



Review Article

MiRNAs and lncRNAs in the regulation of innate immune signaling

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ABSTRACT

The detection and defense against foreign agents and pathogens by the innate immune system is a crucial mechanism in the body. A comprehensive understanding of the signaling mechanisms involved in innate immunity is essential for developing effective diagnostic tools and therapies for infectious diseases. Innate immune response is a complex process involving recognition of pathogens through receptors, activation of signaling pathways, and cytokine production, which are all crucial for deploying appropriate countermeasures. Non-coding RNAs (ncRNAs) are vital regulators of the immune response during infections, mediating the body's defense mechanisms. However, an overactive immune response can lead to tissue damage, and maintaining immune homeostasis is a complex process in which ncRNAs play a significant role. Recent studies have identified microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) as key players in controlling gene expression in innate immune pathways, thereby participating in antiviral defenses, tumor immunity, and autoimmune diseases. MiRNAs act by regulating host defense mechanisms against viruses, bacteria, and fungi by targeting mRNA at the post-transcriptional level, while lncRNAs function as competing RNAs, blocking the binding of miRNAs to mRNA. This review provides an overview of the regulatory role of miRNAs and lncRNAs in innate immunity and its mechanisms, as well as highlights potential future research directions, including the expression and maturation of new ncRNAs and the conservation of ncRNAs in evolution.

1. Introduction

Non-coding RNA (ncRNA) is a type of RNA transcript that constitutes more than 90% of human RNA. Unlike messenger RNA (mRNA), which encodes proteins, ncRNA does not typically encode proteins, except for a few with open reading frames that have coding potential. Instead, ncRNA plays a crucial role in regulating various biological processes, including development, proliferation, transcription, post-transcriptional modification, apoptosis, and cellular metabolism [1–3]. Different types of ncRNA include microRNA (miRNA), small interfering RNA (siRNA), PIWI-interacting RNA (piRNA), transfer RNA-derived small RNA (tsRNA), nuclear small RNA (snRNA), nucleolar small RNA (snoRNA), long non-coding RNA (lncRNA), circular RNA (circRNA), and pseudogenes [1,4,5]. To date, among these ncRNAs that are involved in the innate immune signaling, the most studied are miRNAs and lncRNAs [6–8].

MiRNAs are a type of short ncRNA, typically 22–23 nucleotides in length. Their coding genes are transcribed by RNA polymerase II and they regulate mRNA expression by binding to the 3' untranslated region (3'UTR) of mRNA. Over 60% of coding genes are potential regulatory targets of miRNAs [1,9,10]. lncRNAs are non-coding RNAs that are over 200 nucleotides in length. Their biogenesis process is similar to that of mRNA. lncRNAs play important roles in various biological processes, including cell cycle regulation, chromatin modification, and mRNA translation [11,12].

Innate immunity is the most prevalent and rapidly acting type of immunity. It can recognize and eliminate a broad range of pathogens (Fig. 1).

The innate immune system recognizes pathogen-associated molecular patterns (PAMPs) and host damage-associated molecular patterns (DAMPs) through pattern recognition receptors (PRRs) on the surface of innate immune cells. This recognition triggers inflammation and the

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recruitment of immune cells to eliminate pathogenic microorganisms and self-harming molecules [13,14]. Recent research has made new discoveries about the characteristic functions, biosynthesis, and innate immune signal transduction of ncRNAs. Specifically, there have been advances in understanding how miRNAs and lncRNAs regulates the expression and function of innate immune signal gene-targets.

2. PRRs and their signaling pathways in innate immunity

The PRRs that have been identified include Toll-like receptors (TLRs), C-type lectin-like receptors (CLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), retinoic acid-inducible gene protein I (RIG-I)-like receptors (RLRs), melanoma deficiency factor 2 (absent in melanoma 2, AIM2)-like receptors (ALRs), and 2'-5'oligoadenylate synthetase (2'-5'oligoadenylate synthesis, OAS)-like receptors (OLRs) [15–17]. TLRs are transmembrane proteins expressed in various cells, including dendritic cells, macrophages, and epithelial cells [18]. Upon recognition of PAMPs, TLRs recruit downstream molecules to activate nuclear factor- κ B (NF- κ B), interferon (IFN) regulatory factor (IRF), and mitogen-activated protein kinase (MAPK), leading to the initiation of the innate immune response [19,20]. There are two TLR signaling pathways based on the different downstream molecules: the MyD88-dependent pathway and the IFN- β TIR domain adapter protein (TRIF)-dependent pathway. The MyD88-dependent pathway mainly induces the transcription of inflammatory cytokines, while the TRIF-dependent pathway is unique to TLR3 and TLR4. Upon stimulation by ligands, TLR3 and TLR4 recruit TRIF or TRIF-related adapter molecules (TRAM). The interaction between TRIF and tumor necrosis factor receptor-associated factor 6 (TRAF6) leads to the ubiquitination of receptor-interacting protein-1 (RIP-1) by IKKi/TANK-binding kinase 1 (TBK1). RIP-1 activates the transforming growth factor beta (TGF- β)-activated kinase 1 (TAK1) complex. The interaction of TRIF and TRAF3 recruits TBK1 and IKKi, leading to the phosphorylation of interferon regulatory factor 3 (IRF3) to form a dimer, which binds to the IFN- β promoter in the nucleus and induces interferon expression [18]. CLRs are a group of transmembrane proteins with one or more

carbohydrate recognition domains (CRDs) or C-type lectin-like domains (CTLDs) that are involved in calcium-dependent recognition of pathogen surface carbohydrates [21]. NLRs are cytoplasmic receptors that activate NF- κ B signaling and induce changes in gene expression upon stimulation, leading to the formation of inflammatory complexes. RLR is a cytoplasmic sensor that detects RNA viruses, and upon binding to viral RNA, signals to mitochondrial antiviral signaling protein (MAVS) to induce IFN response mediated by IRF3 and IRF7 [22,23]. ALR is a cytoplasmic DNA sensor that activates the STING-dependent interferon-stimulated gene (ISG) pathway through the endoplasmic reticulum-associated adapter stimulator of interferon genes (STING) upon detection of DNA in the cell [24]. OLR is a group of cytoplasmic nucleic acid sensors, including OAS protein and cyclic GMPAMP synthase (cGAS), which produce second messenger molecules such as cGAMP upon activation by double-stranded nucleic acid in the cytoplasm, which bind and activate TRIF to initiate downstream innate immune response [17,25]. Although the downstream signal transduction pathways of innate immunity, such as STING and MAVS, have been studied in depth, the specific recognition mechanism of different nucleic acid sensors for different nucleic acids in the initiation of innate immune signals remains to be further investigated.

Each component of the innate immune pathway is tightly regulated at both the transcriptional and post-transcriptional levels, and increasing evidence suggests that ncRNAs play a crucial role in innate immune regulation. ncRNAs can regulate various components of the innate immune response, including IRF, TRIF, RIG-I, MAVS, cGAS, STING, and others (Table 1) [26–37]. In addition, well-known inflammatory signaling pathways such as TLR and NF- κ B are activated during innate immune responses by various negative regulators, in particular miRNAs and lncRNAs (Fig. 2).

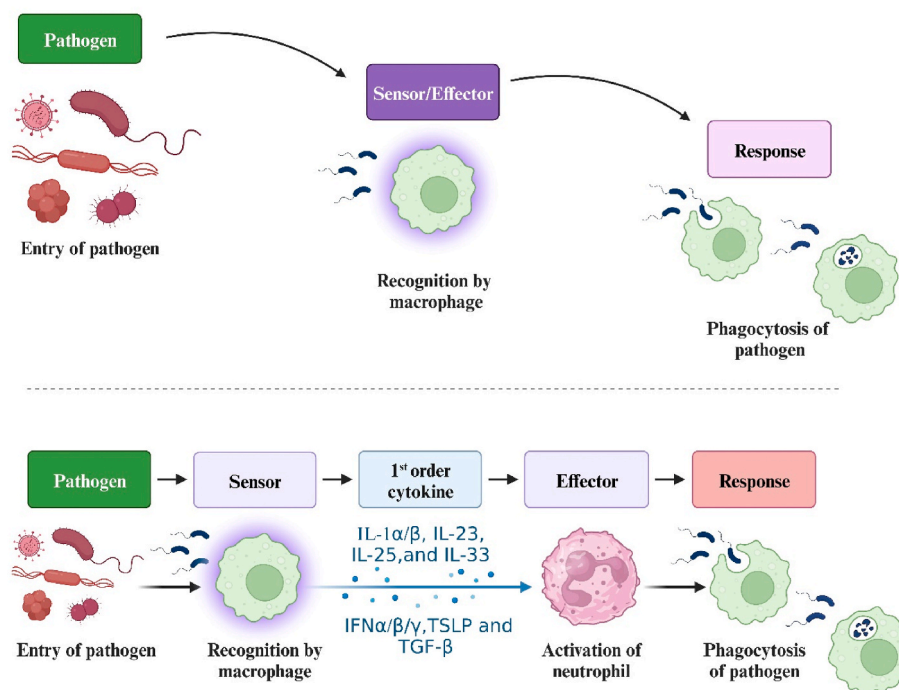


Fig. 1. General principles of the innate immune response. The innate immune system is a first-level biological barrier that detects various pathogens such as viruses, bacteria, parasites, and toxins, or reacts to injuries of various origins.

Table 1

Presents some studies that studied the regulatory role of miRNAs and lncRNAs in innate immunity.

miRNA/ lncRNA	Function in Innate Immunity	Target	References
miR-146a	Regulates inflammation by targeting TRAF6 and IRAK1/2 in TLR signaling pathway	TRAF6 and IRAK1/2	[26]
miR-155	Regulates the differentiation and function of immune cells; regulates the expression of TLRs and downstream signaling molecules	SOCS1, PU.1, TAB2, TAK1, and IRAK1	[27]
miR-9	Regulates TLR signaling pathway and suppresses inflammatory response	NF- κ B and JAK/STAT	[28]
lncRNA-IL7R	Enhances the production of pro-inflammatory cytokines by promoting the TLR signaling pathway	TRAF6, IRAK1, and IRAK4	[29]
lncRNA-NEF	Regulates the production of type I IFN in response to viral infection	RIG-I and MDA5	[30]
lncRNA-Cox2	Regulates macrophage polarization and inflammatory response	CREB/C/EBP β axis	[31]
NEAT1	Promotes the production of pro-inflammatory cytokines and enhances the activation of TLR signaling pathway	NF- κ B and MAPK	[32]
MALAT1	Enhances the activation of TLR signaling pathway and promotes the production of pro-inflammatory cytokines	SIRT1/MAPK/NF- κ B axis	[33]
GAS5	Negatively regulates the production of type I IFN in response to viral infection	RIG-I and MDA5	[34]
lncRNA-EPS	Regulates the expression of inflammatory cytokines and enhances the activation of TLR signaling pathway	TRAF6, IRAK1, and IRAK4	[35]
SNHG6	Regulates TLR signaling pathway and suppresses inflammatory response	NF- κ B and JAK/STAT	[36]
TUG1	Regulates the expression of inflammatory cytokines and enhances the activation of TLR signaling pathway	NF- κ B and MAPK	[37]
THRIL	Enhances the production of pro-inflammatory cytokines by promoting the TLR signaling pathway	TRAF6, IRAK1, and IRAK4	[37]

3. The specific mechanism of NCRNA regulation of innate immune response

3.1. Regulation of innate immunity by miRNAs

3.1.1. Regulation of IRF by miRNAs

IRF proteins are transcription factors with a conserved amino-terminal DNA-binding domain (DBD) that recognizes the promoter of IFN genes, regulating their expression [26]. MiRNA-23b, pol-miR-731, and miR-146a directly act on the 3'UTR of IRF mRNA, reducing its levels and inhibiting type I IFN-mediated immune response. In viral infections, miRNA-23b and pol-miR-731 are upregulated, inhibiting antiviral response [38,39], while the expression of miR-146a decreases in systemic lupus erythematosus patients, correlated with disease activity [40]. Binding of miR-217-5p to the 3'UTR of nucleotide oligomerization domain 1 (NOD1) inhibits its expression, indirectly inhibiting IRF3 [41]. MiRNA can indirectly regulate IRF through various mechanisms. Nc886 indirectly inhibits the phosphorylation of IRF3 through the RIG-I/MAVS pathway, although the specific mechanism remains unclear [42]. Therefore, miRNAs can directly or indirectly modulate the expression or activity of IRF, contributing to antiviral responses and the development of innate immune diseases. However, further research is needed to

elucidate the mechanism by which Nc886 indirectly inhibits the phosphorylation of IRF3 through the RIG-I/MAVS pathway [42].

3.1.2. Regulation of IFN- β and TRIF by miRNAs

TLR3 signaling pathway plays a crucial role in the innate immune response against various viruses. In this pathway, TLR3 directly interacts with TRIF, leading to the activation of IRF3 by TBK1 [43,44]. Interestingly, miRNAs have been shown to regulate the TLR3-TRIF pathway and affect the body's antiviral response. For example, miR-15a-5p can bind to the 3'UTR of TRIF mRNA and downregulate its expression [45]. Moreover, circDtx1, a circular RNA derived from the Deltex E3 ubiquitin ligase 1 (Dtx1) gene, acts as a competing endogenous RNA (ceRNA) that sequesters miR-15a-5p, thereby upregulating TRIF expression and attenuating the inhibitory effect of miR-15a-5p [45]. This indicates that circRNA-miRNA-mRNA regulatory networks can interfere with the regulation of miRNAs on TRIF and collectively participate in the regulation of innate immunity. The TLR3-TRIF pathway is involved in the innate immune response against various viruses, such as influenza virus, respiratory syncytial virus, herpes simplex virus 2, and mouse cytomegalovirus [46].

3.1.3. Regulation of RIG-I by miRNA

RIG-I, a protein encoded by the DDX58 gene, consists of two N-terminal caspase activation and recruitment domains (CARD) and a C-terminal RNA helicase domain, and its primary function is to detect double-stranded 5'-triphosphate RNA (3pRNA) [47]. Upon recognizing viral RNA, the ubiquitination process by the E3 ligase TRIM25 activates the CARD domain of RIG-I, which then interacts with the adapter protein MAVS located on the outer mitochondrial membrane. This triggers downstream activation of transcription factors IRF3 and NF- κ B, resulting in the production of type I interferon and pro-inflammatory cytokines [48]. In both humans and mice, miR-218 has two binding sites in the 3'UTR of the DDX58 gene, and it can directly inhibit the transcription of RIG-I, thereby inhibiting the production of type I interferon and promoting virus immune escape [49]. MiR-202-5p can suppress the expression of TRIM25 at the post-transcriptional level, inhibiting the ubiquitination of RIG-I and making it inactive [50]. Nonetheless, some miRNAs are believed to be RIG-I agonists and contribute to the enhanced immune response [51]. In prostate cancer cells, for instance, miR-139 acts as a RIG-I ligand to activate RIG-I and induce an IFN- β response [52]. Therefore, miRNAs can promote or suppress the innate immune response by regulating the expression level and activity of RIG-I at both the transcriptional and post-transcriptional levels.

3.1.4. Regulation of MAVS by miRNAs

MAVS is a protein that is located on the outer mitochondrial membrane and consists of an N-terminal CARD domain, a proline-rich region, and a C-terminal transmembrane domain [22]. It plays a crucial role in the innate immune signaling pathways mediated by mitochondria [53], and its activity and effectiveness are tightly regulated by ubiquitination and deubiquitination, as well as phosphorylation and dephosphorylation [22,54].

MiRNA can regulate the innate immune response by directly or indirectly controlling the expression of MAVS. Several miRNAs, including miR-3570, miR-122, miR-125a, miR-125b, miR-22, and miR-3470b, have potential complementary sequences to the 3'UTR of MAVS, which they use to inhibit MAVS expression at the post-transcriptional level. This inhibition, in turn, inhibits MAVS-mediated NF- κ B and IRF3 signal transduction, leading to the suppression of the antiviral response and the promotion of viral replication [54–60]. On the other hand, miR-302b targets the mitochondrial transporter SLC25A12, which indirectly regulates MAVS-mediated innate immunity [61]. However, circPDK functions as a competitive endogenous RNA of MAVS and enhances the innate immune response by adsorbing miR-21-3p. Therefore, the regulation of miRNAs on MAVS is also affected by circRNAs.

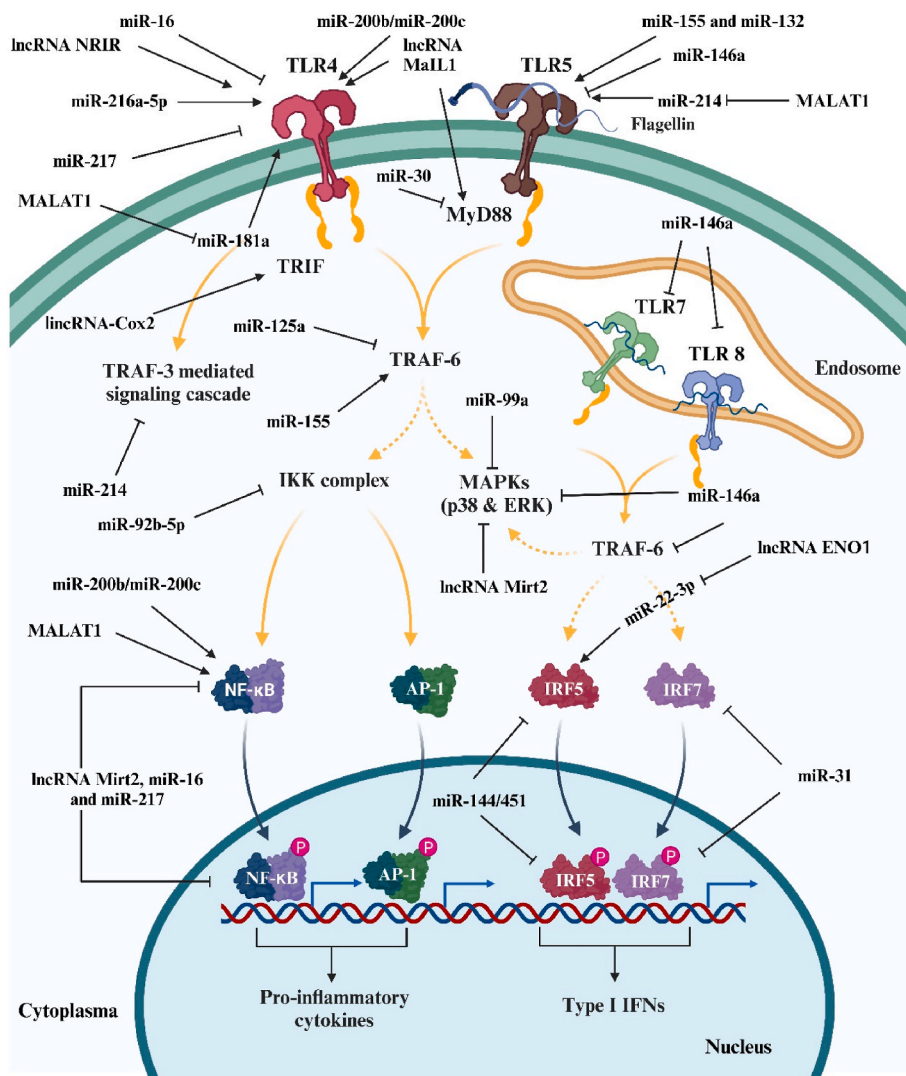


Fig. 2. Schematic illustration of the regulatory role of some microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) on the inflammatory signaling cascades of toll-like receptors (TLRs) and nuclear factor- κ B (NF- κ B) during activation of innate immunity. Activation of the immune system under the influence of various factors (pathogens or trauma) through inflammatory TLR-NF- κ B signaling cascades is a complex and delicate structure, which is also subject to epigenetic regulation through miRNAs.

3.1.5. Regulation of miRNA on cGAS/STING signaling pathway

Activation of cGAS by double-stranded DNA leads to the synthesis of cGAMP from ATP and GTP, which then activates the downstream molecule STING. STING recruits TBK1, which phosphorylates and activates IRF3, ultimately leading to the expression of type I interferon [62]. The 3'UTRs of cGAS and STING mRNA contain potential binding sites for some miRNAs [63,64]. miRNAs can exert an immunosuppressive effect by binding directly to mRNA or indirectly regulating the expression of cGAS/STING. YU et al. [65] demonstrated that miR-23a/b can directly bind to the 3'UTR of cGAS mRNA, leading to inhibition of cGAS expression and consequently inhibiting the innate immune response mediated by cGAS. Similarly, miR-24, miR-210, and miR-24-3p regulate the expression of STING by targeting its 3'UTR region, thereby inhibiting the STING-mediated signaling pathway [63,64,66]. Under hypoxic conditions, miR-25 and miR-93 indirectly regulate the expression of cGAS by acting on the epigenetic factor NCOA3, which maintains cGAS expression levels. This leads to downregulation of cGAS mRNA levels and helps hypoxic tumor cells escape the immune response [67]. In teleost fish, the circular RNA circSamd4a enhances the STING-mediated NF- κ B/IRF3 signaling pathway by adsorbing miR-29a-3p through the sponge effect during the antiviral immune response [68].

3.2. Regulation of innate immunity by lncRNA

3.2.1. Regulation of IRF by lncRNA

lncRNAs can regulate the innate immune response by either adsorbing miRNA through the sponge effect or directly binding to components of the innate immune pathway [41]. For instance, lncRNA NARL, which is related to antibacterial and antiviral functions of NOD1, can bind to miR-217-5p competitively and promote the TLR-TBK1-dependent phosphorylation of IRF3, thus enhancing the immune response [41,69] (Fig. 3). In addition, ncLrrc55-AS can bind to phosphoesterase methyltransferase 1 (PME-1), promote PME-1-mediated demethylation and inactivation of protein phosphatase PP2A (an inhibitor of IRF3 signaling), and enhance IRF3 phosphorylation and signaling [70]. Conversely, lnc-MxA directly binds to the IFN- β promoter, interferes with the binding of IRF3 and the NF- κ B subunit p65 to IFN- β , and inhibits the transcription of IFN- β , resulting in an immunosuppressive effect [71]. These findings suggest that lncRNAs can modulate IRF3 signaling through different mechanisms, leading to either immune-enhancing or immunosuppressive effects.

3.2.2. Regulation of RIG-I by lncRNA

lncRNAs can regulate the signaling pathway mediated by RIG-I and play an immunosuppressive or immune-enhancing role in various diseases such as tumor immunity and viral infections. In murine macrophages, lnc-Lsm3b competes with viral RNA for binding to the CTD of

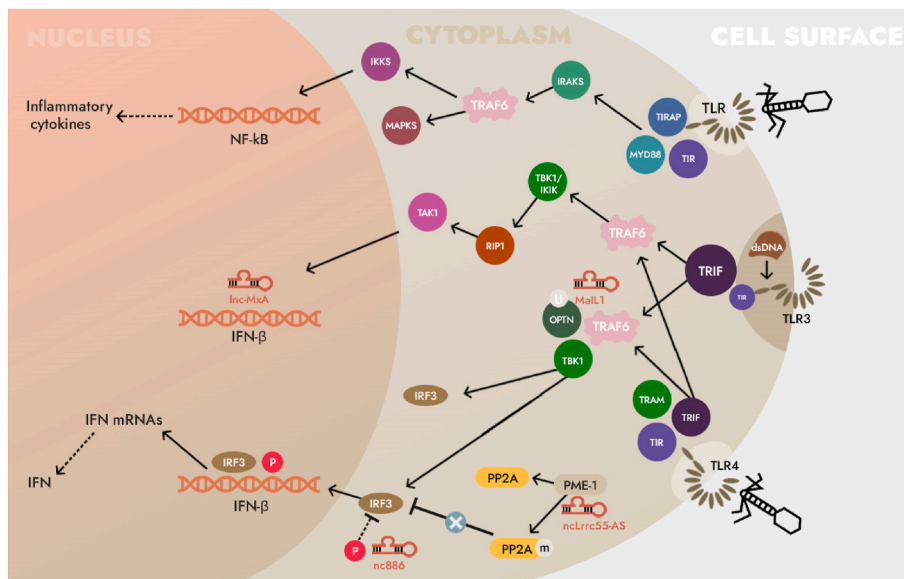


Fig. 3. Shows the regulatory mechanism of non-coding RNAs (ncRNAs) on interferon regulatory transcription factor 3 (IRF3). The Toll-like receptor (TLR) recognizes pathogen-associated molecular patterns (PAMPs) and activates downstream signaling pathways through the Toll/IL-1R (TIR) domain. The TIR domain-containing adaptor protein (TIRAP) and interleukin 1 (IL-1) receptor-associated kinase (IRAK) initiate the downstream signaling cascade through tumor necrosis factor receptor-associated factor (TRAF), leading to the activation of inhibitor of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) kinase (IKK) complex, mitogen-activated protein kinases (MAPKs), and TANK-binding kinase 1 (TBK1). Inducible I κ B kinase (IKKi), receptor-interacting protein 1 (RIP1), and transforming growth factor β -activated kinase 1 (TAK1) also participate in this process. The TIR-domain-containing adaptor protein inducing interferon beta (IFN- β) (TRIF) and TRIF-related adaptor molecule (TRAM) activate the downstream signaling pathway, which eventually leads to the phosphorylation and activation of IRF3, and the expression of interferon (IFN) genes. Optineurin (OPTN) also participates in this process. In addition, ncRNAs, such as long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), can regulate the expression and activity of

IRF3. lncRNAs, such as nucleotide-binding oligomerization domain (NOD1) antibacterial and antiviral-related lncRNA NARL, nLrrc55-AS, and lnc-MxA, can regulate IRF3 phosphorylation and signaling by interacting with different components of the innate immune pathway. miRNAs can also regulate IRF3 activity by binding to its mRNA.

RIG-I during the late stage of RNA virus infection, leading to its inactivation and the subsequent inhibition of IFN I production [72]. However, no homologous gene of lnc-Lsm3b has been found in the human genome due to the species specificity of lncRNA expression [73]. In humans, lncATV is upregulated after virus infection and negatively regulates RIG-I-mediated antiviral innate immunity [73]. After Hantavirus infection, the transcription of lncRNA NEAT1 increases and it promotes IFN- β -mediated innate immunity by eliminating the transcriptional repression effect of proline- and glutamine-rich cleavage factor SFPQ on RIG-I and DDX60 molecules by relocating SFPQ to paraspeckles in the nucleus [74]. Therefore, the regulation of RIG-I by lncRNA may differ across species and involve different mechanisms.

3.2.3. Regulation of MAVS by lncRNAs

lncRNAs can function as endogenous competing RNAs (ceRNAs) of miRNAs, or interfere with mitochondrial homeostasis, thereby inhibiting the activation of MAVS and regulating innate immunity. For instance, MAVS anti-virus-related lncRNA (MARL) acts as an endogenous competing RNA of miR-122 by directly binding to it, inhibiting its activity and expression level, and promoting the expression of MAVS protein. As a result, it inhibits virus replication and promotes antiviral response [56]. However, there are limited studies on the regulation of MAVS by lncRNA. It is unclear whether other lncRNAs regulate the innate immune response by interfering with the combination of miRNA and MAVS, and whether there are lncRNAs that inhibit innate immunity by regulating MAVS. Further research is needed to address these questions.

3.2.4. Regulation of lncRNA on cGAS/STING signaling pathway

The cGAS/STING signaling pathway is involved in the expression of type I interferons and inflammatory cytokines that are critical for DNA-induced innate immunity. The HDP-RNP complex can regulate the synthesis of cGAMP in the DNA-stimulated innate immune response, which can affect the cGAMP-mediated IFN- β mRNA level, and the lncRNA NEAT1 is necessary for HDP-RNP assembly [3], thus indirectly regulating the cGAS pathway. Knocking out lncRNA MALAT1 has been found to inhibit the expression of STING and its transcriptional promoter

activity in lung epithelial cells induced by hyperoxia. MALAT1 promotes the transcription of STING through the MALAT1-CREB signaling pathway, as evidenced by the mRNA expression level of cAMP response element binding protein (CREB) and the binding of STING promoter, which decreases after MALAT1 is silenced [75]. Xia et al. discovered a circRNA, cia-cGAS, that belongs to lncRNA. It binds to cGAS under steady-state conditions, blocks its synthetase activity, and inhibits cGAS-mediated production of IFN in hematopoietic stem cells, thereby maintaining the body's steady-state [76]. These studies demonstrate that lncRNAs can positively or negatively regulate the cGAS/STING signaling pathway through different mechanisms, and the regulation of lncRNAs on the cGAS/STING signaling pathway is a complex process.

4. Conclusion

The precise regulation of the innate immune response is crucial for maintaining immune homeostasis and initiating adaptive immunity. Numerous studies have shown that ncRNAs are involved in regulating innate immune responses, with changes in their expression levels induced during viral infections and autoimmune diseases. Among ncRNAs, miRNAs and lncRNAs have been extensively studied for their regulatory roles in innate immunity. Generally, miRNAs bind to the 3'UTR of mRNA to directly regulate the expression of related proteins in the innate immune pathway, while lncRNAs act as endogenous competing RNAs to prevent the combination of miRNAs and mRNA, regulating innate immunity. However, some lncRNAs can directly bind to components of the innate immune pathway or regulate innate immunity by affecting mitochondrial function. Moreover, the expression of lncRNAs is species-specific, and conserved lncRNAs play roles in processing, localization, and function, whereas non-conserved lncRNAs further complicate the study of their regulation. Furthermore, studies have also revealed the involvement of circRNAs in regulating innate immunity and the development of immune-related diseases, with circRNAs forming complex regulatory networks with miRNAs and mRNAs to regulate innate immunity [77]. Therefore, ncRNAs regulate innate immune responses through multiple mechanisms, and their complex regulatory network requires further exploration to provide

novel insights for the diagnosis and treatment of innate immune-related diseases [78–82]. Besides, the progress made in producing, modifying, and delivering RNA molecules has significantly contributed to the development of RNA-based therapeutics. As our knowledge of RNA biology continues to expand, we are witnessing a parallel growth in the field of RNA therapeutics. The field of RNA therapeutics is experiencing rapid growth and significant expansion. With over fifteen RNA-based therapies already approved by regulatory authorities and several more in advanced stages of clinical development, this powerful and versatile platform shows immense potential in addressing unmet medical needs that current treatments cannot fulfill. While fundamental challenges such as delivery, stability, and immunogenicity have been tackled, the development of RNA drugs continues to progress rapidly. However, there are still opportunities for further improvement and optimization, including targeted delivery to specific cell types, enhancing endosomal escape, and increasing potency [83].

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Author contributions

Ilgiz Gareev and Manuel Encarnacion Ramirez conceptualized and designed the study. Tatiana Ilyasova have participated in the acquisition, analysis and interpretation of the data. Ilgiz Gareev has drafted the manuscript. Evgeniy Goncharov, Denis Ivliev, and Alina Shumadalova contributed to the critical revisions of the manuscript. Ilgiz Gareev supervised the research. All authors agreed on the journal to which the article would be submitted, gave the final approval for the version to be published, and agreed to be accountable for all aspects of the work.

Declaration of competing interest

The authors declare that no conflicts of interest exist.

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