuclear translocation and transcription, modulating the expression of inflammasome sensor NLRP3 and adaptor ASC, thereby enhancing the activation of NLRP3 inflammasome.<sup>48</sup> Thus, evidence has demonstrated that lncRNAs can participate in the regulation of gene expression via a variety of mechanisms and increasing number lncRNAs have been found to exert function in the activation of inflammasomes.

## Regulatory Mechanisms of circRNAs

CircRNAs consisting of a circular configuration through a typical 5' to 3'-phosphodiester bond, has been recently recognized as a new class of functional molecules. The

circRNA has no 5' or 3' free terminus and is much more stable in cellular environment. RNA molecules with a circular configuration were first discovered four decades ago. Over recent years, circRNAs have been found to be involved in the regulation of many diseases, including cancer, cardiovascular diseases, and metabolic diseases.<sup>49,50</sup> However, the function of circRNAs remains largely unknown. A small number of circRNAs have been shown to be involved in post-transcriptional regulation by functioning as "sponges" of miRNAs, thus reducing their ability to target mRNAs.<sup>49,50</sup> At present, the main focus on the role of circRNAs in the regulation of inflammasomes is through sponging miRNAs. For instance, Lian et al showed that circHIPK3 could sponge miR-192 and miR-561 to promote TLR4 and NLRP3 expressions, thereby promoting inflammation in gouty arthritis.<sup>11</sup> Similarly, the study performed by Bian et al demonstrated that circHelz could activate NLRP3 inflammasome to promote myocardial injury by sponging miR-133a-3p in mouse ischemic heart.<sup>51</sup> In addition, exosomes are microvesicles that can contain ncRNAs such as miRNAs and circRNAs, and are secreted by many different types of cells. Stem cell-derived exosomes can be used as carriers to treat diseases. Recently, Yan et al reported that human umbilical cord mesenchymal stem cells-derived exosomes could prevent hindlimb ischemic injury by releasing circHIPK3, which could in turn down regulate miR-421, resulting in increased expression of FOXA3a, leading to inhibition of NLRP3 inflammasome mediated pyroptosis.<sup>52</sup> Intriguingly, there is an interaction between autophagy and inflammasomes activation. Zhang et al showed that circARF3 could alleviate mitophagy-mediated inflammation induced by NLRP3 inflammasome activation via targeting miR-103/TRAF3 in mouse adipose tissue.<sup>53</sup> Except for sponging miRNAs, circRNAs have been found to be involved in transcriptional activation by recruiting transcription factors. For example, Yang et al suggested that circ-HuR suppressed the growth, invasion, and metastasis, of gastric cancer cells in vitro and in vivo. Mechanistically, circ-HuR interacted with CCHC-type zinc finger nucleic acid binding protein, and subsequently restrained its binding to the HuR promoter, thus resulting in the down-regulation of HuR and the repression of tumor progression.<sup>54</sup> Moreover, several studies have shown that circRNAs sponged splicing factors to regulate gene splicing. For example, Barbagallo et al found that circSMARCA5 represented a promising and druggable tumor suppressor in glioblastoma multiforme and

suggested that circSMARCA5 might exert function by tethering RNA binding protein serine and arginine rich splicing factor 1, a splicing factor known to be a positive controller of cell migration.<sup>55</sup> Furthermore, circRNAs can also regulate target gene translation,<sup>56</sup> or act as an adaptor to modulate protein-protein interactions and their activities.<sup>57</sup> In addition, an increasing body of evidence indicates that circRNAs may not be a real class of ncRNAs because some are translatable.<sup>58</sup> These mechanisms may be the potential mechanisms for circRNAs to regulate inflammasomes activation. However, circRNAs are known to play important functions in gene transcription and post-transcription regulation and deserve our further attention, especially in inflammasomes activation.

## The Roles of ncRNAs in Inflammasomes Activation in Inflammatory Diseases

### The Roles of ncRNAs in Inflammasomes Activation in Infectious Diseases

Inflammation is the typical response of the host immune system to microbial infection. However, excessive and unresolved inflammation could contribute to tissue injury such as acute lung injury (ALI), acute liver failure (ALF), or even the occurrence of sepsis.<sup>59</sup> Notably, sepsis refers to a life-threatening organ dysfunction caused by a dysregulated host response to infection that is characterized by systemic inflammatory response syndrome. Sepsis could also lead to ALI, ALF, acute kidney injury (AKI), and heart dysfunction.<sup>60</sup> The incidence of sepsis is as high as 1–2% in all hospitalized patients and therefore poses a serious threat to human life. Due to a lack of specific drugs, sepsis can only be treated by antibiotic treatment, supportive treatment and symptomatic treatment.<sup>61</sup> Therefore, it is vital to gain a deeper understanding of microbial infection, infection-induced tissue damage, and sepsis-induced multiple organ dysfunction so that we can identify new therapeutic targets. Recent studies have found that the excessive activation of inflammasomes contributes to microbial infection-induced inflammation,<sup>43</sup> infection-induced tissue injury,<sup>62–64</sup> and sepsis-induced AKI,<sup>65</sup> and heart dysfunction.<sup>66</sup> Moreover, an increasing number of studies has shown that the use of ncRNAs to target inflammasome pathways or the molecules upstream of inflammasome pathways could alleviate microbial infection-induced injury and sepsis-induced multiple organ dysfunction, thus facilitating the future development of therapeutic strategies (Table 1).

## The Roles of ncRNAs in Regulating Inflammasomes Activation in Different Types of Microbial Infection

Many studies have shown that miRNAs can directly target the key components of the inflammasome pathways involved in microbial infection, particularly NLRP3. The NLRP3 inflammasome is the most widely studied inflammasome and is known to be activated in many inflammatory diseases, including microbial infection. The activation process of NLRP3 inflammasome is showed in Figure 3. Several miRNAs have been found to be significantly reduced in patient serum with the potential as biomarkers, and could reduce inflammation by directly targeting NLRP3. For example, Lou et al showed that miR-20b was downregulated and NLRP3 was upregulated in the macrophages of both patients and mice with tuberculosis (TB).<sup>67</sup> Treatment with a miR-20b mimic alleviated the inflammatory response and deactivated the NLRP3/caspase-1/IL-1 $\beta$  pathway in a mouse model of TB and in alveolar epithelial cells co-cultured with macrophages; these effects occurred via the direct targeting of NLRP3.<sup>67</sup> Moreover, a study involving *Treponema pallidum* subspecies *pallidum* (T pallidum) infection showed that a dramatic reduction in the serum levels of miR-223-3p of patients with syphilis compared with healthy controls, which could target NLRP3 to suppress inflammasome activation and pyroptosis in T pallidum-induced Human Umbilical Vein Endothelial Cells (HUVECs), thus indicating a potential target for syphilis-induced endothelial injury.<sup>68</sup>

Apart from targeting NLRP3 directly, ncRNAs can also regulate the NLRP3 inflammasome activation process. The NLRP3 inflammasome can be activated by a diverse range of stimuli and a 2-signal model has been proposed for to explain this process (Figure 3). Signal 1 is provided by microbial molecules or endogenous cytokines, in which the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) leads to the up-regulation of NLRP3 and pro-IL-1 $\beta$ .<sup>69,70</sup> For instance, Xue et al showed that miR-21 was a critical positive regulator of the NF- $\kappa$ B pathway and NLRP3 inflammasome via A20 in myeloid cells from both humans and mice. The knockout of miR-21 was shown to reduce mortality rates in a lipopolysaccharide (LPS)-induced mouse model of septic shock.<sup>71</sup> Also, bioinformatic analysis showed that miR-21 levels in peripheral blood from patients with septic shock were elevated.<sup>71</sup> In addition, a study conducted by Lee et al demonstrated that miRNA-rich extracellular vesicles (EVs) could contribute to innate immune responses after bacterial lung infection. Mechanistically, miRNAs

**Table 1** The Effect of ncRNAs in Activation of Inflammasomes in Different Inflammatory Diseases

ncRNA	Model	Target	Function in Inflammasome Activation	Level	Reference
<b>Microbial infection</b>					
miR-20b	Macrophages of patients and mice with TB / alveolar epithelial cells co-cultured with macrophages	NLRP3	Reduce inflammatory response by direct target NLRP3	Down	[67]
miR-223-3p	Patients with syphilis/ T pallidum-induced HUVECs	NLRP3	Suppress inflammasome activation and pyroptosis by direct target NLRP3	Down	[68]
miR-21	LPS-induced mice model of septic shock/LPS-induced myeloid cells	A20	Promote NLRP3 inflammasome activation by A20/NF- $\kappa$ B pathway	Up	[71]
miRs contained in alveolar epithelial type-I cells-EVs	P. aeruginosa-induced alveolar macrophages and mice	-	Promote NLRP3 inflammasome activation, neutrophil recruitment, and M1-macrophage polarization	Up	[72]
miR-223	LPS-induced bovine endometritis and bovine endometrial epithelial cell (BEND) line	NLRP3	Reduce inflammatory response by direct target NLRP3	Up	[73]
miR-223-3p	H. pylori-induced THP-1 monocytes	NLRP3	Reduce NLRP3 inflammasome activation and increase H. pylori survival	Up	[74]
miR-223	LPS-induced human dental pulp fibroblasts	NLRP3	Reduce inflammatory response by direct target NLRP3	Down	[75]
miR-223	influenza A virus (IAV)-induced lung epithelial	NLRP3	Reduce inflammatory response by direct target NLRP3	Down	[76]
miR-155	Porphyromonas gingivalis-induced macrophages	NLRP3	Reduce NLRP3 inflammasome-mediated pyroptosis	Up	[77]
lncRNA Gm28309	Brucella strain-induced RAW264.7 cells	$\kappa$ B-Ras2	Reduce inflammation response by miR-3068-5p/NF- $\kappa$ B/NLRP3	Down	[78]
lncRNA XIST	E. coli or S. aureus-induced mammary alveolar cell-T (MAC-T) cells	NF- $\kappa$ B	Reduce inflammatory response by NF- $\kappa$ B/NLRP3 pathway	Up	[79]
<b>ALI</b>					
miR-223/142 EVs	BALF and serum of lung infection-associated ALI in patients/ LPS or Klebsiella pneumoniae-induced macrophages	NLRP3/ASC	Reduce inflammatory response by direct target NLRP3 and ASC	Up	[19]
miR-223	MTDs-induced mice /ARDS patients	NLRP3	Limit the number of Ly6G+ neutrophils and inhibit the activity of the NLRP3 inflammasome	Up	[82]
lncMEG3	LPS-induced mice and mouse alveolar macrophage NR8383	miR-7b	Promote LPS-induced ALI by acting as a molecular sponge for miR-7b to modulate NLRP3 directly	Up	[83]
miR-16	LPS-induced ALI mice and A549 cells	TLR4	Reduce inflammatory response by TLR4/NF- $\kappa$ B/NLRP3 pathway	Down	[85]
miRNA-466	EVs isolated from the BALF of LPS-induced ARDS mice/LPS-induced macrophages	Pro-IL1 $\beta$	Promote inflammation by up-regulating pro-IL-1 $\beta$	Up	[20]
miR-574-5p	LPS-induced human pulmonary microvascular endothelial cells (HPMECs) and ARDS mice	HMGB1	Suppress NF- $\kappa$ B signaling pathway and NLRP3 inflammasome activation by targeting HMGB1	Up	[88]

(Continued)



Table 1 (Continued).

ncRNA	Model	Target	Function in Inflammasome Activation	Level	Reference
miR-223	LPS-induced A549 cells	NLRP3	Suppress NLRP3 inflammasome by targeting NLRP3 directly and the TLR4/NF- $\kappa$ B signaling pathway via RHOB	Down	[89]
miR-199a-3p	LPS-induced A549 and the human macrophage cell line U937	NLRP1	Reduce inflammation by targeting NLRP1 directly	Down	[90]
<b>ALF</b>					
miR-223-3p	LPS/GalN-induced ALF mice	NLRP3	Reduce LPS/D-GalN-induced liver injury by targeting NLRP3 directly	-	[93]
miR-17 exosomes	LPS/GalN-induced ALF mice and LPS-induced	TXNIP	Alleviate LPS/GalN-induced ALF by reducing TXNIP/NLRP3 inflammasome activation	-	[25]
<b>Sepsis-induced heart dysfunction</b>					
lncRNA ZFAS1	CLP-induced sepsis mice and LPS-induced primary cardiomyocytes	miR-590-3p	Promote LPS-induced NLRP3 mediated pyroptosis and inhibit autophagy by AMPK/mTOR pathway through sponging miR-590-3p	Up	[96]
<b>AKI</b>					
lncRNA DLX6-ASI	Septic AKI patients and LPS-induced HK-2 cells	miR-223-3p	Promote LPS-mediated cytotoxicity and pyroptosis by miR-223-3p/NLRP3 pathway	Up	[97]
lncRNA RMRP	AKI patients and LPS-induced HK-2 cells	-	Promote inflammation by activating the NLRP3 inflammasome	Up	[98]
lncRNA Kcnq1ot1	sC5b-9-induced podocytes	miR-486a-3p	Promote podocyte pyroptosis by sponging miR-486a-3p/NLRP3	Up	[99]
miR-223-3p	LPS-induced HK-2 cells	NLRP3	Inhibit NLRP3 inflammasome activation by targeting NLRP3 directly	-	[100]
<b>Auto-immune diseases</b>					
miR-223	IBD patients/ miR-223-/- mice	NLRP3	Reduce myeloid-driven experimental colitis by targeting NLRP3 directly	Up	[108]
miR-223-3p	EAM mice	NLRP3	Promote polarization of dendritic cells (DCs) towards a tolerogenic DC phenotype and regulatory T cell (Treg) generation by inhibiting NLRP3 inflammasome activation	Down	[109]
let-7f-5p	Bone marrow-derived mesenchymal stem cells from systemic lupus erythematosus patients	NLRP3	Attenuate inflammation by targeting NLRP3 directly	Up	[110]
miR-146a	Monosodium urate (MSU)-induced gouty arthritis mice	TRAF6/IRAK1	Reduce paw swelling and index and ankle joint swelling by targeting TRAF6 and IRAK1 mediated NLRP3 inflammasome activation	-	[22]
miR-155	Imiquimod-induced psoriasis mice / keratinocyte-induced HaCaT cells	NLRP3	Promote psoriasis-induced inflammation by NLRP3/caspase-1 signaling	Up	[111]
miR-33	RA patients/ primary macrophages	-	Promote NLRP3 inflammasome activation by increasing accumulation of cellular ROS	Up	[24]
miR-20a	Primary fibroblast-like synoviocytes (FLSs) isolated from adjuvant-induced arthritis (AA)	TXNIP	Reduce formation of the NLRP3 inflammasome by targeting TXNIP directly	-	[26]

(Continued)

Table 1 (Continued).

ncRNA	Model	Target	Function in Inflammasome Activation	Level	Reference
lincRNA-Cox2	LPS-induced microglial cells, BMDMs and BV2/ autoimmune encephalomyelitis mice	NF-κB	Promote NLRP3 inflammasome activation and inhibit autophagy by bonding to NF-κB p65 directly and promote p65 transfer to nucleus	-	[48]
<b>Auto-inflammatory diseases</b>					
miR-197-3p	FMF patients	IL1R1	Inhibit NLRP3 inflammasome activation by targeting IL1R1	Down	[122]
<b>Allergic diseases</b>					
has_circ_0000520	AR patients and mice	miR-556-5p	Promote NLRP3-mediated cell pyroptosis by direct targeting NLRP3	Up	[136]
miR-224-5p	AR mice	TLR4	Inhibit NLRP3 inflammasomes activation by direct targeting TLR4	Down	[137]
miR-133b	AR mice	NLRP3	Inhibit NLRP3 inflammasomes activation by direct targeting NLRP3	Down	[138]
<b>GVHD</b>					
lncRNA NEAT1	EAM and heart transplantation mice/ tolerogenic dendritic cells	miR-3076-3p	Promote immune tolerance by targeting NLRP3	-	[140]
miR-155	LPS-stimulated DCs/ allogeneic hematopoietic cell transplantation recipient mice	-	Promote GVDH by increasing NLRP3 inflammasome	Up	[143]
<b>Other sterile inflammatory diseases</b>					
miR-233	Anterior cruciate ligament transection-induced osteoarthritis (OA) rat	NLRP3	Inhibit NLRP3 inflammasome activation by targeting NLRP3 directly	Up	[144]
lncRNA SNHG7	OA rat/ IL-1β-induced chondrocytes	FSTL-1	Promote FSTL-1-mediated NLRP3 inflammasome activation and TLR4/NF-κB signaling pathways by targeting miR-124-3p	Up	[146]
lncRNA SNHG7	OA patients/ IL-1β-induced chondrocytes	PPARGC1B	Inhibiting NLRP3 inflammasome activation and apoptosis via the miR-214-5p/PPARGC1B axis	Down	[147]
miR-148a	Alcoholic hepatitis (AH) patients/ AH and alcoholic liver disease mice/ alcohol-induced hepatocyte	TXNIP	Ameliorate alcohol-induced inflammasome activation and pyroptosis in hepatocytes through TXNIP inhibition	Down	[27]
<b>Fibrosis related diseases</b>					
miR-21	Liver fibrosis patient/ BDL or AngII infusion-induced liver fibrosis rat/ AngII-induced hepatic stellate cells (HSCs)	Spry1/ Smad7	Promote NLRP3 inflammasomes activation and resultant collagen production via the Spry1/ERK/NF-κB and Smad7/Smad2/3/NOX4 pathways by targeting Spry1 and Smad7 directly	Up	[151]
miR-379-5p	Arsenite-exposed mice/arsenite-induced HSCs and human hepatic cells	GSDMD	Inhibit arsenite-induced increase in GSDMD levels and the release of IL-1β by targeting GSDMD directly	Down	[21]

(Continued)

Table 1 (Continued).

ncRNA	Model	Target	Function in Inflammasome Activation	Level	Reference
lnc-Lfar1	CCl4-and bile duct ligation (BDL) induced liver fibrosis mice/LPS or IFN- $\gamma$ -induced primary KCs, RAW264.7 cells and bone marrow-derived macrophages (BMMs)	NF- $\kappa$ B	Promote carbon tetrachloride (CCl4)- and BDL-induced proinflammatory M1 macrophage activation and NLRP3 inflammasome-mediated pyroptosis by NF- $\kappa$ B pathway	Down	[152]
miR-21	BLM-induced lung fibrosis rat	Spry1	Inhibit AngII-induced activation of the NLRP3 inflammasome by targeting Spry1 in lung fibroblasts	Up	[157]
MenSCs-Exo containing miR let-7	BLM-induced lung fibrosis mice	LOX1	Inhibit activation of NLRP3 inflammasome by affecting ROS and mtDNA damage via targeting LOX1 directly	-	[159]
miR-96	Carbon black nanoparticle-induced lung fibrosis rat and human bronchial epithelial cells	FOXO3a	Attenuate fibrosis through inhibiting NLRP3 inflammasome by targeting FOXO3a	Up	[23]

**Abbreviations:** ACLT, anterior cruciate ligament transection; AH, alcoholic hepatitis; AKI, acute kidney injury; ALF, acute liver failure; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ASC, apoptosis-associated speck-like protein containing CARD; BALF, bronchoalveolar lavage fluid; BDL, bile duct ligation; BEND cell, bovine endometrial epithelial cell; BLM, Bleomycin; BMMs, bone marrow-derived macrophages; CCl4, carbon tetrachloride; CLP, cecal ligation and puncture; DAMPs, damage-associated molecular patterns; DCs, dendritic cells; E. coli, Escherichia coli; EAM, experimental autoimmune myocarditis; EVs, extracellular vesicles; FSTL-1, Follistatin-like Protein 1; GVDH, graft-versus-host disease; H. pylori, Helicobacter pylori; HMGB1, high-mobility group protein B1; HSCs, hepatic stellate cells; HUVECs, Human Umbilical Vein Endothelial Cells; IAV, influenza A virus; IBD, inflammatory bowel disease; IL-1 $\beta$ , Interleukin-1 beta; IRAK1, interleukin-1 receptor-associated kinase; LPS, lipopolysaccharide; MAC-T cell, mammary alveolar cell-T; MSU, monosodium urate; MTDs, mitochondrial DAMPs; NLRP1, Nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 1; NLRP3, Nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 3; OA, osteoarthritis; P. aeruginosa, Pseudomonas aeruginosa; RA, rheumatoid arthritis; ROS, reactive oxygen species; S. aureus, Staphylococcus aureus; TB, tubercle bacillus; TLR4, Toll-like receptor 4; TRAF6, TNF receptor associated factor 6; Treg, regulatory T cell; TXNIP, thioredoxin-interacting protein.

contained in alveolar epithelial type-I cells (ATIs)-EVs including miR-17, miR-93, miR-221, miR-320, miR-92a, mir-199a and mir-330, were actively delivered into alveolar macrophages, subsequently promoting NLRP3 inflammasome activation, neutrophil recruitment, and M1-macrophage polarization in response to *P. aeruginosa* pneumonia in vitro and in vivo.<sup>72</sup> These studies involving miRNAs provide a novel insight into the development of biomarkers, therapeutic strategies, and the mechanisms that underlie microbial infection.

Furthermore, miR-223 and miR-155 were found to be involved in infection by targeting NLRP3 in both animal and cell models. Zhao et al reported that miR-223 could attenuate the inflammatory conditions in bovine endometritis by targeting NLRP3 in vivo and in vitro.<sup>73</sup> In addition, it is worth noting that *Helicobacter pylori* (*H. pylori*) could modulate different immune responses in order to survive. In addition, Pachathundikandi et al reported that *H. pylori* could regulate NLRP3 expression in infected THP-1 monocytes. At the molecular level, the expression levels of hsa-miR-223-3p were significantly increased after *H. pylori* infection; this reduced NLRP3 expression and increased survival.<sup>74</sup> Similarly, Wang et al

demonstrated that miRNA-223 negatively regulated LPS-induced inflammatory responses by targeting NLRP3 in human dental pulp fibroblasts.<sup>75</sup> Another study showed that the miR-223/NLRP3 axis was involved in stromal interaction molecule 1-mediated lung epithelial injury in influenza A virus-induced infection.<sup>76</sup> Furthermore, the expression of miR-155 was up-regulated in *Porphyromonas gingivalis*-induced macrophages and the knockdown of miR-155 could reduce NLRP3 inflammasome-mediated pyroptosis.<sup>77</sup> These studies showed that miRNAs mainly participated in microbial infection by regulating NLRP3 inflammasome pathways. Other components of NLRP3 inflammasomes, such as caspase-1, GSDMD, and IL-1b, along with other inflammasomes such as AIM2, NLRP1, and NLRC4, should also be investigated further. Clinical studies are also needed to demonstrate their value in microbial infection.

As with miRNAs, only a few lncRNAs have been found to be involved in microbial infection by regulating the NF- $\kappa$ B/NLRP3 pathway in vitro. For example, Deng et al showed that lncRNA Gm28309 was involved in regulating inflammation induced by *Brucella*. The overexpression of Gm28309, or the inhibition of miR-3068-5p, repressed p65

phosphorylation and reduced the NLRP3 inflammasome, along with IL-1 $\beta$  and IL-18 secretion, in S2308 *Brucella* strain-induced RAW264.7 cells. Mechanistically, Gm28309 acts as a competing endogenous RNA (ceRNA) for miR-3068-5p to activate the NF- $\kappa$ B pathway by targeting  $\kappa$ B-Ras2, an inhibitor of NF- $\kappa$ B signaling. Moreover, the number of intracellular *Brucella* is higher when Gm28309 is overexpressed or when miR-3068-5p or p65 is inhibited.<sup>78</sup> In addition, lncRNA XIST is abnormally increased in bovine mastitis tissues and inflammatory mammary alveolar cell-T (MAC-T) cells, while silencing of lncRNA XIST significantly increases the expression of *E. coli* or *S. aureus*-induced pro-inflammatory cytokines. Mechanistically, lncRNA XIST is promoted by the activated NF- $\kappa$ B pathway and, in turn, generated a negative feedback loop to regulate the NF- $\kappa$ B/NLRP3 inflammasome pathway, thus mediating inflammation in vitro.<sup>79</sup> These two studies demonstrated that lncRNAs participated in *Brucella*, *E. coli*, or *S. aureus*-induced infection.

From the above research status, the ncRNAs inflammasome pathways in microbial infections are mainly concentrated on miRNAs and NLRP3 inflammasome, and the mechanisms are mainly concentrated on the signal 1 of NLRP3 inflammasome activation (Table 1). However, there is still a lack of research on inflammasomes regulated by circRNAs in microbial infection. Due to its circular structure and the fact that it is not easily degraded, circRNAs are more suitable as biomarkers; studies have shown that circRNA also participated in the inflammasome pathways,<sup>80</sup> and deserved further research attention.

### The Roles of ncRNAs in Inflammasomes Activation in Infection-Induced Acute Organ Failure

**The Roles of ncRNAs in Inflammasomes Activation in ALI**  
An increasing number of studies have shown that the activation of inflammasomes played an important role in ALI, also known as acute respiratory distress syndrome (ARDS). The activation of inflammasomes in both the lung parenchyma and resident immune cells generates IL-1 $\beta$  and IL-18, both of which drive the cascade of lung inflammation forwards.<sup>81</sup>

Some studies have shown that ncRNAs directly targeted the components of inflammasomes in ALI (Table 1). The miR-223, the first miRNA found to target NLRP3, is the most studied miRNA in ALI. For example, Zhang et al reported that the secretion of EVs containing miR-223/142 was robustly enhanced and detectable in bronchoalveolar lavage fluid (BALF) and the serum of lung infection-

associated ALI, and therefore has potential as a biomarker. The miR-223/142 mimics-enriched EVs have been shown to selectively target lung macrophages and suppress the inflammatory responses triggered by LPS or *Klebsiella pneumoniae*. Mechanistically, miR-223 and miR-142 synergistically suppressed the activation of the NLRP3 inflammasome by inhibiting NLRP3 and ASC in LPS-induced macrophages.<sup>19</sup> At present, the most commonly used animal models of ALI are LPS-induced and trauma-induced as pathogen associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs)-induced ALI, respectively. The miR-223 was found to exert a treatment effect in trauma-induced ALI. Feng et al demonstrated that miR-223 expression was increased in the lungs of mitochondrial DAMPs (MTDs)-induced mice or ARDS patients following trauma/ transfusion or following the physiological remission of ALI/ ARDS and miR-223 produced by Ly6G+ neutrophils. This could limit the number of Ly6G+ neutrophils and inhibit the activity of the NLRP3 inflammasome in a negative feedback manner to alleviate MTDs-induced ALI in miR-223 -/+ mice, thus regulating the pathogenesis of DAMPs-induced ALI.<sup>82</sup> However, one study described low expression levels of miR-7b in NR8383 cells and lung tissues from LPS-induced mice, with no significant difference detected with regards miR-223. The authors also showed that silencing of the up-regulated lncMEG3 could alleviate LPS-induced ALI by acting as a molecular sponge for miR-7b to modulate NLRP3 directly in LPS-induced mice and LPS-induced mouse alveolar macrophage NR8383.<sup>83</sup> This difference may be due to the induction of different stimuli; however, more research is needed to verify this in clinical samples.

Furthermore, several studies have shown that miRNAs could target other components of inflammasomes or molecules upstream of inflammasomes in ALI except for NLRP3. TLR4, as an essential LPS signaling receptor, can activate NF- $\kappa$ B and participate in many inflammatory diseases.<sup>84</sup> For instance, Yang et al suggested that NF- $\kappa$ B, the NLRP3 inflammasome, and inflammatory factors, were reduced by miR-16 by directly targeting TLR4 in LPS-induced ALI mice and A549 cells.<sup>85</sup> In addition, Shikano et al conducted a microarray of EVs isolated from the BALF of LPS-induced ARDS mice and demonstrated increased expression levels of the miRNA-466 family. Mechanistically, miRNA-466g and 466m-5p affected the priming pathway by up-regulating pro-IL1b in macrophages, thus exacerbating inflammation in vitro.<sup>20</sup> High

mobility group box 1 (HMGB1), as a molecular of PAMPs, can be released after pyroptosis induced by the inflammasomes that are involved in various inflammatory diseases which in turn can activate inflammasomes.<sup>86,87</sup> A recent study showed that miR-574-5p expression could be induced by the TLR4/NF- $\kappa$ B pathway upon LPS stimulation and in turn, miR-574-5p could suppress the inflammatory response, including the NF- $\kappa$ B signaling pathway and NLRP3 inflammasome activation by targeting HMGB1 in LPS-induced human pulmonary microvascular endothelial cells and ARDS mice, thus forming a negative feedback mechanism.<sup>88</sup> These studies suggest that ncRNAs act on TLR4/NF- $\kappa$ B, pro-IL-1b, and HMGB1, and may also represent therapeutic targets.

Other studies have shown that miR-223 and miR-199a-3p could attenuate LPS-induced cell injury in LPS-induced A549 cells. For example, miR-223 was shown to be involved in LPS-induced ALI by reducing inflammation. At the molecular level, miR-223 could suppress the NLRP3 inflammasome by targeting NLRP3 directly and the TLR4/NF- $\kappa$ B signaling pathway via RHOB *in vitro*.<sup>89</sup> Activation of the NLRP1 has also been demonstrated in ALI; for example, microarray analysis showed that miR-199a-3p was significantly downregulated in ALI lung tissues. The downregulation of miR-199a-3p has also been shown to induce the activation of NLRP1 and the cleavage of pro-IL-1 $\beta$  and pro-IL-18 by targeting NLRP1 directly, thus aggravating the inflammatory response in LPS-induced A549 and the human macrophage cell line U937.<sup>90</sup> These studies demonstrated that ncRNAs could represent potential therapeutic targets for ALI.

**The Roles of ncRNAs in Inflammasomes Activation in ALF**  
ALF is a rapid and severe clinical syndrome characterized by the activation of intense inflammatory responses and the extensive death of hepatocytes, thus resulting in organ dysfunction and failure. Ongoing evidence describes a pivotal role for inflammasomes in this intense inflammatory response.<sup>91,92</sup> Intraperitoneally injections of LPS and D-GalN are usually used to establish a mouse model of LPS/GalN-induced ALF, also known as endotoxin acute hepatitis (EAH). So far, only a few studies have proved that ncRNAs have therapeutic effects on ALF, including miR-223-3p and miR-17 (Table 1). Calvente et al showed that the synthetic miR-223 analog miR-223 3p could attenuate LPS/D-GalN-induced liver injury by negatively regulating the NLRP3 inflammasome in LPS/D-GalN-induced EAH mice.<sup>93</sup> In addition, TXNIP acts as

a regulator of thioredoxin and can bind to NLRP3 via the leucine-rich repeat domain. A lack of TXNIP impairs activation of the NLRP3 inflammasome and subsequent IL-1 $\beta$  secretion.<sup>94</sup> Liu et al demonstrated that the administration of adipose mesenchymal stem cell exosome (AMSC-Exo), co-localized with hepatic macrophages, significantly ameliorated ALF as determined by reduced serum levels of alanine aminotransferase and aspartate aminotransferase and hepatic inflammasome activation in LPS/GalN-induced ALF mice. Mechanically, AMSC-derived exosomes containing miR-17 could alleviate LPS/GalN-induced ALF by the miR-17-mediated reduction of TXNIP/NLRP3 inflammasome activation in macrophages *in vivo* and *in vitro*.<sup>25</sup> These two studies prove that miR-223-3p and AMSC-Exo with miR-17 may represent promising methods for the treatment of ALF.

### The Roles of ncRNAs in Inflammasomes Activation in Sepsis-Induced AKI and Heart Dysfunction

Several studies have shown that ncRNAs participate in sepsis-induced AKI and sepsis-induced heart dysfunction by regulating inflammasomes; this process is also closely related to the amplification of excessive inflammation (Table 1). Autophagy dysfunction can lead to diseases with hyperinflammation and the excessive activation of NLRP3 inflammasome, thus acting as a major regulator of inflammasomes. More importantly, autophagy has a protective role in some inflammatory diseases associated with the NLRP3 inflammasome;<sup>95</sup> this needs to be investigated further. A recent study showed that lncRNA ZFAS1 was highly expressed in sepsis-induced heart dysfunction *in vivo* and in an *in vitro* model. The knockdown of lncRNA ZFAS1 robustly abolished LPS-induced pyroptosis and attenuated the inhibition of autophagy *in vivo* and *in vitro*. Mechanistically, lncRNA ZFAS1 regulated autophagy and the NLRP3 inflammasome-mediated pyroptosis of cardiomyocytes by AMPK/mTOR signaling by sponging miR-590-3p.<sup>96</sup>

Several studies have focused on AKI from the perspective of ncRNAs and the activation of the NLRP3 inflammasome. For example, Tan et al demonstrated that lncRNA DLX6-AS1 was up-regulated in serum samples from septic AKI patients and in LPS-induced HK-2 cells. Mechanistically, lncRNA DLX6-AS1 mediated LPS-mediated cytotoxicity and pyroptosis in HK-2 via the miR-223-3p/NLRP3 axis.<sup>97</sup> In addition, a recent study showed that lncRNA RMRP was upregulated in sera from patients with AKI and in LPS-induced HK-2 cells



and could promote inflammation by activating the NLRP3 inflammasome *in vitro*, thus providing a potential strategy for treating AKI.<sup>98</sup> However, this study did not explain the specific mechanism by which lncRNA RMRP promoted NLRP3 activation. These two studies showed that lncRNA DLX6-AS1 and lncRNA RMRP had the potential to be biomarkers and might exert therapeutical effects. Furthermore, another study showed that lncRNA Kcnq1ot1 was upregulated in sC5b-9-induced podocytes, and that silencing Kcnq1ot1 could inhibit the effect of sC5b-9 on podocyte pyroptosis via a ceRNA mechanism by sponging miR-486a-3p which could bind directly to NLRP3. This might facilitate podocyte-targeted treatment for renal inflammatory diseases.<sup>99</sup> Furthermore, ncRNAs/inflammasomes pathways might represent the downstream targets for drugs in the treatment of AKI. For example, baicalin, a traditional Chinese medicine, could attenuate LPS-induced renal tubular epithelial cell injury by inhibiting the TXNIP/NLRP3 signaling pathway by increasing miR-223-3p expression in LPS-induced HK-2 cells.<sup>100</sup>

These studies indicate that ncRNAs are involved in multiple organ injury by regulating the activation of inflammasomes via diverse targets, including NLRP3, TLR4, pro-IL-1b, HMGB1, NLRP1 and TXNIP (Table 1). In addition, these studies showed that ncRNAs have therapeutic potential for microbial infection and tissue injury, although further research is needed to apply these in the clinic. Furthermore, with regards to the regulation of ncRNAs, the NLRP3 inflammasome pathway is the best investigated; very little is known about the involvement of other inflammasomes. Given the presumably large amounts of DNA released by dying cells during microbial infection and tissue injury, it is largely expected that the AIM2 inflammasome could play a role. Furthermore, the noncanonical inflammasome can also be activated in microbial infection and tissue injury. Further studies relating to ncRNAs in microbial infection and tissue injury should also feature inflammasomes.

## The Roles of ncRNAs in Inflammasomes Activation in Sterile Inflammatory Diseases

Autoimmune diseases, autoinflammatory diseases (AIDs), and allergic diseases are common aseptic inflammatory diseases in recent years. These diseases are all caused by abnormal immune responses without microbial infection, but differences exist among these three diseases. Autoimmune diseases are characterized by an immune

response that inappropriately targets the body's own healthy organs.<sup>101</sup> AIDs are disorders of the innate immune system characterized by recurrent systematic inflammation and serious complications. Allergic diseases refer to a group of diseases caused by abnormal immune response of the body to harmless foreign substances, resulting in harm to the body. The main distinction between autoimmune diseases and AIDs is that autoimmune diseases are typically defined by a malfunction of the adaptive immune system while in AIDs the innate immune system is affected, which lacks autoantibodies and no antigen-specific T cells are involved.<sup>102</sup> The difference of autoimmune diseases and allergic diseases is that an autoimmune disease is an immune response of the immune system against itself, while an allergic disease is an immune response against substances outside the body.<sup>103</sup> In addition, GVHD is a significant challenge for all patients receiving allografts which deserves our attention. Although the etiology are different, abnormal immune responses can cause tissue and organ damage and threaten the health of body. In addition, it has been found that the activation of inflammasomes plays an important role in these diseases in recent years.<sup>103–105</sup> Intriguingly, ncRNAs are emerging as the new inflammasome regulatory molecules. The following summarizes the role of ncRNAs in these sterile inflammatory diseases by regulating inflammasomes.

### The Roles of ncRNAs in Inflammasomes Activation in Autoimmune Diseases

Autoimmune diseases were initially considered to be rare; however, rigorous epidemiological studies have now demonstrated that autoimmune diseases affected 3–5% of the population.<sup>101</sup> More importantly, there are almost 100 distinct autoimmune diseases, some of which are organ-specific such as primary biliary cirrhosis and some of which reflect a variety of immunological dysfunctions involving multiple organs, such as systemic lupus erythematosus (SLE); these conditions are associated with a poor prognosis and most of the current treatment drugs have certain side effects.<sup>106</sup> Therefore, there is an urgent need to explore the molecular mechanisms of autoimmune diseases, the chronic and systemic inflammatory disorders characterized by dysfunction of the immune system, and ultimately the loss of immunological self-tolerance, to identify new therapeutic targets. Recent research found that active inflammasomes can trigger a series of inflammatory cascades and lead to the differentiation and

polarization of naïve T cells and the secretion of various cytokines, thus inducing various types of autoimmune diseases,<sup>105</sup> such as SLE, rheumatoid arthritis (RA), systemic sclerosis (SSc) and inflammatory bowel disease (IBD).<sup>107</sup> Interestingly, an increasing number of studies have shown that ncRNAs regulated the activation of inflammasomes in autoimmune diseases (Table 1).

Several miRNAs are known to exert their function by directly targeting NLRP3 in autoimmune diseases. For example, miR-223 has been reported to be involved in various diseases by directly targeting NLRP3, including IBD and autoimmune myocarditis (EAM). Neudecker et al demonstrated that levels of miR-223 were increased in intestinal biopsies from patients with active IBD and in preclinical models of intestinal inflammation. The miR-223<sup>-y</sup> mice presented with exacerbated myeloid-driven experimental colitis with heightened clinical, histopathological, and cytokine readouts.<sup>108</sup> In addition, Chen et al reported that the transfer of miR-223-3p-overexpressing dendritic cells DCs protected mice against the development of EAM. Mechanistically, miR-223-3p inhibited the expression of the NLRP3 inflammasome expression, thus promoting the polarization of DCs towards a tolerogenic DC phenotype and regulatory T cell (Treg) generation.<sup>109</sup> In addition, Tan et al reported that let-7f-5p was up-regulated in bone marrow-derived mesenchymal stem cells (BMSCs) from systemic lupus erythematosus patients (SLE-BMSCs) and that let-7f-5p could attenuate inflammation in SLE-BMSCs by targeting NLRP3, at least in part, thus representing a promising therapy for SLE.<sup>110</sup>

In addition, NF- $\kappa$ B is a critical transcription factor that induces pro-IL-1 $\beta$  and upregulates the synthesis of NLRP3.<sup>70</sup> TRAF6 and IRAK1 are key proteins in the TLR/NF- $\kappa$ B pathway. Zhang et al observed significant increases in paw swelling and index and ankle joint swelling in miR-146a knockout mice when compared with WT controls in a monosodium urate (MSU)-induced gouty arthritis model. At the molecular level, miR-146 knockout could increase inflammatory response and up-regulate NLRP3 expression partly by targeting TRAF6 and IRAK1.<sup>22</sup> In addition, Luo et al suggested that miR-155 expression levels were significantly increased in an in vivo model of psoriasis when compared with normal tissues; the silencing of miR-155 was confirmed to significantly reduce psoriasis-associated inflammatory responses and NLRP3/caspase-1 signaling in vitro.<sup>111</sup>

Furthermore, in vitro experiments have also demonstrated the therapeutic potential of miR-33 and miR-20a

in autoimmune diseases. ROS can stimulate tissue inflammation and induce NLRP3 inflammasome activation as signal 2 (Figure 3). For instance, Xie et al reported that miR-33 impaired mitochondrial oxygen consumption rates, resulting in the accumulation of cellular ROS; this stimulated NLRP3 expression, caspase-1 activity, and IL-1 $\beta$  secretion, in primary macrophages. The miR-33 levels and NLRP3 inflammasome activity were increased in peripheral blood monocytes from patients with rheumatoid arthritis (RA) compared with healthy donors, thus indicating that the miR-33/NLRP3 inflammasome pathway might be involved in RA development.<sup>24</sup> In addition, RA is a heterogenic and systemic autoimmune disease characterized by synovitis and joint structural damage. As described earlier, TXNIP is a key protein that activates the NLRP3 inflammasome. Xu et al reported that the overexpression of miR-20a could reduce the activation of the NLRP3 inflammasome by targeting TXNIP directly in primary fibroblast-like synoviocytes (FLSs) isolated from adjuvant-induced arthritis (AA), which might be a treatment for RA.<sup>26</sup> These studies showed that miRNAs had the potential to treat autoimmune diseases.

Crosstalk has been identified between inflammasomes and autophagy, both of which have been shown to be regulated by lncRNAs. Xue et al showed that lincRNA-Cox2 was also involved in EAM and identified a link between lincRNA-Cox2 and the crosstalk between inflammasomes and autophagy in macrophages and microglia. These authors found that lincRNA-Cox2 bound directly to NF- $\kappa$ B p65 to promote p65 transfer from the cytoplasm to the nucleus, thus modulating the expression of the inflammasome sensor NLRP3 and the adaptor ASC. The knockdown of lincRNA-Cox2 inhibited the activation of inflammasomes and prevented the lincRNA-Cox2-triggered activation of caspase-1, thus leading to reduced levels of IL-1 $\beta$  secretion and weakened TIR-domain-containing adapter-inducing interferon- $\beta$  (TRIF) cleavage, thereby enhancing TRIF-mediated autophagy in LPS-induced microglial cells and BMDMs. These results identified a role for lncRNAs in NLRP3 inflammasome activation and autophagy, thus providing new opportunities for therapeutic intervention in neuroinflammation-dependent diseases. Furthermore, these authors also reported that the knockdown of lincRNA-Cox2 provided a protective effect from experimental autoimmune encephalomyelitis, a notable increase in resting microglia, the inhibition of IL-1 $\beta$  secretion, and enhanced autophagy in the central nervous system.<sup>48</sup>

Collectively, these studies showed that ncRNAs regulated inflammasome pathways to play an important role in autoimmune diseases and provided a foundation for us to investigate the molecular mechanisms involved so that we can elucidate new forms of treatment. However, most of the current researches on the ncRNAs-inflammasome pathways in autoimmune diseases mainly focus on the NLRP3 inflammasome (Table 1). In recent years, it has been found that other inflammasomes also play an important role in autoimmune diseases. For instance, two ALR family members, the interferon (IFN)-inducible protein 16 (IFI16) and AIM2, have been linked to the pathogenesis of various autoimmune diseases where it triggers production of specific autoantibodies. Following interaction with cytoplasmic or nuclear nucleic acids, ALRs can form a functional inflammasome and produce IL-1 $\beta$  and IL-18 positively correlates with diverse autoimmune diseases severity.<sup>113</sup> Therefore, targeting ALR sensors and their downstream pathways by ncRNAs also represents a promising alternative therapeutic approach for autoimmune diseases. In addition, literature relating to lncRNAs and relevant circRNAs are sparse. In view of the important regulatory role of lncRNAs and circRNAs in cell biological processes, there is an urgent need for researchers to focus on this field in future.

## The Roles of ncRNAs in Inflammasomes Activation in Autoinflammatory Diseases

The name “autoinflammatory diseases (AIDs)” was proposed in 1999 by McDermott et al.<sup>114</sup> Since its initial definition more than 30 new genes associated with autoinflammatory diseases have been identified, affecting different parts of the innate immune system. Depending on their molecular mechanism, AIDs can be separated into inflammasomopathies or IL-1 $\beta$ -activation syndromes (Familial Mediterranean Fever (FMF), NLRP3-AID, Mevalonate kinase deficiency (MKD), deficiency of the IL-1 receptor antagonist, deficiency of IL-36 receptor antagonist), protein-folding disorders (TNF receptor-associated periodic syndrome), NF- $\kappa$ B-activation disorders (Blau syndrome), interferonopathies (Aicardi-Goutières syndromes), and other cytokine-signaling disorders and complementopathies (ie: paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome). In this review, we will mainly discuss inflammasomopathies.<sup>115</sup> Among these inflammasomopathies, the most common diseases are FMF, NLRP3-AIDs (formerly known as Cryopyrin

associated periodic syndromes - CAPS) and MKD which are all associated with inflammasomes hyperactivation. Additionally, these diseases are all belong to monogenic AIDs. Some polygenic or multifactorial AIDs have been also found, like systemic juvenile idiopathic arthritis (sJIA), which are more complex. They arise from permutations and combinations of common gene variants, where each variant alone confers only a small risk but together or with other extraneous influences becomes pathogenic.<sup>115</sup> More importantly, sJIA was found due to a CASP1 variant causing inflammasomes hyperactivation recently.<sup>116</sup> Dysregulation of inflammasomes and overproduction of IL-1 play a major role in the pathogenesis of these auto-inflammatory diseases, including FMF, NLRP3-AIDs and sJIA which will be discussed below.<sup>117</sup> Notably, ncRNAs as important regulators of inflammasomes have the potential as diagnostic biomarkers and therapeutic targets for autoinflammatory diseases. Advances in our understanding of the role of ncRNAs in the autoinflammatory diseases might result in new treatment strategies.

FMF is an inherited autosomal recessive autoinflammatory disease caused by mutations in the MEditerranean FeVer (MEFV) gene. MEFV gene encodes the protein pyrin, the core of pyrin inflammasomes, whose activation result in FMF. Notably, many FMF patients with similar genotypes can express different disease phenotypes. These differences in disease phenotype can be explained by modifying genes, epigenetic factors, or environmental effects. As important epigenetic modifiers, ncRNAs were found to be involved in the occurrence of FMF. For example, Wada et al observed specific miRNA patterns in different subgroups dependent on MEFV mutations.<sup>118</sup> In addition, Akkaya-Ulum et al performed a miRNA array on whole blood RNA samples from 6 healthy controls (-/-), 6 FMF patients (M694V/M694V), 6 carriers who displayed the disease phenotype (M694V/-) and 6 healthy carriers (M694V/-), founding that miR-20a-5p was significantly up regulated whereas miR-197-3p was down regulated in homozygotes patients and both let-7d-3p and miR-574-3p were up regulated in heterozygote patients group. What's more, these miRNAs were found to be associated with inflammatory pathway related genes according to DAVID analysis.<sup>119</sup> Similarly, Amariyo et al performed the study to identify miRNAs expression profile in the peripheral blood of 10 M694V homozygous FMF patients and 10 healthy controls, founding four miRNAs were upregulated (miR-144-3p, miR-21-5p, miR-4454, and miR-451a), and three were downregulated (miR-107, let-7d-5p, and miR-

148b-3p) compared to healthy controls.<sup>120</sup> What's more, Hortu et al evaluated the role of fifteen miRNAs that were found to be associated with autoinflammatory diseases and have a part in immune response were evaluated in 51 patients with genetically diagnosed FMF who had clinical symptoms and 49 healthy volunteers. They found 11 miRNAs (miR-125a, miR-132, miR-146a, miR-155, miR-15a, miR-16, miR-181a, miR-21, miR-223, miR-26a, and miR-34a) in the patient group were significantly down-regulated compared with the control group and 5 miRNAs (miR-132, miR-15a, miR-181a, miR-23b, miR-26a) in the patients who took colchicine seemed to be up-regulated and 5 miRNAs (miR-146a, miR-15a, miR-16, miR-26a, miR-34a) in the patients who took colchicine were significantly down-regulated, indicating the important role of miRNAs in the pathogenesis of FMF.<sup>121</sup> Thus, a number of studies have proved that miRNAs are differentially expressed in FMF patients and controls, indicating that these miRNAs play an important role in FMF, which may be related to the activation of pyrin inflammasomes, but these studies have no further mechanisms and functional verification. Intriguingly, a study conducted by Akkaya-Ulum et al showed that miR-197-3p was decreased in FMF patients compared with controls and miR-197-3p could target IL1R1 gene and suppress cell migration, IL-1b secretion, caspase-1 activation and apoptosis in monocytes and synovial fibroblasts, indicating a promising treatment target in FMF.<sup>122</sup> Therefore, in the future, more research is needed to explore the role of ncRNAs in FMF, finding potential biomarkers and therapeutic targets.

For other monogenic inflammasomopathies, research on ncRNAs is still vacant, such as CAPS, MKD, NLRP1 and NLRC4 inflammasome related AIDs.<sup>123,124</sup> It has been found that targeting components of inflammasomes directly or inhibiting their activation has promising preventive or therapeutic effects on these inflammasomopathies.<sup>125</sup> Therefore, discovered ncRNAs which can directly target components of inflammasomes (Figure 3), all have the potential as new targets for inflammasomes mediated AIDs. In addition, increasing studies have found ncRNAs can regulate other inflammasomes except NLRP3. For instance, miR-590-3p and miR-9a-5p could inhibit NLRP1 mediated inflammasomes activation in diabetic retinopathy and ischemic stroke-induced brain injury respectively by targeting NLRP1 directly.<sup>126,127</sup> Moreover, lncRNA Neat1 associates with the NLRP3, NLRC4, and AIM2 inflammasomes in mouse macrophages to enhance

their assembly and subsequent pro-caspase-1 processing.<sup>10</sup> Future studies can verify the role of these potential ncRNAs in various inflammasomes mediated AIDs.

About sJIA, a kind of polygenic AIDs, is characterized by the overexpression of inflammasome-associated genes, leading to a dysregulation of the innate immune response, with a severe complication of macrophage activation syndrome (MAS).<sup>128</sup> Notably, sJIA and recurrent MAS were found due to a CASP1 variant causing inflammasomes hyperactivation.<sup>116</sup> Notably, two studies showed the correlation between miRNAs and sJIA. A microarray profile was performed in the plasma of patients with sJIA and healthy controls, founding 48 differential expressional miRNAs. Further they demonstrated that miR-26a was expressed specifically and highly in sJIA plasma and suggested that miR-26a might regulate the levels of cytokines in sJIA.<sup>129</sup> In addition, it was found that miRNAs could contribute to monocyte/macrophage polarization with resulting consequences on MAS development.<sup>130</sup> The study performed by Do et al showed that miR-125a-5p and miR-181c were elevated in active sJIA, significantly reducing macrophage CD163 expression through 2 distinct mechanisms. MiR-181 species directly targeted CD163 mRNA for degradation and overexpression of miR-181c inhibited CD163 anti-inflammatory responses to hemoglobin or HMGB1 complexes. In contrast, miR-125a-5p could function indirectly, as transcriptome analysis of miR-125a-5p overexpression identified "cytokine-cytokine receptor interactions" as the most significantly repressed gene pathway, including decreased IL10RA, required for IL-10-mediated CD163 expression. Their data showed that miRNAs utilized multiple mechanisms to integrate well-characterized polarization phenotypes and regulate macrophage functional properties seen in sJIA.<sup>131</sup> These studies show that ncRNAs have the potential as biomarkers and therapeutic targets. In the future, we need to pay attention to whether ncRNAs can regulate inflammasomes activation in sJIA.

What's more, other disease entities, such as Kawasaki disease and idiopathic recurrent pericarditis disease, gout or calcium pyrophosphate deposition disease are also believed to be related to polygenic AIDs.<sup>128</sup> AIDs are an expanding spectrum of diseases, and more effort is needed to understand the pathogenesis.

The incidence of AIDs is rising, and diagnosis of AIDs is often based on clinical presentation and genetic testing and the timeline from onset to diagnosis takes up to 7.3



years, highlighting the indisputable need to identify new treatment and diagnostic targets.<sup>115</sup> ncRNAs, as important regulators in the activation of inflammasomes, are worthy of attention by researchers.

### The Roles of ncRNAs in Inflammasomes Activation in Allergic Diseases

The incidence of allergic diseases is getting higher and higher, and it seriously affects people's quality of life. In recent years, it has been found that a variety of allergic diseases are related to the activation of inflammasomes, such as asthma, rhinitis, dermatitis and conjunctivitis,<sup>102,132</sup> mainly about NLRP3 inflammasome. Moreover, NLRC4 was also found to be up-regulated in neutrophilic asthma,<sup>133</sup> and Wang et al reported that AIM2 inflammasome was activation in murine allergic rhinitis (AR) and might mediate HMGB1 release.<sup>134</sup> What's more, honey bee venom could induce AIM2 inflammasome activation in human keratinocytes, which might promote subsequent allergic responses.<sup>135</sup> Therefore, targeting the activation of these inflammasomes helps to reduce the inflammatory response, thereby reducing the damage caused by allergies. Several studies showed that ncRNAs could regulate NLRP3 inflammasomes activation in AR as promising treatment targets. For example, Yu et al reported that they found a novel *has\_circ\_0000520* was up-regulated and *miR-556-5p* was down-regulated in AR patients and mice compared with controls, further proving that *has\_circ\_0000520* ablation and *miR-556-5p* overexpression could suppress NLRP3-mediated cell pyroptosis to attenuate AR in mice models. Mechanistically, *miR-556-5p* targeted both *has\_circ\_0000520* and 3'-untranslated region (3'-UTR) of NLRP3, and knockdown of *has\_circ\_0000520* inactivated NLRP3-mediated epithelium pyroptosis through *miR-556-5p* in a ceRNA-dependent manner.<sup>136</sup> In addition, two studies showed miRNAs could attenuate the symptoms of AR in mice by regulating NLRP3 inflammasome. Wu et al showed that *miR-224-5p* was significantly decreased in nasal mucosa of AR mice and overexpression of *miR-224-5p* markedly attenuated sneezing and nasal rubbing events, IgE level in serum, and pathological alterations in nasal mucosa. Mechanistically, *miR-224-5p* treatment could remarkably suppress NLRP3 inflammasome activation and TLR4/MyD88/NF- $\kappa$ B pathway in AR mice by targeting TLR4 directly.<sup>137</sup> Similarly, the study conducted by Xiao et al showed that *miR-133b* ameliorated allergic inflammation and symptoms by targeting NLRP3 directly in AR

mice.<sup>138</sup> These three studies demonstrate the therapeutic potential of ncRNAs in AR by regulating NLRP3 inflammasomes activation.

There are only a few studies regarding ncRNAs-inflammasome pathways in allergic diseases. As the activation of different inflammasomes has been continuously discovered to play an important role in allergic diseases, the role of ncRNAs in allergic diseases by regulating the activation of inflammasomes should also receive our attention.

### The Roles of ncRNAs in Inflammasomes Activation in GVHD

GVHD is a significant challenge for all patients receiving allografts; improvement in the outcomes of GVHD has been the primary reason for the reduction in non-relapse mortality over time.<sup>139</sup> Thus, it is critical that we gain a better understanding of the mechanisms that underlie immune rejection. A growing body of evidence suggests that immune tolerance is an ideal state for patients with GVHD. DCs, the most potent form of antigen-presenting cells (APCs), are central mediators in immune tolerance. Gaining an improved understanding of the molecular mechanisms involved in the induction of tolerance-DCs (tol-DCs) will help us to identify important targets for treatment.<sup>140</sup> Intriguingly, several studies have demonstrated the crucial role for inflammasomes in the pathogenesis of GVHD and have provided a potential new avenue for the targeted therapy of this severe complication.<sup>141–143</sup>

Recent studies have shown that lncRNA NEAT1 and *miR-155* were involved in tol-DCs by targeting NLRP3 inflammasomes (Table 1). Zhang et al found that lncRNA NEAT1 served as a ceRNA by sponging *miR-3076-3p* and could induce immune tolerance by targeting NLRP3 in DCs. The knockdown of lncRNA NEAT1 has also been shown to induce immune tolerance in mouse models of EAM and heart transplantation, thus indicating that lncRNA NEAT1 may be a promising therapeutic target for immune-related diseases.<sup>140</sup> Moreover, Chen et al reported that the expression levels of *miR-155* were up-regulated in LPS-stimulated DCs and that *miR-155* deficiency in the recipient could alleviate acute GVHD. At the molecular level, *miR-155*-deficient dendritic cells cause less severe GVHD by reducing migration and defective activation of the NLRP3 inflammasome.<sup>143</sup> However, published research in this area is very limited and requires further attention.



## The Roles of ncRNAs in Inflammasomes Activation in Other Sterile Inflammatory Diseases

Several studies have shown that miRNAs and lncRNAs are involved in osteoarthritis (OA) by regulating NLRP3 inflammasomes (Table 1). For example, Zhou et al used a model of anterior cruciate ligament transection (ACLT)-induced osteoarthritis (OA) and performed differential miRNAomics analysis of the synovial membrane in knee osteoarthritis (KOA) induced by ACLT in rats. These authors found that miR-233 regulated NLRP3 inflammasomes by directly suppressing the NLRP3 3'-UTR and was implicated in synovial membrane injury; this may be an important mechanism underlying the pathogenesis of KOA.<sup>144</sup> Similarly, another study reported that sinomenine (SIN) could represent a potential target for the treatment of OA via a similar mechanism. In another study, Dong et al demonstrated that the administration of SIN markedly improved the degradation of articular cartilage in ACLT-induced OA mice, downregulated the levels of inflammatory cytokines and the protein expression of the components within the NLRP3 inflammasome, and upregulated the expression of miR-223-3p in OA mice and IL-1 $\beta$ -stimulated chondrocytes. At the molecular level, the overexpression of miR-223-3p blocked apoptosis and the inflammatory response in chondrocytes by directly targeting NLRP3 in vitro, thus highlighting SIN as a potential target for the treatment of OA.<sup>145</sup> These two studies both focused specifically on the miR-223/NLRP3 pathway.

In contrast, two other studies investigated the effect of lncRNA SNHG7 in OA. However, these authors arrived at the opposite conclusion. Wang et al demonstrated that the downregulation of lncRNA SNHG14 could inhibit the FSTL-1-mediated activation of the NLRP3 and TLR4/NF- $\kappa$ B signaling pathways by targeting miR-124-3p in a rat model of OA by destabilizing the medial meniscus and IL-1 $\beta$ -induced chondrocytes, thus attenuating inflammatory reactions in OA. Follistatin-like Protein 1 (FSTL-1) is a TGF- $\beta$  super-family binding protein that can enhance the transcription of NLRP3 and procaspase 1 genes in the NLRP3 inflammasome.<sup>146</sup> However, one recent study showed that lncRNA SNHG7 was significantly downregulated while miR-214-5p was significantly upregulated in OA patients and IL-1 $\beta$ -induced primary chondrocytes; lncRNA SNHG7 were shown to prevent IL-1 $\beta$  induced OA by inhibiting the NLRP3 inflammasome and apoptosis via the miR-214-5p/PPARGC1B axis in vitro. Mechanistically, lncRNA SNHG7 serves as a competitive endogenous RNA by sponging miR-214-5p

which targets PPARGC1B.<sup>147</sup> PPARGC1B is able to activate PPAR $\gamma$  and has been identified as an anti-inflammatory protein in many diseases and functions by inhibiting the activation of p38 and the NF- $\kappa$ B pathway, as well as the NLRP3 inflammasome. Thus, the effect of lncRNA SNHG7 in OA needs further research attention.

Furthermore, miR-148a have been associated with alcoholic hepatitis (AH). Heo et al performed miRNA profiling and PCR analysis and identified a substantial reduction in the levels of miR-148a in the liver of patients with AH, further highlighting that alcohol decreases the levels of miR-148a expression in hepatocytes via FoxO1, thus facilitating TXNIP overexpression and the activation of the NLRP3 inflammasome; these processes induced hepatocyte pyroptosis in vivo and in vitro.<sup>27</sup>

Collectively, these studies demonstrated that ncRNAs played an important role in OA, and AH, and are therefore promising therapeutic targets. However, most of the existing research has focused on the direct targeting of NLRP3 by miRNAs. Very few studies have investigated the potential role of lncRNAs and circRNAs.

## The Roles of ncRNAs in Inflammasomes Activation in Fibrosis Related Diseases

Fibrosis can exert a severe effect on the function of organs, such as the lungs, liver, and heart, and are involved in the occurrence and development of a variety of diseases; excessive inflammation is a key factor in fibrosis. Excessive inflammation promotes fibrosis and aggravates the disease progression. In recent years, studies have shown that inflammasomes promote the progression of fibrosis and that regulating the activation of inflammasomes can improve the degree of fibrosis.<sup>148,149</sup> It is noteworthy that ncRNAs can regulate the inflammasomes involved in fibrosis-related diseases, particularly hepatic fibrosis and lung fibrosis (Table 1).

There are several studies relating to the regulatory effects of ncRNAs on inflammasomes in hepatic fibrosis. For example, Spry1 (Protein sprouty homolog 1) has been shown to inhibit the ERK/NF- $\kappa$ B pathway while Smad2/3 has been shown to mediate NOX4-derived ROS production.<sup>150</sup> Ning et al reported that circulating mir-21 was upregulated in patients with liver fibrosis. At the molecular level, mir-21 can mediate AngII-activated NLRP3 inflammasomes and resultant collagen production via the Spry1/ERK/NF- $\kappa$ B and Smad7/Smad2/3/NOX4 pathways by targeting Spry1 and Smad7 directly. Ang-

(1-7) has been shown to protect against BDL or AngII infusion-induced hepatic fibrosis and inhibit mir-21 expression in vivo and in vitro.<sup>151</sup> Moreover, it has been reported that miRNAs could also directly target GSDMD, the executive molecule for inflammasome activation. The overexpression of miR-379-5p blocks the arsenite-induced increase in GSDMD levels and the release of IL-1 $\beta$  by targeting GSDMD directly in arsenite-induced hepatocytes, thus revealing a new molecular mechanism for arsenite-induced liver damage, inflammation, and fibrosis.<sup>21</sup> In addition, one lncRNA was found to exert a function in hepatic fibrosis by regulating the NF- $\kappa$ B/NLRP3 pathway. Silencing lnc-Lfar1 by a lentivirus-shRNA was found to alleviate CCl<sub>4</sub>- and BDL-induced proinflammatory M1 macrophage activation and NLRP3 inflammasome-mediated pyroptosis while in vitro experiments demonstrated that the knockdown of lnc-Lfar1 significantly suppressed the LPS- and IFN- $\gamma$ -induced proinflammatory activation of macrophages and inhibited LPS/ATP- and LPS/Nigericin-induced NLRP3 inflammasome-mediated pyroptosis. Mechanistically, lnc-Lfar1 regulated the LPS- and IFN- $\gamma$ -induced proinflammatory activation of macrophages through the NF- $\kappa$ B pathway,<sup>152</sup> thus providing a potential therapeutic target against inflammation-related disorders, including hepatic fibrosis. Therefore, these studies indicated that ncRNAs regulation by suitable means had great potential for the development of therapy against hepatic inflammation/fibrosis. In addition, increasing studies have showed that ncRNAs could attenuate liver fibrosis by regulating inflammation in animal model of hepatic fibrosis related diseases. For example, miR-378 expression was increased in livers of dietary obese mice and patients with non-alcoholic steatohepatitis (NASH) and liver-specific expression of miR-378 triggered the development of NASH and fibrosis by activating TNF $\alpha$  signaling.<sup>153</sup> Moreover, miR-223 was highly elevated in hepatocytes in high-fat diet (HFD)-fed mice and in human NASH samples. Genetic deletion of miR-223 induced a full spectrum of non-alcoholic fatty liver disease in long-term HFD-fed mice including steatosis, inflammation, fibrosis, and hepatocellular carcinoma.<sup>154</sup> Additionally, enforcing the expression of circFBXW4 inhibited hepatic stellate cells activation, proliferation and induced apoptosis, attenuated mouse liver fibrogenesis injury and showed anti-inflammation effect.<sup>155</sup> Furthermore, miR-155 KO mice are protected from alcohol-induced steatosis and inflammation.<sup>156</sup> These ncRNAs have been proved at the animal level to

play an important role in liver fibrosis-related diseases. In the future, new technologies and methods should be explored to target ncRNAs for clinical trials.

Furthermore, three miRNAs have been found to be involved in lung fibrosis by regulating the NLRP3 inflammasome pathway. Sun et al reported that AngII exacerbated bleomycin (BLM)-induced lung fibrosis in rats and elevated the levels of mir-21 and the NLRP3 inflammasome. In contrast, ACE2/Ang (1-7) has been shown to attenuate BLM-induced lung fibrosis, and decreased mir-21 levels and the NLRP3 inflammasome. At the molecular level, mir-21 has been shown to mediate the inhibitory effect of ACE2/Ang (1-7) on the AngII-induced activation of the NLRP3 inflammasome by targeting Spry1 in lung fibroblasts.<sup>157</sup> In addition, LOX1, a receptor for oxidized low-density lipoprotein (oxLDL) in endothelial cells, has been shown to be upregulated in many inflammation-related pathophysiological events.<sup>158</sup> Sun et al reported that the use of mesenchymal stem cell-derived exosomes (MenSC-Exo) significantly improved BLM-induced lung fibrosis and alveolar epithelial cell damage in mice. Mechanistically, MenSCs-Exo was able to transport miRNA Let-7 into recipient alveolar epithelial cells by directly targeting LOX1; this could influence activation of the NLRP3 inflammasome by affecting ROS and mtDNA damage.<sup>159</sup> In addition, FOXO3a is a transcription factor of the O subclass in the forkhead family that inhibits pyroptosis by regulating inflammatory responses, including the inhibition of inflammasome activation.<sup>52,160</sup> Zhou et al revealed that miR-96-targeted FOXO3a expression was identified to be involved in the regulation of NLRP3 inflammasome, serving as an important regulatory mechanism for pathogenesis of carbon black nanoparticle, a core constituent of air pollutants like fine particulate matter (PM<sub>2.5</sub>), -induced pulmonary fibrosis in vitro.<sup>23</sup>

The inflammatory response induced by inflammasomes is an important factor that can lead to fibrosis. Collectively, these studies have shown that targeting ncRNAs may reduce fibrosis by reducing the activation of inflammasomes and therefore represent potential therapeutic targets.

## The Roles of ncRNAs in Inflammasomes Activation in Other Diseases

There are many other diseases that involve the activation of inflammasomes in a process that is regulated by

ncRNAs, including diabetes, atherosclerosis, and cancer. Here, we summarize some of the important research findings related to these disease states so as to provide further inspiration for research targeting inflammation-related diseases.

For example, one study showed that lncRNA Gm15441 could suppress its own antisense transcript TXNIP thus reducing TXNIP-stimulated NLRP3 inflammasome activation in response to PPAR $\alpha$  agonism and fasting; this provided evidence for a mechanism by which PPAR $\alpha$  attenuates the activation of inflammasomes in the liver in response to metabolic stress.<sup>31</sup> Therefore, this lncRNA deserves further research attention. In addition, we should focus on other genes that can regulate inflammasome activation, including SIRT1. SIRT1 is a NAD<sup>+</sup>-dependent protein deacetylase; the induction of this gene is associated with multiple physiological processes, including cellular stress response and the immune response.<sup>161</sup> Mao et al suggested that the transfection of exosomes from human mesenchymal stem cells (hMSCs) containing lncRNA KLF3-AS1 in rats, and the incubation of exosomes containing lncRNA KLF3-AS1 with hypoxic cardiomyocytes, both verified that the overexpression of lncRNA KLF3-AS1 in exosomes could reduce the myocardial infarction (MI) area, decrease cellular apoptosis and pyroptosis, and attenuate the progression of MI. Mechanistically, lncRNA KLF3-AS1 is secreted in exosomes from hMSCs and acts as a ceRNA to sponge miR-138-5p to regulate SIRT1; this inhibits cell pyroptosis and attenuates the progression of MI.<sup>162</sup> Another study showed that SIRT1 could alleviate hepatic ischemia-reperfusion injury via the miR-182-mediated XBP1/NLRP3 pathway in *in vivo* assays carried out in mice in which SIRT1 had been specifically knocked out in the liver, and in *in vitro* assays. Mechanistically, the expression of miR-182 was positively regulated by SIRT1 in a mouse model of hepatic IR injury; miR-182 inhibited the expression of XBP1 by binding to the 3'-UTR of XBP1, thus providing a new perspective on the hepatoprotective mechanisms of SIRT1 in hepatic IR injury.<sup>163</sup> In addition, AIM2 is known to act as a DNA sensor and can be activated by mtDNAs following the mitochondrial damage that occurs in many inflammatory diseases. Liang et al demonstrated that lncRNA MRG3 could regulate the AIM2 inflammasome in cerebral I/R injury. The knockdown of up-regulated lncRNA MEG3 was shown to inhibit OGD/R-induced pyroptosis and inflammation. At the molecular level, the knockdown of lncRNA MEG3 inhibited the expression of AIM2 by sponging miR-485

*in vitro*.<sup>164</sup> Furthermore, some studies have focused on circRNAs and the regulation of inflammasome pathways. In high glucose-induced vascular injury, Cheng et al reported that hsa\_circ\_0068087 was upregulated in HG-induced HUVECs and that the downregulation of hsa\_circ\_0068087 ameliorated TLR4/NF- $\kappa$ B/NLRP3 inflammasome-mediated inflammation and endothelial cell dysfunction under high glucose conditions by sponging miR-197 *in vitro*.<sup>165</sup>

Collectively, through these studies in other non-diseases, the effect of other key molecules on ncRNAs regulating inflammasomes and its role in inflammatory diseases also pay more attention.

## The Crosstalk Among ROS, ncRNAs and Inflammasomes

ROS can stimulate tissue inflammation and induce inflammasomes activation, which is one of the main damage factors in a variety of inflammatory diseases. It was recently shown that NLRP3 might directly sense the presence of ROS produced by normal or malfunctioning mitochondria or indirectly by other activators of NLRP3.<sup>112</sup> For example, mtROS can promote the dissociation of thioredoxin from TXNIP and subsequently increase the interaction between TXNIP and NLRP3, leading to NLRP3 inflammasome activation and IL-1 $\beta$  maturation.<sup>166</sup> In addition, inflammasomes activation-induced pyroptosis can increase the level of ROS further.<sup>167</sup> AND then ROS activate NF- $\kappa$ B which in turn upregulates NLRP3 forming a negative feedback regulation. Notably, it has been discovered that ncRNAs are not only important regulators of the inflammasome pathway, but also have a close regulatory role with ROS in recent years.<sup>168,169</sup> Therefore, knowing the crosstalk among ncRNAs, ROS, inflammasomes helps us further understand the therapeutic potential of ncRNAs in the inflammatory diseases.

ROS can cause differential expression of ncRNAs in a variety of diseases.<sup>163</sup> Whether these ncRNAs can regulate the activation of inflammasomes needs further research. In addition, several studies showed that ncRNAs could regulate inflammasomes activation by regulate ROS. For instance, miR-200a low-expression increased Keap1 to block Nrf2 antioxidant pathway, and then enhanced ROS-driven TXNIP to activate NLRP3 inflammasome.<sup>170</sup> Moreover, Liu et al reported that knockdown of lncRNA XIST could promote NLRP3

inflammasome activation mediated pyroptosis by triggering miR-335/SOD2/ROS signal pathway in A549 cells.<sup>171</sup> Furthermore, miR-33 impaired mitochondrial oxygen consumption rates, resulting in the accumulation of cellular ROS, thus stimulating NLRP3 inflammasomes activation.<sup>24</sup> However, these two studies did not discuss whether ROS was activated by increasing the binding of TXNIP and NLRP3 or NF- $\kappa$ B-mediated transcriptional enhancement of NLRP3. In addition, in addition to NLRP3 inflammasomes, the activation of other inflammasomes such as NLRP1 and AIM2 has also been reported to be involved in ROS. Therefore, ncRNAs may also be involved.<sup>172,173</sup>

Therefore, as ROS is an important mediator of inflammatory diseases and an important activator of inflammasomes, exploring the interaction between ncRNAs and them is more helpful to understand the therapeutic potential of ncRNAs in inflammatory diseases.

## Measures to Target ncRNAs Inflammasomes Pathways in Inflammatory Diseases

Knowing how to target ncRNAs helps us to deeply explore the mechanisms of ncRNAs regulating inflammasomes and their role in inflammatory diseases, and can guide the transition from basic research to clinical practice.

MiRNAs levels can be modulated by utilizing transient transfections of miRNAs mimics or miRNAs antagonists.<sup>14</sup> The most common strategies for controlling lncRNAs expression are antisense oligonucleotides (ASOs) and duplex RNAs.<sup>174</sup> Notably, lncRNAs can act in either the nucleus or cytoplasm, therefore determining the subcellular localization is also important for understanding mechanism and designing strategies for manipulating lncRNAs expression and function. Duplex RNAs are a reliable approach for targeting lncRNAs in the cytoplasm and inhibiting gene expression. Whereas it has been shown that ASOs are more reliable gene silencing agents than duplex RNAs for RNAs that are localized to cell nuclei. The silencing of circRNAs is similar to lncRNAs and also depends on the distribution of nucleoplasm. ASOs may, therefore, be the silencing method of choice when a target RNA is thought to function in the nucleus, while duplex RNAs may be a better choice when a target is thought to function in the cytoplasm.<sup>174</sup>

Notably, recent advancements in CRISPR/Cas9 technologies for gene knockout, knock-in, and point mutations may facilitate understanding the biological roles of ncRNAs and aid in the development of ncRNA-based targeted therapy. Gene-editing therapy can directly control the level of certain ncRNAs in cells, local tissues or organs which may yield less side effects than exogenously synthesized compounds, such as interfering RNAs and chemical drugs.<sup>175</sup> For example, Piwecka et al used CRISPR-Cas9 technology to remove the locus encoding the circCdr1as from the mouse genome, founding out the effect of circCdr1 to normal brain function.<sup>176</sup> Therefore, we believe that this budding and maturing technology can contribute to the exploration of the function of ncRNAs, drug discovery and the treatment of various diseases that were previously considered incurable.

These are currently the most commonly used methods for targeting ncRNAs, and more research is needed in the future to explore methods for targeting ncRNAs to promote the development of targeted ncRNAs drugs.

## Conclusion

As a key component of the innate immune system and a trigger of adaptive immunity, inflammasomes play a crucial role in inflammatory diseases. Research in the field of ncRNAs is growing at a fast pace as these molecules have been found to perform a critical role in the regulating inflammasome pathways in inflammatory diseases. We hope that this review will help to provide a better understanding of the inflammasome pathways that are regulated by ncRNAs in the pathogenesis of inflammatory diseases.

However, a number of important questions remain unanswered. First, given the large number of ncRNAs differentially expression in inflammatory diseases and with the potential to regulate inflammasomes activation, it is crucial to identify the most important ncRNAs in various inflammatory diseases. Second, the field of inflammasomes is at its infancy in inflammatory diseases. It is urgent to explore which inflammasome plays the most important effect in these inflammatory diseases and whether ncRNAs can regulate different inflammasomes activation at the same time like lncRNA NEAT1. Third, the mechanisms of the interaction between ncRNAs and inflammasomes is not yet in-depth. Considering that lncRNAs and circRNAs can exert functionality by directly binding to DNA, RNA, and proteins and participate in



transcriptional and post-transcriptional regulation, future studies should focus on specific ncRNAs and explore how they influence inflammasomes activation in specific inflammatory diseases. Fourth, there is still a lack of research on ncRNAs as markers in inflammatory diseases. To fully explore the potential of ncRNAs in inflammatory diseases diagnosis and targeted therapy, future research on the use of ncRNAs as biomarkers and therapeutics should not only focus on their identification and functional characterization, but also on using a large number of statistically significant patient cohorts to characterize diagnostic effect. Additionally, development of technologies for efficient detection of ncRNAs and their tissue-specific delivery methods are critical to the success of the diagnostics and therapeutics.

## Author Contributions

All authors participated in drafting or revising of the manuscript, and approved the final manuscript. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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