Non-coding RNA Research 8 (2023) 534–541

Contents lists available at ScienceDirect

Non-coding RNA Research

journal homepage: www.keaipublishing.com/en/journals/non-coding-rna-research

Review Article

MiRNAs and lncRNAs in the regulation of innate immune signaling

Ilgiz Gareev [a,*], Manuel de Jesus Encarnacion Ramirez [b], Evgeniy Goncharov [c], Denis Ivliev [d], Alina Shumadalova [a], Tatiana Ilyasova [a], Chunlei Wang [e]

[a] Bashkir State Medical University, Ufa, Republic of Bashkortostan, 450008, Russia
[b] Department of Neurosurgery, Peoples' Friendship University of Russia (RUDN University), 6 Miklukho-Maklaya Street, Moscow, 117198, Russian Federation
[c] Traumatology and Orthopedics Center, Central Clinical Hospital of the Russian Academy of Sciences, 117593, Moscow, Russia
[d] Department of Neurosurgery, Smolensk State Medical University of the Ministry of Health of the Russian Federation, Smolensk, Russia
[e] Department of Neurosurgery, The First Affiliated Hospital of Harbin Medical University, Harbin, 150001, China

ARTICLE INFO

Keywords:
Innate immune
ncRNAs
miRNAs
lncRNAs
Regulation

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

* Corresponding author.
E-mail address: ilgiz_gareev@mail.ru (I. Gareev).

https://doi.org/10.1016/j.ncrna.2023.07.002
Received 28 July 2023; Accepted 31 July 2023
Available online 1 August 2023

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-κB (NF-κB), 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-κB 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 STING 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-kB are activated during innate immune responses by various negative regulators, in particular miRNAs and lncRNAs (Fig. 2).

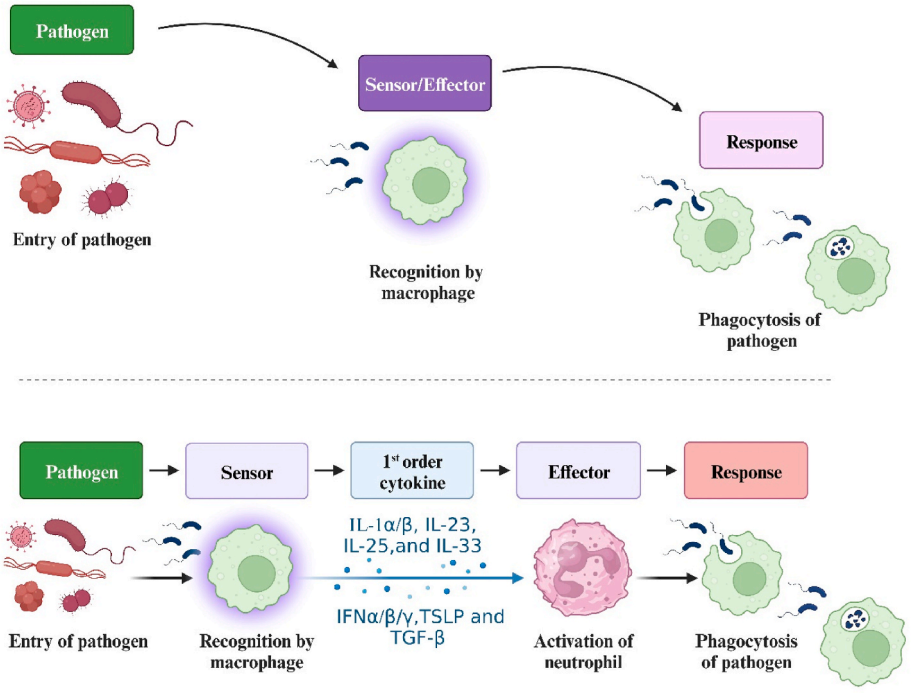

Fig. 1. General principles of the innate immune response. The innate immune system is a first-level biological barrier that detects various pathogens such as viruses, bacteria, parasites, and toxins, or reacts to injuries of various origins.

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-κB 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/EBPβ axis	[31]
NEAT1	Promotes the production of pro-inflammatory cytokines and enhances the activation of TLR signaling pathway	NF-κB and MAPK	[32]
MALAT1	Enhances the activation of TLR signaling pathway and promotes the production of pro-inflammatory cytokines	SIRT1/MAPK/ NF-κB 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-κB and JAK/ STAT	[36]
TUG1	Regulates the expression of inflammatory cytokines and enhances the activation of TLR signaling pathway	NF-κB 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-κB, 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-κB 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, circPOK 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.

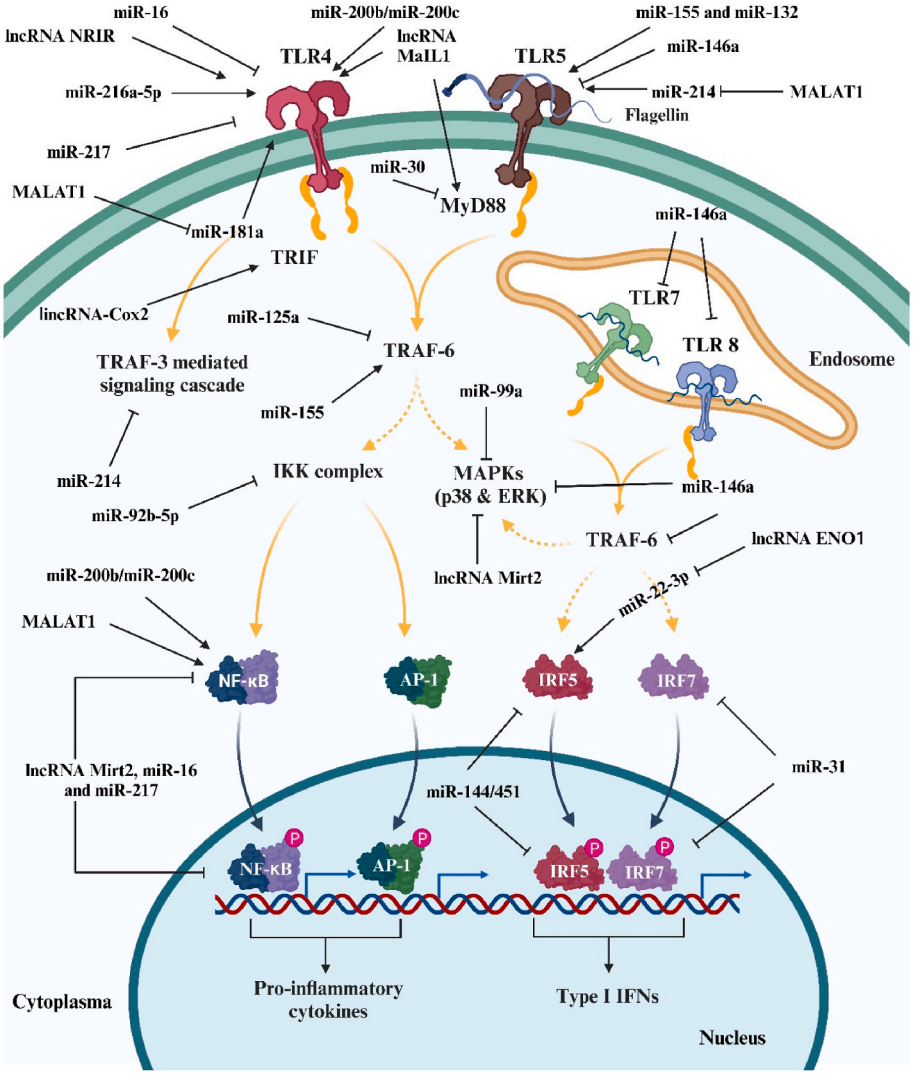

Fig. 2. Schematic illustration of the regulatory role of some microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) on the inflammatory signaling cascades of toll-like receptors (TLRs) and nuclear factor-κB (NF-κB) during activation of innate immunity. Activation of the immune system under the influence of various factors (pathogens or trauma) through inflammatory TLR-NF-Kb 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-κB/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 methylesterase 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-κB 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

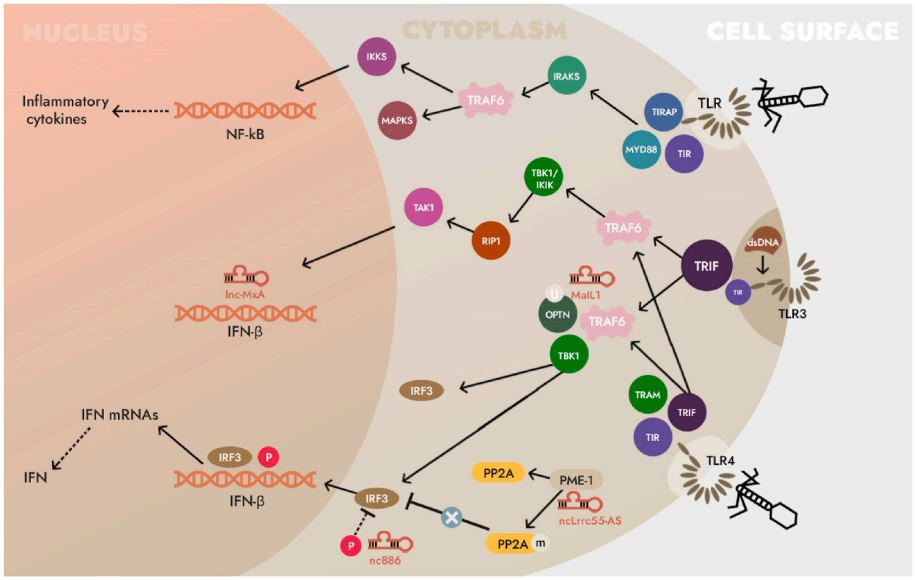

Fig. 3. Shows the regulatory mechanism of non-coding RNAs (ncRNAs) on interferon regulatory transcription factor 3 (IRF3). The Toll-like receptor (TLR) recognizes pathogen-associated molecular patterns (PAMPs) and activates downstream signaling pathways through the Toll/IL-1R (TIR) domain. The TIR domain-containing 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-κB) kinase (IKK) complex, mitogen-activated protein kinases (MAPKs), and TANK-binding kinase 1 (TBK1). Inducible IκB 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, ncLrrc55-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].

Funding

This work was supported by the Bashkir State Medical University Strategic Academic Leadership Program (PRIORITY-2030).

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.

References

[1] F.J. Slack, A.M. Chinnaiyan, The role of non-coding RNAs in oncology, Cell 179 (5) (2019 Nov 14) 1033–1055, https://doi.org/10.1016/j.cell.2019.10.017.
[2] I. Gareev, O. Beylerli, G. Aliev, V. Pavlov, A. Izmailov, Y. Zhang, Y. Liang, G. Yang, The role of long non-coding RNAs in intracranial aneurysms and subarachnoid hemorrhage, Life 10 (9) (2020 Aug 20) 155, https://doi.org/10.3390/life10090155.
[3] O. Beylerli, I. Gareev, V. Pavlov, X. Chen, S. Zhao, The role of long noncoding RNAs in the biology of pituitary adenomas, World Neurosurg. 137 (2020 May) 252–256, https://doi.org/10.1016/j.wneu.2019.10.137.
[4] O. Beylerli, I. Gareev, A. Sufianov, T. Ilyasova, Y. Guang, Long noncoding RNAs as promising biomarkers in cancer, Non-coding RNA Res. 7 (2) (2022 Feb 25) 66–70, https://doi.org/10.1016/j.ncrna.2022.02.004.
[5] A. Sufianov, S. Begliarzade, V. Kudriashov, R. Nafikova, T. Ilyasova, Y. Liang, Role of miRNAs in vascular development, Non-coding RNA Res. 8 (1) (2022 Sep 29) 1–7, https://doi.org/10.1016/j.ncrna.2022.09.010.
[6] E.K. Robinson, S. Covarrubias, S. Carpenter, The how and why of lncRNA function: an innate immune perspective, Biochim. Biophys. Acta Gene Regul. Mech. 1863 (4) (2020 Apr), 194419, https://doi.org/10.1016/j.bbagrm.2019.194419.
[7] J.K. Kim, T.S. Kim, J. Basu, E.K. Jo, MicroRNA in innate immunity and autophagy during mycobacterial infection, Cell Microbiol. 19 (1) (2017 Jan), https://doi.org/10.1111/cmi.12687.
[8] Y. Wang, Y. Wang, W. Luo, X. Song, L. Huang, J. Xiao, F. Jin, Z. Ren, Y. Wang, Roles of long non-coding RNAs and emerging RNA-binding proteins in innate antiviral responses, Theranostics 10 (20) (2020 Jul 23) 9407–9424, https://doi.org/10.7150/thno.48520.
[9] A. Vishnoi, S. Rani, miRNA biogenesis and regulation of diseases: an updated overview, Methods Mol. Biol. 2595 (2023) 1–12, https://doi.org/10.1007/978-1-0716-2823-2_1.
[10] M. Tafrihi, E. Hasheminasab, MiRNAs: biology, biogenesis, their web-based tools, and databases, MicroRNA 8 (1) (2019) 4–27, https://doi.org/10.2174/2211536607666180827111633.
[11] J. Zhu, H. Fu, Y. Wu, X. Zheng, Function of lncRNAs and approaches to lncRNA-protein interactions, Sci. China Life Sci. 56 (10) (2013 Oct) 876–885, https://doi.org/10.1007/s11427-013-4553-6.
[12] S. Napoli, LncRNAs and available databases, Methods Mol. Biol. 2348 (2021) 3–26, https://doi.org/10.1007/978-1-0716-1581-2_1.
[13] X.W. Qin, J. He, Y. Yu, C. Liu, Z.Y. Luo, Z.M. Li, S.P. Weng, C.J. Guo, J.G. He, The roles of Mandarin fish STING in innate immune defense against Infectious spleen and kidney necrosis virus infections, Fish Shellfish Immunol. 100 (2020 May) 80–89, https://doi.org/10.1016/j.fsi.2020.02.062.
[14] E. Malekos, S. Carpenter, Short open reading frame genes in innate immunity: from discovery to characterization, Trends Immunol. 43 (9) (2022 Sep) 741–756, https://doi.org/10.1016/j.it.2022.07.005.
[15] K.A. Fitzgerald, J.C. Kagan, Toll-like receptors and the control of immunity, Cell 180 (6) (2020 Mar 19) 1044–1066, https://doi.org/10.1016/j.cell.2020.02.041.
[16] C.A. Thaiss, N. Zmora, M. Levy, E. Elinav, The microbiome and innate immunity, Nature 535 (7610) (2016 Jul 7) 65–74, https://doi.org/10.1038/nature18847.
[17] C.A. Thaiss, M. Levy, S. Itav, E. Elinav, Integration of innate immune signaling, Trends Immunol. 37 (2) (2016 Feb) 84–101, https://doi.org/10.1016/j.it.2015.12.003.
[18] M.K. Vidya, V.G. Kumar, V. Sejian, M. Bagath, G. Krishnan, R. Bhatta, Toll-like receptors: significance, ligands, signaling pathways, and functions in mammals, Int. Rev. Immunol. 37 (1) (2018 Jan 2) 20–36, https://doi.org/10.1080/08830185.2017.1380200.
[19] A.S. Maharjan, D. Pilling, R.H. Gomer, Toll-like receptor 2 agonists inhibit human fibrocyte differentiation, Fibrogenesis Tissue Repair 3 (2010 Nov 24) 23, https://doi.org/10.1186/1755-1536-3-23.
[20] S.R. Park, D.J. Kim, S.H. Han, M.J. Kang, J.Y. Lee, Y.J. Jeong, S.J. Lee, T.H. Kim, S. G. Ahn, J.H. Yoon, J.H. Park, Diverse Toll-like receptors mediate cytokine production by Fusobacterium nucleatum and Aggregatibacter actinomycetemcomitans in macrophages, Infect. Immun. 82 (5) (2014 May) 1914–1920, https://doi.org/10.1128/IAI.01226-13.
[21] A. Vázquez-Mendoza, J.C. Carrero, M. Rodriguez-Sosa, Parasitic infections: a role for C-type lectins receptors, BioMed Res. Int. 2013 (2013), 456352, https://doi.org/10.1155/2013/456352.
[22] B. Liu, C. Gao, Regulation of MAVS activation through post-translational modifications, Curr. Opin. Immunol. 50 (2018 Feb) 75–81, https://doi.org/10.1016/j.coi.2017.12.002.
[23] C. Castanier, N. Zemirli, A. Portier, D. Garcin, N. Bidère, A. Vazquez, D. Arnoult, MAVS ubiquitination by the E3 ligase TRIM25 and degradation by the proteasome is involved in type I interferon production after activation of the antiviral RIG-I-like receptors, BMC Biol. 10 (2012 May 24) 44, https://doi.org/10.1186/1741-7007-10-44.
[24] E.E. Gray, D. Winship, J.M. Snyder, S.J. Child, A.P. Geballe, D.B. Stetson, The AIM2-like receptors are dispensable for the interferon response to intracellular DNA, Immunity 45 (2) (2016 Aug 16) 255–266, https://doi.org/10.1016/j.immuni.2016.06.015.
[25] V. Hornung, R. Hartmann, A. Ablasser, K.P. Hopfner, OAS proteins and cGAS: unifying concepts in sensing and responding to cytosolic nucleic acids, Nat. Rev. Immunol. 14 (8) (2014 Aug) 521–528, https://doi.org/10.1038/nri3719.
[26] Z. Zhang, X. Zou, R. Zhang, Y. Xie, Z. Feng, F. Li, J. Han, H. Sun, Q. Ouyang, S. Hua, B. Lv, T. Hua, Z. Liu, Y. Cai, Y. Zou, Y. Tang, X. Jiang, Human umbilical cord mesenchymal stem cell-derived exosomal miR-146a-5p reduces microglial-mediated neuroinflammation via suppression of the IRAK1/TRAF6 signaling pathway after ischemic stroke, Aging (Albany NY) 13 (2) (2021 Jan 21) 3060–3079, https://doi.org/10.18632/aging.202466.
[27] T.S. Elton, H. Selemon, S.M. Elton, N.L. Parinandi, Regulation of the MIR155 host gene in physiological and pathological processes, Gene 532 (1) (2013 Dec 10) 1–12, https://doi.org/10.1016/j.gene.2012.12.009.
[28] Z. Amini-Farsani, M. Yadollahi-Farsani, S. Arab, F. Forouzanfar, M. Yadollahi, S. Asgharzade, Prediction and analysis of microRNAs involved in COVID-19 inflammatory processes associated with the NF-kB and JAK/STAT signaling pathways, Int. Immunopharm. 100 (2021 Nov), 108071, https://doi.org/10.1016/j.intimp.2021.108071.
[29] H. Cui, N. Xie, Z. Tan, S. Banerjee, V.J. Thannickal, E. Abraham, G. Liu, The human long noncoding RNA lnc-IL7R regulates the inflammatory response, Eur. J. Immunol. 44 (7) (2014 Jul) 2085–2095, https://doi.org/10.1002/eji.201344126.
[30] H. Imam, A.S. Bano, P. Patel, P. Holla, S. Jameel, The lncRNA NRON modulates HIV-1 replication in a NFAT-dependent manner and is differentially regulated by early and late viral proteins, Sci. Rep. 5 (2015 Mar 2) 8639, https://doi.org/10.1038/srep08639.
[31] Q. Wang, Y. Xie, Q. He, Y. Geng, J. Xu, LncRNA-Cox2 regulates macrophage polarization and inflammatory response through the CREB-C/EBPβ signaling pathway in septic mice, Int. Immunopharm. 101 (Pt B) (2021 Dec), 108347, https://doi.org/10.1016/j.intimp.2021.108347.
[32] Y. Pan, T. Wang, Z. Zhao, W. Wei, X. Yang, X. Wang, W. Xin, Novel insights into the emerging role of Neat1 and its effects downstream in the regulation of inflammation, J. Inflamm. Res. 15 (2022 Jan 26) 557–571, https://doi.org/10.2147/JIR.S338162.
[33] J. Yang, X. Lin, L. Wang, T. Sun, Q. Zhao, Q. Ma, Y. Zhou, LncRNA MALAT1 enhances ox-LDL-induced autophagy through the SIRT1/MAPK/NF-κB pathway in macrophages, Curr. Vasc. Pharmacol. 18 (6) (2020) 652–662, https://doi.org/10.2174/1570161118666200317153124.
[34] S. Feng, G. Ji, J. Ma, Z. Wang, Y. Zhao, C. Tao, Long noncoding RNA GAS5 does not regulate HBV replication, J. Med. Virol. 91 (11) (2019 Nov) 1949–1959, https://doi.org/10.1002/jmv.25547.
[35] M.K. Atianand, W. Hu, A.T. Satpathy, Y. Shen, E.P. Ricci, J.R. Alvarez-Dominguez, A. Bhatta, S.A. Schattgen, J.D. McGowan, J. Blin, J.E. Braun, P. Gandhi, M. J. Moore, H.Y. Chang, H.F. Lodish, D.R. Caffrey, K.A. Fitzgerald, A long noncoding

RNA lincRNA-EPS acts as a transcriptional brake to restrain inflammation, Cell 165 (7) (2016 Jun 16) 1672–1685, https://doi.org/10.1016/j.cell.2016.05.075.
[36] W.J. Gong, T. Zhou, S.L. Wu, Y.F. Huang, L.P. Xiang, J.Q. Xu, Y. Han, Y.N. Lv, F. Zeng, Y. Zhang, A novel immune-related ceRNA network that predicts prognosis and immunotherapy response in lung adenocarcinoma, Ann. Transl. Med. 9 (18) (2021 Sep) 1484, https://doi.org/10.21037/atm-21-4151.
[37] Y. Chen, Z. Li, X. Chen, S. Zhang, Long non-coding RNAs: from disease code to drug role, Acta Pharm. Sin. B 11 (2) (2021 Feb) 340–354, https://doi.org/10.1016/j.apsb.2020.10.001.
[38] Z. Li, B. Chen, M. Feng, H. Ouyang, M. Zheng, Q. Ye, Q. Nie, X. Zhang, MicroRNA-23b promotes avian leukosis virus subgroup J (ALV-J) replication by targeting IRF1, Sci. Rep. 5 (2015 May 18), 10294, https://doi.org/10.1038/srep10294.
[39] B.C. Zhang, Z.J. Zhou, L. Sun, pol-miR-731, a teleost miRNA upregulated by megalocytivirus, negatively regulates virus-induced type I interferon response, apoptosis, and cell cycle arrest, Sci. Rep. 6 (2016 Jun 17), 28354, https://doi.org/10.1038/srep28354.
[40] Y. Tang, X. Luo, H. Cui, X. Ni, M. Yuan, Y. Guo, X. Huang, H. Zhou, N. de Vries, P. P. Tak, S. Chen, N. Shen, MicroRNA-146A contributes to abnormal activation of the type I interferon pathway in human lupus by targeting the key signaling proteins, Arthritis Rheum. 60 (4) (2009 Apr) 1065–1075, https://doi.org/10.1002/art.24436.
[41] W. Zheng, Q. Chu, T. Xu, The long noncoding RNA NARL regulates immune responses via microRNA-mediated NOD1 downregulation in teleost fish, J. Biol. Chem. 296 (2021 Jan-Jun), 100414, https://doi.org/10.1016/j.jbc.2021.100414.
[42] Y.S. Lee, X. Bao, H.H. Lee, J.J. Jang, E. Saruuldalai, G. Park, W.R. Im, J.L. Park, S. Y. Kim, S. Shin, S.H. Jeon, S. Kang, H.S. Lee, J.S. Lee, K. Zhang, E.J. Park, I.H. Kim, Y.S. Lee, Nc886, a novel suppressor of the type I interferon response upon pathogen intrusion, Int. J. Mol. Sci. 22 (4) (2021 Feb 18) 2003, https://doi.org/10.3390/ijms22042003.
[43] P. Dai, H. Cao, T. Merghoub, F. Avogadri, W. Wang, T. Parikh, C.M. Fang, P. M. Pitha, K.A. Fitzgerald, M.M. Rahman, G. McFadden, X. Hu, A.N. Houghton, S. Shuman, L. Deng, Myxoma virus induces type I interferon production in murine plasmacytoid dendritic cells via a TLR9/MyD88-, IRF5/IRF7-, and IFNAR-dependent pathway, J. Virol. 85 (20) (2011 Oct) 10814–10825, https://doi.org/10.1128/JVI.00104-11.
[44] L.A. O'Neill, A.G. Bowie, The family of five: TIR-domain-containing adaptors in Toll-like receptor signalling, Nat. Rev. Immunol. 7 (5) (2007 May) 353–364, https://doi.org/10.1038/nri2079.
[45] W. Zheng, Q. Chu, L. Yang, L. Sun, T. Xu, Circular RNA circDtx1 regulates IRF3-mediated antiviral immune responses through suppression of miR-15a-5p-dependent TRIF downregulation in teleost fish, PLoS Pathog. 17 (3) (2021 Mar 18), e1009438, https://doi.org/10.1371/journal.ppat.1009438.
[46] Y.G. Li, U. Siripanyaphinyo, U. Tumkosit, N. Noranate, A. A-Nuegoonpipat, Y. Pan, M. Kameoka, T. Kurosu, K. Ikuta, N. Takeda, S. Anantapreecha, Poly (I:C), an agonist of toll-like receptor-3, inhibits replication of the Chikungunya virus in BEAS-2B cells, Virol. J. 9 (2012 Jun 14) 114, https://doi.org/10.1186/1743-422X-9-114.
[47] S. Heidegger, A. Wintges, F. Stritzke, S. Bek, K. Steiger, P.A. Koenig, S. Göttert, T. Engleitner, R. Öllinger, T. Nedelko, J.C. Fischer, V. Makarov, C. Winter, R. Rad, M.R.M. van den Brink, J. Ruland, F. Bassermann, T.A. Chan, T. Haas, H. Poeck, RIG-I activation is critical for responsiveness to checkpoint blockade, Sci. Immunol. 4 (39) (2019 Sep 13), eaau8943, https://doi.org/10.1126/sciimmunol.aau8943.
[48] W. Lin, J. Zhang, H. Lin, Z. Li, X. Sun, D. Xin, M. Yang, L. Sun, L. Li, H. Wang, D. Chen, Q. Sun, Syndecan-4 negatively regulates antiviral signalling by mediating RIG-I deubiquitination via CYLD, Nat. Commun. 7 (2016 Jun 9), 11848, https://doi.org/10.1038/ncomms11848.
[49] Y. Qiu, X. Geng, J. Ban, Y. Liu, MicroRNA-218 inhibits type I interferon production and facilitates virus immune evasion via targeting RIG-I, Biotechnol. Appl. Biochem. 67 (3) (2020 May) 396–403, https://doi.org/10.1002/bab.1882.
[50] W. Liu, Y. Jin, W. Zhang, Y. Xiang, P. Jia, M. Yi, K. Jia, MiR-202-5p inhibits RIG-I-dependent innate immune responses to RGNNV infection by targeting TRIM25 to mediate RIG-I ubiquitination, Viruses 12 (3) (2020 Feb 27) 261, https://doi.org/10.3390/v12030261.
[51] T.A. Karlsen, J.E. Brinchmann, Liposome delivery of microRNA-145 to mesenchymal stem cells leads to immunological off-target effects mediated by RIG-I, Mol. Ther. 21 (6) (2013 Jun) 1169–1181, https://doi.org/10.1038/mt.2013.55.
[52] R.K. Nam, T. Benatar, Y. Amemiya, A. Seth, MiR-139 induces an interferon-β response in prostate cancer cells by binding to RIG-1, Cancer Genomics Proteomics 18 (3) (2021 May-Jun) 197–206, https://doi.org/10.21873/cgp.20252.
[53] K. Yasukawa, T. Koshiba, Mitochondrial reactive zones in antiviral innate immunity, Biochim. Biophys. Acta Gen. Subj. 1865 (3) (2021 Mar), 129839, https://doi.org/10.1016/j.bbagen.2020.129839.
[54] Z.D. Zhang, T.C. Xiong, S.Q. Yao, M.C. Wei, M. Chen, D. Lin, B. Zhong, RNF115 plays dual roles in innate antiviral responses by catalyzing distinct ubiquitination of MAVS and MITA, Nat. Commun. 11 (1) (2020 Nov 2) 5536, https://doi.org/10.1038/s41467-020-19318-3.
[55] T. Xu, Q. Chu, J. Cui, D. Bi, Inducible MicroRNA-3570 feedback inhibits the RIG-I-dependent innate immune response to rhabdovirus in teleost fish by targeting MAVS/IPS-1, J. Virol. 92 (2) (2018 Jan 2), e01594-17, https://doi.org/10.1128/JVI.01594-17.
[56] Q. Chu, T. Xu, W. Zheng, R. Chang, L. Zhang, Long noncoding RNA MARL regulates antiviral responses through suppression miR-122-dependent MAVS downregulation in lower vertebrates, PLoS Pathog. 16 (7) (2020 Jul 17), e1008670, https://doi.org/10.1371/journal.ppat.1008670.
[57] A.C. Hsu, K. Dua, M.R. Starkey, T.J. Haw, P.M. Nair, K. Nichol, N. Zammit, S. T. Grey, K.J. Baines, P.S. Foster, P.M. Hansbro, P.A. Wark, MicroRNA-125a and -b inhibit A20 and MAVS to promote inflammation and impair antiviral response in COPD, JCI Insight 2 (7) (2017 Apr 6), e90443, https://doi.org/10.1172/jci.insight.90443.
[58] J. Yan, Y. Zhang, Y. Su, L. Tian, P. Qin, X. Xu, Y. Zhou, microRNA-125a targets MAVS and TRAF6 to modulate interferon signaling and promote HCV infection, Virus Res. 296 (2021 Apr 15), 198336, https://doi.org/10.1016/j.virusres.2021.
[59] S. Wan, U. Ashraf, J. Ye, X. Duan, A. Zohaib, W. Wang, Z. Chen, B. Zhu, Y. Li, H. Chen, S. Cao, MicroRNA-22 negatively regulates poly(I:C)-triggered type I interferon and inflammatory cytokine production via targeting mitochondrial antiviral signaling protein (MAVS), Oncotarget 7 (47) (2016 Nov 22) 76667–76683, https://doi.org/10.18632/oncotarget.12395.
[60] P. Hou, H. Wang, G. Zhao, G. Hu, X. Xia, H. He, MiR-3470b promotes bovine ephemeral fever virus replication via directly targeting mitochondrial antiviral signaling protein (MAVS) in baby hamster Syrian kidney cells, BMC Microbiol. 18 (1) (2018 Dec 27) 224, https://doi.org/10.1186/s12866-018-1366-6.
[61] K. Yasukawa, D. Kinoshita, K. Yaku, T. Nakagawa, T. Koshiba, The microRNAs miR-302b and miR-372 regulate mitochondrial metabolism via the SLC25A12 transporter, which controls MAVS-mediated antiviral innate immunity, J. Biol. Chem. 295 (2) (2020 Jan 10) 444–457, https://doi.org/10.1074/jbc.RA119.010511.
[62] L. Sun, J. Wu, F. Du, X. Chen, Z.J. Chen, Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway, Science 339 (6121) (2013 Feb 15) 786–791, https://doi.org/10.1126/science.1232458.
[63] T. Xu, Q. Chu, J. Cui, Rhabdovirus-inducible MicroRNA-210 modulates antiviral innate immune response via targeting STING/MITA in fish, J. Immunol. 201 (3) (2018 Aug 1) 982–994, https://doi.org/10.4049/jimmunol.1800377.
[64] A. Shen, D. Zheng, Y. Luo, T. Mou, Q. Chen, Z. Huang, Z. Wu, MicroRNA-24-3p alleviates hepatic ischemia and reperfusion injury in mice through the repression of STING signaling, Biochem. Biophys. Res. Commun. 522 (1) (2020 Jan 29) 47–52, https://doi.org/10.1016/j.bbrc.2019.10.182.
[65] Q. Yu, L. Chu, Y. Li, Q. Wang, J. Zhu, C. Wang, S. Cui, miR-23a/b suppress cGAS-mediated innate and autoimmunity, Cell. Mol. Immunol. 18 (5) (2021 May) 1235–1248, https://doi.org/10.1038/s41423-021-00668-x.
[66] M. Khan, J.S. Harms, Y. Liu, J. Eickhoff, J.W. Tan, T. Hu, F. Cai, E. Guimaraes, S. C. Oliveira, R. Dahl, Y. Cheng, D. Gutman, G.N. Barber, G.A. Splitter, J.A. Smith, Brucella suppress STING expression via miR-24 to enhance infection, PLoS Pathog. 16 (10) (2020 Oct 27), e1009020, https://doi.org/10.1371/journal.ppat.1009020.
[67] M.Z. Wu, W.C. Cheng, S.F. Chen, S. Nieh, C. O'Connor, C.L. Liu, W.W. Tsai, C. J. Wu, L. Martin, Y.S. Lin, K.J. Wu, L.F. Lu, J.C. Izpisua Belmonte, miR-25/93 mediates hypoxia-induced immunosuppression by repressing cGAS, Nat. Cell Biol. 19 (10) (2017 Oct) 1286–1296, https://doi.org/10.1038/ncb3615.
[68] H. Su, W. Zheng, J. Pan, X. Lv, S. Xin, T. Xu, Circular RNA circSamd4a regulates antiviral immunity in teleost fish by upregulating STING through sponging miR-29a-3p, J. Immunol. 207 (11) (2021 Dec 1) 2770–2784, https://doi.org/10.4049/jimmunol.2100469.
[69] M. Aznaourova, H. Janga, S. Sefried, A. Kaufmann, J. Dorna, S.M. Volkers, P. Georg, M. Lechner, J. Hoppe, S. Dökel, N. Schmerer, A.D. Gruber, U. Linne, S. Bauer, L.E. Sander, B. Schmeck, L.N. Schulte, Noncoding RNA MaIL1 is an integral component of the TLR4-TRIF pathway, Proc. Natl. Acad. Sci. U. S. A. 117 (16) (2020 Apr 21) 9042–9053, https://doi.org/10.1073/pnas.1920393117.
[70] Y. Zhou, M. Li, Y. Xue, Z. Li, W. Wen, X. Liu, Y. Ma, L. Zhang, Z. Shen, X. Cao, Interferon-inducible cytoplasmic lncLrrc55-AS promotes antiviral innate responses by strengthening IRF3 phosphorylation, Cell Res. 29 (8) (2019 Aug) 641–654, https://doi.org/10.1038/s41422-019-0193-0.
[71] X. Li, G. Guo, M. Lu, W. Chai, Y. Li, X. Tong, J. Li, X. Jia, W. Liu, D. Qi, X. Ye, Long noncoding RNA lnc-MxA inhibits beta interferon transcription by forming RNA-DNA triplexes at its promoter, J. Virol. 93 (21) (2019 Oct 15), e00786-19, https://doi.org/10.1128/JVI.00786-19.
[72] M. Jiang, S. Zhang, Z. Yang, H. Lin, J. Zhu, L. Liu, W. Wang, S. Liu, W. Liu, Y. Ma, L. Zhang, X. Cao, Self-recognition of an inducible host lncRNA by RIG-I feedback restricts innate immune response, Cell 173 (4) (2018 May 3) 906–919, https://doi.org/10.1016/j.cell.2018.03.064, e13.
[73] J. Fan, M. Cheng, X. Chi, X. Liu, W. Yang, A human long non-coding RNA LncATV promotes virus replication through restricting RIG-I-mediated innate immunity, Front. Immunol. 10 (2019 Jul 19) 1711, https://doi.org/10.3389/fimmu.2019.01711.
[74] H. Ma, P. Han, W. Ye, H. Chen, X. Zheng, L. Cheng, L. Zhang, L. Yu, X. Wu, Z. Xu, Y. Lei, F. Zhang, The long noncoding RNA NEAT1 exerts antihantaviral effects by acting as positive feedback for RIG-I signaling, J. Virol. 91 (9) (2017 Apr 13), e02250-16, https://doi.org/10.1128/JVI.02250-16.
[75] J.H. Chen, D.D. Feng, Y.F. Chen, C.X. Yang, C.X. Juan, Q. Cao, X. Chen, S. Liu, G. P. Zhou, Long non-coding RNA MALAT1 targeting STING transcription promotes bronchopulmonary dysplasia through regulation of CREB, J. Cell Mol. Med. 24 (18) (2020 Sep) 10478–10492, https://doi.org/10.1111/jcmm.15661.
[76] P. Xia, S. Wang, B. Ye, Y. Du, C. Li, Z. Xiong, Y. Qu, Z. Fan, A circular RNA protects dormant hematopoietic stem cells from DNA sensor cGAS-mediated exhaustion, Immunity 48 (4) (2018 Apr 17) 688–701.e7, https://doi.org/10.1016/j.immuni.2018.03.016.
[77] Q. Wu, X. Ning, L. Sun, Megalocytivirus induces complicated fish immune response at multiple RNA levels involving mRNA, miRNA, and circRNA, Int. J. Mol. Sci. 22 (6) (2021 Mar 19) 3156, https://doi.org/10.3390/ijms22063156.
[78] O. Beylerli, D. Khasanov, I. Gareev, E. Valitov, A. Sokhatskii, C. Wang, V. Pavlov, G. Khasanova, A. Ahmad, Differential non-coding RNAs expression profiles of invasive and non-invasive pituitary adenomas, Non-coding RNA Res. 6 (3) (2021 Jun 30) 115–122, https://doi.org/10.1016/j.ncrna.2021.06.004.

[79] A. Sufianov, S. Begliarzade, T. Ilyasova, Y. Liang, O. Beylerli, MicroRNAs as prognostic markers and therapeutic targets in gliomas, Non-coding RNA Res. 7 (3) (2022 Jul 6) 171–177, https://doi.org/10.1016/j.ncrna.2022.07.001.
[80] A. Sufianov, S. Begliarzade, T. Ilyasova, X. Xu, O. Beylerli, MicroRNAs as potential diagnostic markers of glial brain tumors, Non-coding RNA Res. 7 (4) (2022 Sep 22) 242–247, https://doi.org/10.1016/j.ncrna.2022.09.008.
[81] A. Beilerli, S. Begliarzade, A. Sufianov, T. Ilyasova, Y. Liang, O. Beylerli, Circulating ciRS-7 as a potential non-invasive biomarker for epithelial ovarian cancer: an investigative study, Non-coding RNA Res. 7 (3) (2022 Jul 31) 197–204, https://doi.org/10.1016/j.ncrna.2022.07.004.
[82] I. Gareev, V. Kudriashov, A. Sufianov, S. Begliarzade, T. Ilyasova, Y. Liang, O. Beylerli, The role of long non-coding RNA ANRIL in the development of atherosclerosis, Non-coding RNA Res. 7 (4) (2022 Sep 6) 212–216, https://doi.org/10.1016/j.ncrna.2022.09.002.
[83] C. Zhang, B. Zhang, RNA therapeutics: updates and future potential, Sci. China Life Sci. 66 (1) (2023 Jan) 12–30, https://doi.org/10.1007/s11427-022-2171-2.