

REVIEW

Long noncoding RNAs: Novel regulators of virus-host interactions

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Summary

Long noncoding RNAs (lncRNAs) represent a key class of cellular regulators, involved in the modulation and control of multiple biological processes. Distinct classes of lncRNAs are now known to be induced by host cytokines following viral infections. Current evidence demonstrates that lncRNAs play essential roles at the host-pathogen interface regulating viral infections by either innate immune responses at various levels including activation of pathogen recognition receptors or by epigenetic, transcriptional, and posttranscriptional effects. We review the newly described mechanisms underlying the interactions between lncRNAs, cytokines, and metabolites differentially expressed following viral infections; we highlight the regulatory networks of host antiviral responses and emphasize the need for interdisciplinary research between lncRNA biology and immunology to deepen understanding of viral pathogenesis.

KEYWORDS

cell metabolism, epigenetic regulation, innate immune response, long noncoding RNA, pathogen recognition receptor

Abbreviations: CARDs, caspase activation and recruitment domains; CTD, C-terminal domain; EVA71, enterovirus A71; GOT2, glutamic-oxaloacetic transaminase 2; HBV, hepatitis B virus; HCMV, human cytomegalovirus; IFN- α , interferon alpha; IKK, I κ B kinase; IRF3, interferon regulatory factor 3; IRGs, immune response genes; ISGs, interferon-stimulated genes; KSHV, Kaposi's sarcoma-associated herpesvirus; L-ASP, L-aspartic acid; lncRNA, long noncoding RNA; MDA5, melanoma differentiation-associated gene 5; miRNA, microRNA; NADPH, nicotinamide adenine dinucleotide phosphate; ncRNAs, noncoding RNAs; NEMO, NF- κ B essential modulator; P, phosphorylation; piRNAs, piwi-interacting RNA; PRRs, pathogen recognition receptors; RIG-I, retinoic acid-inducible gene-I; SARS-CoV, severe acute respiratory syndrome-associated coronavirus; TLRs, Toll-like receptors; TMEV, Theiler's murine encephalomyelitis virus; TNF- α , tumor necrosis factor- α ; VSV, vesicular stomatitis virus; α -KG, α -ketoglutarate

1 | INTRODUCTION

In recent years, with the advent of microRNA (miRNA) research and the development of high-throughput sequencing technologies, numerous novel long noncoding RNAs (lncRNAs) have been discovered and functionally annotated.¹ The discovery of lncRNAs dates back to 1990 when the first lncRNA, *H19*, was identified in mammals and the first functionally characterized lncRNA, *Xist*, was implicated in the X chromosome inactivation in the female embryos of eutherian mammals in 1991.^{2,3} In 2002, a large-scale discovery of lncRNAs was achieved by sequence analyses of 60 770 murine full-length complementary DNAs (cDNAs).⁴ As of November 2018, approximately 16 066 human lncRNAs and nearly 29 566 transcripts have been released by GenCode (Version 29).⁵ However, we still possess an extremely limited understanding of lncRNAs, which is exemplified by the fact that less than 200 lncRNAs have been investigated and functionally annotated thus far.⁶ New genetic and cell regulatory mechanisms have been revealed by the discoveries and functional annotation of noncoding RNAs, which have made a major impact on the development of life sciences. Studies have found that lncRNAs participate in the regulation of various biological processes by interactions with both nucleic acids and proteins and are also intimately involved in the development of malignancy and in host response to infectious diseases.^{7,8} In addition, research has also revealed that viral infections can cause abnormal lncRNA expression in host cells and that some lncRNAs are also encoded by viruses.^{9,10} These host and virally encoded lncRNAs regulate infections through various regulatory mechanisms, such as participating in innate immune responses and altering cellular metabolic pathways.^{11,12} Therefore, increased investigation and the functional characterization of the lncRNA repertoire elicited during the innate immune response and alterations in cellular metabolism following viral infection will help to elucidate the host defense mechanisms against viruses and provide potential targets for therapeutic intervention and a deeper understanding of viral pathogenesis.

1.1 | Origin and types of lncRNAs

lncRNAs are arbitrarily defined as a class of RNA molecules greater than 200 nucleotides (nts) in length, transcribed by RNA polymerase II or III, without a protein-coding open reading frame. Similar to protein-coding mRNAs, most lncRNAs are 5' capped, spliced,¹³ and can be either polyadenylated or nonpolyadenylated (ie, are bimorphic).^{14,15} lncRNAs are distributed in both the nucleus and cytoplasm, typically have low expression levels, and exhibit poor conservation between species, although their structure is well conserved.^{16,17} The abundance of lncRNA transcripts is typically at least an order of magnitude lower than that of mRNAs, with an estimated 80% of lncRNAs tissue-specific.¹⁸⁻²⁰ According to the positional relationship between lncRNAs and their target genes on the chromosome, lncRNAs can be classified into five groups^{21,22}: (1) sense lncRNAs: located on the positive DNA strand and partially overlap with protein-coding genes (see Figure 1A); (2) intronic lncRNAs: located

entirely within an intron sequence of a target gene (Figure 1B); (3) long intergenic noncoding RNAs (lincRNAs): coexist on the same strand and are located upstream of the target gene with a spacing of less than 10 kb (Figure 1C); (4) antisense lncRNAs: located on the opposite strand of their target gene, and partially, or completely, overlap with the coding region (Figure 1D); and (5) bidirectional lncRNAs: located on the negative strand of the target gene with a spacing of less than 1 kb whereby transcriptional orientation is opposing and the transcripts do not overlap (Figure 1E).

1.2 | The currently known functional properties of lncRNAs

It has been estimated that about 70% of the human genome can be transcribed, among which, only approximately 1% to 2% of the transcripts encode proteins, and the remaining 98% are noncoding RNAs (ncRNAs).^{5,23} Among the ncRNAs, tRNAs and rRNAs are well known for their structural and scaffolding roles, while the vast majority of the remaining ncRNA fraction have been regarded as "transcriptional noise," and, until recently, their biology and roles in transcriptional processes are largely ignored. Gradually, studies have confirmed the functional importance of ncRNAs and that they play pivotal roles in cellular and metabolic activities,⁸ with small ncRNAs and lncRNAs now known to account for an estimated 20% to 42% of ncRNAs.²⁴ Small ncRNAs, such as miRNAs, are involved in the regulation of a variety of cellular activities leading to gene silencing by base pairing with specific complementary nucleotide sequences of the mRNAs of their target genes.²⁵ In contrast, lncRNAs greater than 200 nts in length exert their functions by a greater variety of known mechanisms through interactions with either target proteins or nucleic acids via their specific and complex secondary structures.²⁶⁻³⁰ These known mechanisms can be classified into seven distinct groups: (1) lncRNA binds to transcription factors to form a transcription complex, which affects downstream gene expression by inhibiting RNA polymerase II or by mediating chromatin remodeling and histone modifications³¹⁻³⁴; (2) lncRNA forms a complementary double-stranded region with the mRNA transcript of its target gene, thereby interfering with the cleavage, transport, and/or translation of the targeted mRNA³⁵; (3) lncRNA competes with a target gene for transcription factors, thereby silencing the target gene expression; (4) lncRNA acts as a scaffold to bring multiple proteins together to regulate gene transcription³⁶; (5) lncRNA binds to a specific protein, altering the activity or cytoplasmic localization of the protein³⁷; (6) a lncRNA gene transcribes an additional ncRNA, such as pseudogenes and circular RNAs, and because of the similarity to the mRNA sequence of the target gene, the ncRNA can operate as a molecular sponge that attracts miRNAs, thereby insulating the transcription and translation of the functional genes from miRNA effects and enabling cross talk between different ncRNA classes³⁸; and finally (7) lncRNAs can be transcribed as the precursors of small molecule RNAs, such as miRNAs and piwi-interacting RNAs (piRNAs).³⁹ In summary, lncRNAs can regulate gene expression through DNA and RNA modifications by a variety of modes, such as by serving as signal molecules, decoy molecules, guide

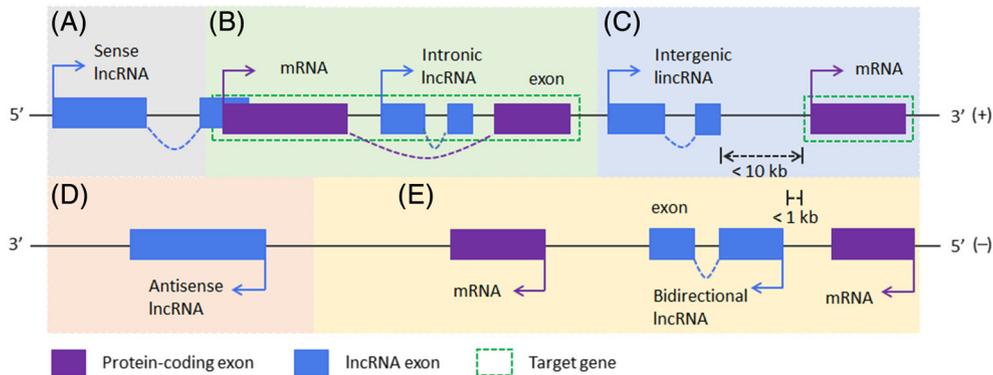


FIGURE 1 Current classification of long noncoding RNAs (lncRNAs) based on the positional relationship between lncRNAs and adjacent protein-encoding genes. A, Sense lncRNAs partially overlap with protein-coding genes. B, Intronic lncRNAs are located on an intron of the target gene. C, Intergenic lncRNAs are located between two protein-coding genes (<10 kb apart from the target gene). D, Antisense lncRNAs are located on the negative strand and partially or completely overlap with the protein-coding gene. E, Bidirectional lncRNAs are located on the negative strand, which are transcribed in the opposite direction, but does not overlap with the target gene. Arrows indicate the direction of gene transcription. Genomic DNA plus (+) and minus (-) strands are labeled accordingly. The target gene of sense lncRNA, intronic lncRNA, and antisense lncRNA is shown in panel B and that of intergenic lncRNA and bidirectional lncRNA is shown in panel C

molecules, molecular sponges, and scaffolds.^{27,40} lncRNAs participate in multiple biological processes such as cell differentiation, carcinogenesis, and immune responses and play important roles in the development and, thereby, potentially in the prevention of human diseases.^{28,29,41,42} In the past decade, lncRNA biology has become a new frontier in life sciences and attracted many researchers to the field. In this review, we will focus on the present state of understanding of lncRNAs in the context of innate antiviral immunity.

2 | DIFFERENTIAL EXPRESSION OF LNCRNAs

2.1 | Viral infection and differential expression of lncRNAs

Virus infection elicits changes in the expression of cellular lncRNAs. By means of gene chip analyses, Winterling and colleagues revealed 17 differentially expressed lncRNAs in human alveolar epithelial cells (A549) infected with influenza virus A/WSN/33 (H1N1).⁴³ Subsequently, using high-throughput sequencing, numerous research groups identified thousands of differentially expressed lncRNAs following viral infection. In order to systematically study the regulatory effects of the neurotropic enterovirus A71 (EVA71) infection on lncRNAs, Yin et al performed a comprehensive analysis of EVA71-infected rhabdomyosarcoma (RD) cells and observed differential expression of greater than 4800 lncRNAs.⁴⁴ Similarly, Meng et al identified 8541 differentially expressed lncRNAs in EVA71-infected human peripheral blood mononuclear cells.⁴⁵ Also, using the RNA sequencing (RNA-Seq) technique, Shi et al identified a total of 760 and 1210 lncRNAs that were upregulated and downregulated, respectively, in RD cells infected with Coxsackievirus A16 (CVA16). Interestingly, there was an apparent bias in the lncRNA class differentially regulated upon CVA16 infection as

approximately 43.6% and 22.3% were intergenic and sense lncRNAs, respectively, demonstrating a significant enrichment upon viral infection of the former lncRNA class.⁴⁶ Peng and colleagues have analyzed the lung transcriptome in severe acute respiratory syndrome-associated coronavirus (SARS-CoV)-infected mice and reported that the expression of 504 annotated and 1406 unannotated lncRNAs had significant changes.⁴⁷ In addition, other viral families, such as Zika virus,⁴⁸ hepatitis B virus (HBV),⁴⁹⁻⁵¹ and hepatitis C virus,⁵² have been shown upon host infection to lead to differential expression of host lncRNAs compared with uninfected controls. Therefore, the differential expression of lncRNAs in various cell types following viral infection appears to be a widespread phenomenon and not a property attributable to one viral family or host target cell.

Surprisingly, some viruses also encode their own lncRNAs to modulate the host immune response. For example, human cytomegalovirus (HCMV) encodes a 2.7 kb lncRNA, $\beta 2.7^{53}$; $\beta 2.7$ inhibits the induction of stress responses and apoptosis in infected cells, which facilitates HCMV replication.⁹ Gammaherpesviruses transcribe their own structurally and functionally intricate lncRNAs, which modulate cellular and viral gene expression to maintain viral latency or to induce lytic reactivation.⁵⁴ In addition, a 3.91 kb lncRNA M3-04 generated by gammaherpesviruses regulates viral replication in mice by interacting with antisense miRNAs and the latency gene M2.⁵⁵ Other herpesviruses also encode multiple functional lncRNAs, such as the Epstein-Barr virus encoding ncRNA, *BamH I-A* rightward transcripts,⁵⁶ Kaposi's sarcoma-associated herpesvirus (KSHV) encoding *UCA1*,⁵⁷ and herpesvirus saimiri encoding U-rich RNAs.⁵⁸ Additionally, the 3'-untranslated region (UTR) of the flavivirus RNA genome is capable of transcribing an active lncRNA, termed the subgenomic flavivirus RNA (sfRNA), which protects viral RNAs from degradation by the host nuclease Xrn1 and suppresses antiviral RNA interference (RNAi) in infected human cells in culture and, also, interestingly, in mosquitoes by direct interaction with the RNAi machinery.^{10,59} Therefore, viral infection

can induce differential expression of a series of lncRNAs in cells, suggesting that lncRNAs may play important functional roles in viral infection.

2.2 | Cytokines and differential expression of lncRNAs

Cytokines play an essential role in regulating the development, maturation, and differentiation of nonspecific innate immune cells. lncRNAs are found to be deregulated upon viral infection or following interferon (IFN) treatment, and some lncRNAs can modulate viral infection in an IFN-dependent manner.⁶⁰ To investigate whether IFN regulates the transcription of lncRNAs, Carnero et al stimulated human hepatoma (Huh7) cells with high doses of type I interferon alpha (IFN- α) and found that IFN- α significantly upregulated the expression of lncRNAs *ISR2*, *ISR8*, and *ISR12*.⁶¹ Similarly, treatment of Huh7 cells by IFN- α 2 or type III IFN- λ induced an upregulation of the expression of lncRNAs *BST2* and *ISG15*. Inhibition experiments showed that lncRNA *BST2* is a positive regulator of the host antiviral factor *BST2*.⁶² Tumor necrosis factor- α (TNF- α) also induces the differential expression of the lncRNA *Lethe*, which responds to NF- κ B stimulation and reduces inflammation.⁶³ The lncRNA *NKILA* which is induced by proinflammatory cytokines binds to NF- κ B/I κ B and directly masks the phosphorylation motifs of I κ B, thereby inhibiting IKK-induced I κ B phosphorylation and downstream NF- κ B activation, and thereby preventing excessive activation of the NF- κ B pathway in epithelial cells.⁶⁴ Therefore, the inductive effect of cytokines is closely related to and modulated by the differential expression of host lncRNAs.

2.3 | Metabolites and differential expression of lncRNAs

Metabolites not only function within cellular metabolic pathways but have also been implicated in the regulation and differential expression of lncRNAs. The specific β 3-adrenergic receptor agonist, CL-316,243, induces the differentiation of brown adipocytes, and a total of 21 differentially expressed lncRNAs have been detected in both cellular and adipose tissues.⁶⁵ This has led to the identification of the lncRNA *Blnc1* as a key regulator of brown cell differentiation and function. *Blnc1* forms a nuclear ribonucleoprotein complex with the transcription factor EBF2, to stimulate and activate the thermogenic adipose program.⁶⁵ In addition, lncRNA *Blnc1* itself is a target of EBF2, and through a feedforward regulatory loop, the cells and tissues differentiate into a pyrogenic phenotype that favors adipogenesis.

The prostate-specific lncRNA *PCGEM1* can be induced by androgens, which promotes glucose uptake. Coupling with the pentose phosphate pathway, *PCGEM1* promotes the synthesis of nucleic acids and lipids and balances the redox reaction by generating NADPH.⁶⁶ In addition, lncRNA *PCGEM1* affects glutamine metabolism at the transcriptional level. Taken together, lncRNA *PCGEM1* is a key transcriptional regulator of cellular metabolic pathways.

In the process of viral infection, lncRNAs can act as mediators to link viral infection to innate immunity and cellular metabolism. lncRNAs are involved in not only cytokine-mediated innate antiviral immune responses but also the regulation of cellular metabolic pathways, altering the efficiency of viral replication in cells. The perturbation of the transcription of ncRNAs elicited by virus infection often leads to disturbance of homeostasis, resulting in disease.⁶⁷ lncRNAs regulate viral infections by modifying innate immune responses and cellular metabolic pathways at various levels including the activation of pathogen recognition receptors (PRRs), epigenetic modulation, and transcriptional and posttranscriptional modification.²⁹

3 | REGULATION OF VIRAL REPLICATION BY LNCRNA-MEDIATED INNATE IMMUNITY

3.1 | Activation of pathogen recognition receptor-related signals by lncRNAs

Innate immunity is the first line of defense against viral infections and plays a key role in identification of viral RNAs, induction of interferon-stimulated genes (ISGs), and proinflammatory responses in the early stages of the infection process.^{68,69} Whether viral infection activates innate immunity is dependent on the activation of PRRs and PRR-dependent signaling pathways. Virus infection can also activate retinoic acid-inducible gene-I (RIG-I), Toll-like receptors (TLRs), melanoma differentiation-associated gene 5 (MDA5), and Nod-like receptor (NLR) pathways,⁷⁰ which in turn activate interferon regulatory factors, such as IRF3, IRF7, and the major proinflammatory transcription factor NF- κ B.^{71,72} The lncRNAs *Lethe* and *lnc-Lsm3b* have been shown to bind directly to immunosensors and block downstream signaling of the innate immune pathway (Table 1). The lncRNA *Lethe* competitively binds with and blocks NF- κ B from binding to specific promoter regions of its target genes, thereby preventing a cascade of signal transduction events.⁶³ The IFN-inducible, host-derived lncRNA, *lnc-Lsm3b*, directly competes with vesicular stomatitis virus (VSV) RNA for the binding to the RIG-I monomer, limiting the conformational transition of the RIG-I PRR. Feedback in the later stages of the innate immune response inactivates RIG-I (Figure 2A),⁷³ thereby inhibiting the development of virus infection or activating type I interferon-mediated immune cells, such as dendritic, NK, and T cells, either directly or indirectly eliminating viral infections.⁸⁷ In addition, *lnc-Lsm3b* interferes with the interaction between caspase activation and recruitment domain (CARD) proteins, present in numerous innate immune effectors and the mitochondrial antiviral signaling (MAVS) protein by stabilizing the interaction between the N-terminal CARD of RIG-I and the helicase domain. It has been demonstrated that TRIM25-mediated ubiquitination of RIG-I K63 is also inhibited by *lnc-Lsm3b* upon RNA virus stimulation. Taken together, these findings implicate *lnc-Lsm3b* as a potent negative regulator of innate RIG-I signaling pathway upon RNA virus infections.⁷³

TABLE 1 Host lncRNAs implicated in the innate antiviral immune response

lncRNAs	Name	Stimuli	Functions/Mechanisms	Refs.
PRR-related signal transduction	<i>Lethe</i>	TNF- α	<i>lncRNA Lethe</i> competitively binds with NF- κ B and inhibits the interaction between NF- κ B and the promoter, thereby preventing downstream signal transduction.	Rapicavoli et al ⁶³
	<i>Lsm3b</i>	VSV	Binding of <i>lnc-Lsm3b</i> restricts the conformational change of the RIG-I protein, which inactivates the function of RIG-I, thereby limiting the production of type I interferon IFN- β .	Jiang et al ⁷³
Pretranscriptional level	<i>lincRNA-Cox2</i>	Pam3CKK4, LPS	<i>lincRNA-Cox2</i> interacts with hnRNP A/B or the SWI/SNF complex to regulate the expression of the innate immune-associated cytokines, chemokines, and ISGs that mediate inflammatory responses.	Hu et al ⁷⁴ and Carpenter et al ⁷⁵
	<i>NeST</i>	Theiler's virus	<i>NeST</i> binds to WDR5, which is implicated in nucleosomal core histone methylation, thereby negatively regulating the transcription of type II interferons in CD8 ⁺ T cells.	Gomez et al ⁷⁶
	<i>NRAV</i>	IAV	<i>NRAV</i> inhibits the transcriptional initiation of antiviral genes by affecting the histone modifications of <i>MXA</i> and <i>IFITM3</i> (H3K4me3 and H3K27me3).	Ouyang et al ⁷⁷
	<i>Aspro5</i>	HIV	<i>Aspro5</i> recruits a variety of histone modification enzymes to form a heterochromatic structure inhibiting the transcriptional activity of the viral promoter.	Saayman et al ⁷⁸
	<i>NRON</i>	HIV	A complex of the <i>lincRNA NRON</i> , a scaffold protein, and three NFAT kinases forms a large cytoplasmic RNA-protein scaffold to inhibit the function of the transcription factor NFAT.	Sharma et al ³⁶
Transcriptional level	<i>NEAT1</i>	HIV	<i>NEAT1</i> interacts with the NONO protein to promote the formation of paraspeckles in the nucleus and to deactivate the splicing factor SFPQ in the transcription of IL-8.	Imamura et al ³⁷
	<i>lincRNA-EPS</i>	LPS	<i>lincRNA-EPS</i> controls nucleosome localization and inhibits IRG transcription by interacting with heterogeneous nuclear ribonucleoprotein L.	Atianand et al ⁷⁹
	<i>sRNA</i>	Flaviviruses	<i>sRNA</i> prevents the activation of the IFN- β promoter and the initiation of transcription by inhibiting the phosphorylation of IRF3.	Pijman et al ⁸⁰ and Chang et al ⁸¹
Posttranscriptional level	<i>sRNA</i>	Dengue virus	<i>sRNA</i> binds to the host RNA binding protein and CAPRIN1 and inhibits the transcription of <i>IFITM2</i> and <i>PKR</i> ; <i>sRNA</i> also binds to the ubiquitin ligase TRIM25 and negatively regulates <i>RIG-I</i> expression.	Manokaran et al ⁸² and Bidet et al ⁸³
	<i>NEAT1</i> <i>ISG20</i>	HIV Sendai virus; IAV; poly I:C	<i>NEAT1</i> inhibits nuclear export of HIV-1 mRNAs and reduces replication efficiency in viral cells. Acts as a competitive endogenous RNA (ceRNA) of <i>ISG20</i> mRNA, <i>lncRNA ISG20</i> binds to miRNA-326, releases its transcriptional repression of <i>ISG20</i> mRNA, and activates the innate immune response.	Zhang et al ⁸⁴ Chai et al ⁸⁵
Metabolic level	<i>ACOD1</i>	VSV	<i>ACOD1</i> binds to GOT2, an important aminotransferase during metabolism in the cytoplasm, and elevates the activity of GOT2, which in turn regulates the metabolism of L-aspartate and α -ketoglutarate, thereby promoting viral replication.	Wang et al ⁸⁶

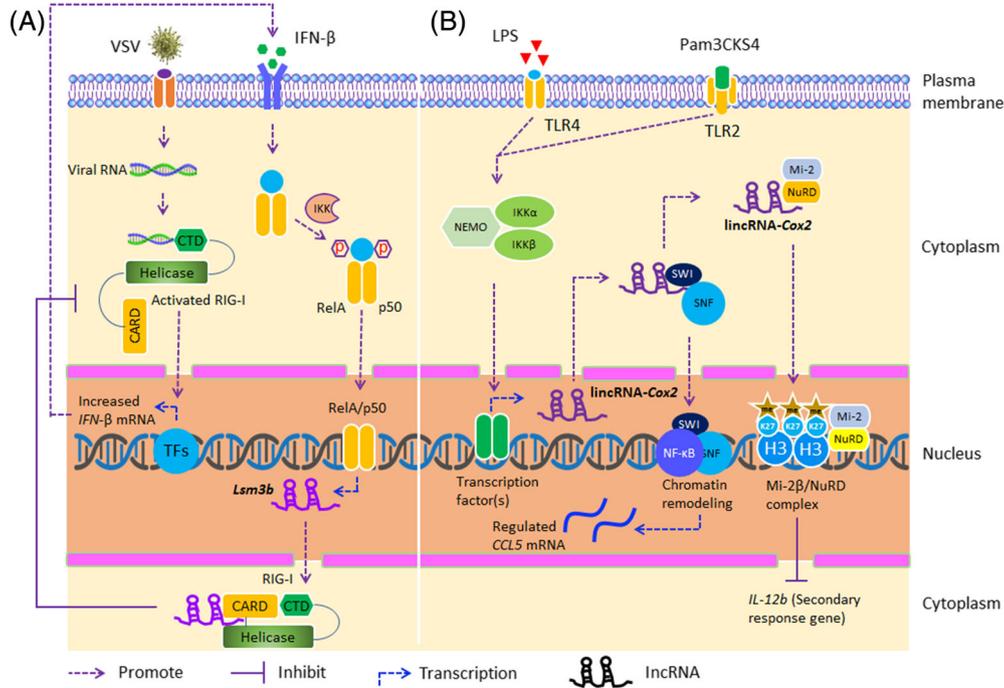


FIGURE 2 Long noncoding RNAs (lincRNAs) regulate innate immune responses through activation of RIG-I and via deregulation of epigenetic mechanisms. A, Under normal circumstances in the resting state of macrophages, RIG-I exists in the autoinhibited state with the CARD2 domain of RIG-I binding to the insertion region of the helicase. With the invasion of the 5'-triphosphate double-stranded viral RNA, the CTD senses and binds the viral RNA, which leads to the structural transformation of RIG-I into an open conformation and the release of CARDs, thereby mediating downstream signaling and induction of IFN- β expression. After sensing the extracellular IFN- β signal, TLR2 upregulates the expression of linc-Lsm3b, which inhibits RIG-I-mediated immune responses by binding to RIG-I and suppresses the production of IFN- β and other anti-inflammatory factors. B, TLR2 and TLR4 induce the expression of lincRNA-Cox2 through the NF- κ B signal pathway upon LPS or Pam3CCKS4 stimulation. On the one hand, lincRNA-Cox2 promotes the binding of the Mi-2/NuRD complex in the promoter region of IL-12b, decreasing histone H3K27 acetylation and increasing H3K27 dimethylation, which leads to lincRNA-Cox2-mediated transinhibition of the secondary response gene IL-12b. Alternatively, upon LPS stimulation, lincRNA-Cox2 is assembled into the SWI/SNF complex and acts to recruit NF- κ B to the complex, which plays an important role in the regulation of SWI/SNF-associated chromatin remodeling and the transactivation of advanced inflammatory response genes

3.2 | lincRNAs regulate innate immunity through epigenetic regulation of gene transcription

Epigenetic regulation is a reversible modification of genetic functions by modifying expression without alteration of the underlying nucleotide sequence during the pretranscriptional regulation of eukaryotic genes.⁸⁸ lincRNAs can regulate gene expression at the epigenetic level through chromatin remodeling pathways.^{29,89} For example, lipopolysaccharide (LPS) (or the synthetic triacylated lipopeptide Pam3CCKS4) can induce formation of a lincRNA-Cox2 and SWI/SNF complex which modulates the assembly of NF- κ B subunits to the SWI/SNF complex in macrophages, triggering chromatin remodeling and transactivation of the late-primary inflammatory response genes in response to microbial challenge (Figure 2B and Table 1).^{74,75} lincRNA-Cox2 regulates the expression of numerous ISGs, such as *OAS1*, *OAS2*, *OASL*, *IFI204*, and *ISG15* through the binding of hnRNP-A/B or A2/B1.^{75,90} Surprisingly, the expression of the adjacent gene *Cox2*, which is also an essential immunoregulatory factor, is not affected by lincRNA-Cox2 raising the possibility that another layer of transcriptional regulation is potentially affected by ncRNAs and other protein effectors remains undiscovered.

It is well established that many lincRNA-mediated epigenetic regulations occur through modification of the nucleosomal core histone H3. Trimethylation of the N-terminal lysines of H3 at residues 4 and 27 (H3K4me3 and H3K27me3, respectively) can determine the structural state of the chromatin (ie, "loose" euchromatin or "tight" heterochromatin), and correspondingly, the expression of the cis-linked genes can be switched to "on" or "off."^{76,91} In A549 cells, by regulating the abundance of the lincRNA negative regulator of antiviral response (NRAV), located on chromosome 12q24.31, H3K27me3 is significantly enriched, thereby promoting the expression of ISGs, such as the immune effector proteins MxA and IFITM3. In turn, innate antiviral immunity is activated, and viral genome replication is inhibited.⁷⁷ In addition, the lincRNA-Cox2 promotes the assembly of the reconstituted Mi-2 nucleosome and the deacetylase (Mi-2/NuRD) repressor complex in the promoter region of the secondary response gene *IL-12b*, resulting in a decrease of histone H3K27 acetylation and an elevation of H3K27 dimethylation, respectively. This epigenetic mechanism contributes to the lincRNA-Cox2-mediated transinhibition of the *IL-12b* gene.⁹²

The lincRNA *NeST* can promote the formation of H3K4me3 by forming a complex with the WD (Trp-Asp) repeat-containing protein

WDR5, thereby repressing the IFN- γ promoter. This ultimately results in an increase in type II interferon transcript levels in the activated CD8⁺ T cells.⁷⁶ Interestingly, this enhancer-like lncRNA *NeST* is located adjacent to the IFN- γ -encoding locus in both the mouse (*Ifng*) and human (*IFNG*) genomes. *NeST* was initially discovered as a candidate susceptibility locus for infection by Theiler's murine encephalomyelitis virus (TMEV), a single-stranded, positive sense RNA cardiovirus, family *Picornaviridae*. The acronym *NeST* abbreviates in French as *nettoie Salmonella pas Theiler's* ("cleanup Salmonella not Theiler's"). In both the murine and human genomes, not only is synteny conserved but the *NeST* lncRNA is also encoded on the opposite DNA strand to that coding for IFN- γ in both species. Thereby, the survival of TMEV is prolonged in mice, but the pathogenicity of *Salmonella enterica* is attenuated.⁷⁶ Whether such host-derived lncRNAs, such as *NeST*, represent lncRNA targets with pharmaceutical potential where bacterial infection could be attenuated without predisposing to viral infections in humans is clearly worthy of further study.

Apart from lncRNAs encoded by the human host, lncRNAs derived from the virus itself are also emerging as important elements for epigenetic regulation during infection.⁹³ The HIV-encoded lncRNA *aspro5* recruits the host de novo DNA (cytosine-5)-methyltransferase (DNMT3a), the histone deacetylase HDAC1, the histone-lysine N-methyltransferase, and the polycomb protein enhancer of zeste homolog 2 (EZH2) to the 5' long terminal repeat of the integrated proviral DNA. This leads to the formation of H3K9me2, H3K27me3, histone deacetylation, and associated transcriptional inert heterochromatic structures. These changes in the chromatin structure inhibit transcriptional activity of the promoter, thereby silencing the expression of the viral gene and likely contributing to latency and immune evasion of the integrated retroviral genome.⁷⁸

3.3 | lncRNAs regulate innate immunity at the transcriptional level

Transcriptional regulation is one of the most important mechanisms in controlling eukaryotic gene expression. lncRNAs can saturate the binding sites of transcription factors and thus inhibit the transcription and expression of IFNs and ISGs.^{94,95} On the other hand, lncRNAs can also recruit transcription factors to promoters and enhancers to initiate transcription of innate immune genes.^{82,96,97} For example, lncRNA-DC has been shown to regulate the activity of a number of transcription factors. When cells are stimulated by pathogens, lncRNA-DC, which has been found to be specifically expressed in dendritic cells, binds to the transcription factor STAT3 and blocks the binding site for SHP1. The sustained activation of STAT3 induced by the phosphorylation of tyrosine residue 705 promotes the expression of genes involved in dendritic cell differentiation.⁹⁸ lncRNA-DC is also implicated in the immune response to HBV and acts by reducing the concentration of secreted TNF- α , IL-6, IL-12, and IFN- γ , as well as increasing the IL-1 β concentration in dendritic cells.⁹⁹

lncRNAs can form a complex with heterogeneous nuclear ribonucleoproteins (hnRNPs) to regulate the expression of ISGs. lncRNA

#32 is one such antiviral factor; knockdown of lncRNA #32 significantly reduces the mRNA level of the interferon-inducible proteins OASL, IP-10, RSAD2, and APOBEC3A. lncRNA #32 forms a stable complex with hnRNP, which activates transcription factor 2 (ATF2) to promote the transcription of ISG effectors.¹⁰⁰ Similarly, the complex of lncRNA *NRON* with GTPase-activating proteins and three NFAT kinases in the cytoplasm of T cells serves as a molecular scaffold for the activation of the nuclear factor NFAT. Upon stimulation, activated NFAT is released from the complex and promotes nuclear transport, thereby initiating gene transcription (Table 1).³⁶ In addition, by reducing or increasing the abundance of lncRNA *NRON* (an inhibitor of NFAT) through the early viral protein Nef and the late protein Vpu, respectively, the function of NFAT is controlled to achieve a subtle balance between HIV proliferation and cell death.¹⁰¹

In addition, some lncRNAs, such as the lncRNA *THRIL* (linc-1992), *NEAT1*, and lincRNA-*EPS*, can indirectly regulate the transcription of immune-related genes. TNF- α is a critical cytokine that activates NF- κ B-mediated inflammatory responses. *THRIL* forms a complex with hnRNPL, which in turn activates the TNF- α transcription by binding to the TNF- α promoter.⁹⁰ TNF- α regulates *THRIL* expression through a negative feedback. The expression of additional cytokines and chemokines, such as IL-8, CCL1, CSF1, and CXCL10, is also regulated by the lncRNA *THRIL*.

NEAT1 is an important regulator of antiviral responses, whose expression is elevated by viral infections including HIV-1, Japanese encephalitis virus, rabies virus, influenza A virus (IAV), herpes simplex virus, and Hantavirus.^{37,102,103} In the cytoplasm, *NEAT1* interacts with the NONO protein to promote the formation of paraspeckles in the nucleus. Paraspeckles are subnuclear structures, termed ribonucleo-protein bodies, found in the interchromatin spaces in nuclei and are thought to regulate gene expression by inhibiting nuclear RNA export. The targeting of paraspeckles by retroviruses may serve to impede host responses to viral infection and help establish latency. *NEAT1* also functions in the relocalization of the splicing factor SFPQ from the promoter region of the antiviral cytokine IL-8 to the paraspeckle. In this way, the inhibition of transcription by SFPQ is released, leading to the induction of IL-8 expression and inhibition of HIV-1 replication (Figure 3A).³⁷

Without interference from pathogens, lincRNA-*EPS*, which possesses immunoregulatory properties in macrophages, accumulates in the regulatory region of immune response genes (IRGs). By interacting with hnRNPL via a CANACA motif located at its 3'-end, lincRNA-*EPS* regulates nucleosome localization and IRG transcription, thereby reducing proinflammatory responses.⁷⁹

Interestingly, certain virus-encoded lncRNAs with transcriptional regulatory functions play important roles in host-virus interactions.^{78,104} The flavivirus-encoded lncRNA, *sfrNA*, is highly conserved in the 3'-UTR of the flavivirus genome.⁸⁰ Studies have shown that *sfrNA* inhibits the activation of interferon regulatory factor 3 (IRF3) by blocking IRF3 phosphorylation, thereby preventing the activation of the IFN- β promoter and inhibiting the transcription of IFN- β .^{81,105} Dengue virus serotype 2 (DENV2)-induced *sfrNA* inhibits the transcription of *IFITM2* and the double-stranded RNA-dependent protein

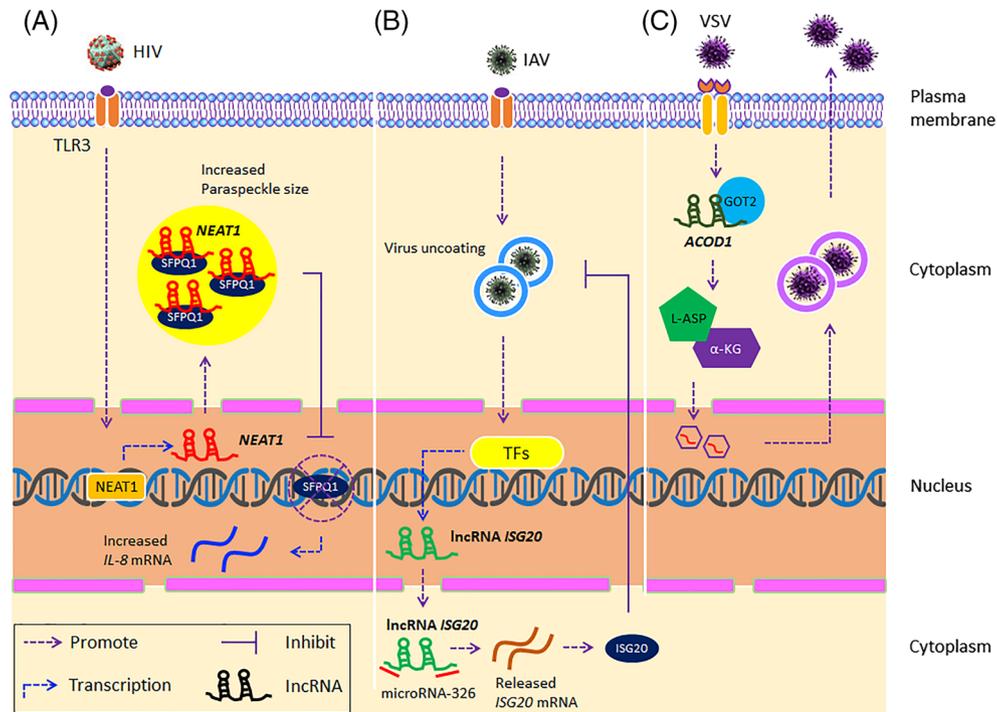


FIGURE 3 Additional roles of long noncoding RNAs (lncRNAs) in innate antiviral immunity. A, In A549 cells, NEAT1 relocates the negative regulatory factor SFPQ from the IL-8 promoter to subnuclear structures known as paraspeckles, thereby reducing the inhibitory effect of SFPQ on the IL-8 promoter and promoting the transcription of IL-8. B, miRNA-326 regulates the expression of ISG20 by binding to the 3'-untranslated region (UTR) of the ISG20 mRNA. lncRNA ISG20 competitively interacts with miRNA-326, thereby releasing free ISG20 mRNA and facilitating the translation of the ISG20 mRNA. C, lncRNA-ACOD1 causes a conformational change of GOT2, an essential aminotransferase during cell metabolism in the cytoplasm, at a position close to the substrate binding site, which enhances the catalytic activity of GOT2, thereby increasing the production of L-ASP and α -KG, increasing metabolic efficiency, and promoting VSV replication and infection

kinase R (PKR) by binding to the host RNA-binding proteins G3BP1, G3BP2, and CAPRIN1, which in turn negatively regulates the expression of IFITM2 and PKR.⁸³ It has also been confirmed that DENV2-induced sfRNA prevents deubiquitination of the ubiquitin ligase TRIM25 by direct binding to TRIM25, thereby negatively regulating RIG-I expression and inhibiting innate immune responses.⁸²

KSHV-infected cells express a lncRNA, termed polyadenylated nuclear RNA (PAN RNA), which modulates the cellular immune response by interacting with both viral and cellular DNA and proteins.¹⁰⁶ The PAN RNA plays an important role in controlling viral gene transcription and subversion of the host immune response.^{107,108} The PAN lncRNA exerts these effects by interacting with specific histone demethylases (UTX and JMJD3) and physically binds to the KSHV genome to mediate activation of viral gene expression by removing suppressive trimethylated H3K23 marks.¹⁰⁹ In addition to interacting with histone demethylases, PAN RNA also interacts with SUZ12 and EZH2 which are components of the Polycomb repression complex 2 (PRC2), a chromatin-modifying (histone methylation) complex, which represses gene expression at numerous loci.¹⁰⁴

Despite these advances, limited information has been revealed to date about virus-encoded lncRNAs with regulatory functions at the transcriptional level. In the future, the discovery and functional

characterization of this lncRNA class of virally encoded transcripts will help in the delineation of virus-host interactions and may afford the opportunity to develop therapeutics that inhibit virus-specific lncRNAs.

3.4 | Posttranscriptional regulation of innate immunity by lncRNAs

lncRNAs also regulate posttranscriptional modification of mRNAs by involvement in splicing and processing, enhancing mRNA stability, and improving nuclear export efficiency. Upon exposure to amyloid β peptide (A β peptide), the expression level of the antisense lncRNA *BACE1-AS*, transcribed by the beta-secretase 1 gene (*BACE1*), is elevated. This increases the stability of the *BACE1* mRNA and generates additional A β peptide through a posttranscriptional, feedforward mechanism.¹¹⁰ Some lncRNAs can reduce the nuclear export efficiency of viral mRNAs and inhibit viral replication. HIV-1 infection can induce a differential expression of the lncRNA *NEAT1* in T cells, which serves as a binding scaffold maintaining the integrity of paraspeckles and prevents the transport of spliced HIV-1 pre-mRNA to the cytoplasm for translation (Table 1).⁸⁴ lncRNA-*p21* acts as an inhibitor and reduces the translation efficiency of its target gene by pairing with the target mRNA.¹¹¹

lncRNA can also minimize the inhibitory effect of miRNAs through additional mechanisms, such as competitive binding or via so-called sponge effects where miRNAs are titrated from other targets, thereby promoting the translation of the miRNA-targeted mRNAs.¹¹² In A549 cells treated with poly(I:C) and Sendai virus, lncRNA *ISG20*, acting as a competitive endogenous RNA (ceRNA), competes with miRNA-326, resulting in a decreased abundance of miRNA-326 at the 3'-UTR of the *ISG20* mRNA. In addition, the reduced binding efficiency of microRNA-326 to *ISG20* mRNA also promotes *ISG20* translation and inhibits IAV replication (Figure 3B).⁸⁵ Similarly, lncRNA-*BGL3*, acting as a ceRNA, regulates the translation of phosphatase and tensin homolog (*PTEN*) genes by competitively binding with a series of miRNAs, including miR-17, miR-93, miR-20a, miR-20b, miR-106a, and miR-106b.¹¹³

3.5 | lncRNAs affect viral replication by regulating cell metabolism

Viruses as obligate intracellular parasites lack the basic metabolic mechanism necessary for replication in host cells. To solve this problem, they hijack host metabolic pathways to derive the resources for viral replication. Hence, viruses act to regulate the metabolism of the host to improve their own replication efficiency. HNF4 α is a nuclear receptor that serves as a master regulator of hepatocyte differentiation by functioning in the activation of glycolysis in hepatocytes, inhibition of apoptosis of host cells, and promotion of flavivirus hepatitis C replication.¹¹⁴ It has also been revealed by lipidomics that fatty acid and lipid mediators are critical in the replication of IAV in A549 cells.^{115,116} The involvement of lncRNAs in cellular metabolism plays a crucial role in innate immunity induced by viral infection. Wang et al found that deletion of lncRNA *ACOD1* greatly attenuates VSV infection mediated by the IFN-I/IRF3-independent pathway. In addition, the lncRNA *ACOD1* elevates the catalytic activity of glutamic-oxaloacetic transaminase 2 (*GOT2*) by directly binding to *GOT2* in the cytoplasm, and through which the metabolism of L-aspartic acid (L-ASP) and α -ketoglutarate (α -KG) is promoted, leading to the immune escape for VSV (Figure 3C).⁸⁶ Taken together, these studies reveal a new regulatory mechanism of lncRNAs through which host metabolism, rather than classical innate immune pathways, is regulated to promote viral genomic replication and virus proliferation.

4 | SUMMARY AND PROSPECTS

lncRNAs interact with proteins and nucleic acids through specific binding to tertiary conformational structures or complementary nucleotide base pairing within genes, respectively, thereby playing essential roles in the regulatory network of innate immune responses and viral replication. Firstly, virus-induced lncRNAs promote immune responses following a self-recognition mode. Acting as a potent molecular decoy, the inducible "self" lncRNA blocks the RIG-I binding site to limit viral RNA-induced innate immune responses and maintain immune homeostasis. Secondly, ncRNAs can regulate innate immunity at the

transcriptional level by activating transcription initiation complexes or competing for transcription factor binding sites. In addition, host lncRNAs can release more free mRNAs and enhance the expression of innate immune-related genes by increasing mRNA stability and relieving the restrictions imposed by miRNAs. Thirdly, lncRNAs can also promote the assembly of posttranslational histone modification complexes by recruiting histone methyltransferases to regulate the expression of innate immune factors, such as IFNs and ISGs at the epigenetic level. Taken together, these findings provide strong evidence for the role of the ubiquitous and versatile classes of lncRNAs in antiviral regulation. Although many breakthroughs have been achieved towards the understanding of lncRNA-mediated innate immune responses, the study of lncRNAs is only in its infancy when compared with other ncRNAs, such as microRNAs. IFN-I-independent lncRNAs can also promote viral replication by regulating cellular metabolism, and this serves as a new paradigm for the regulation of viral infection other than via effects on innate immunity.⁸⁶ This mechanism adds a further layer of complexity to the regulatory networks previously established in viral infection. The connection between lncRNAs, metabolism, and virus infection has set a new direction for the study of immune regulatory mechanisms; however, this is far from fully understood, and the discovery and functional annotation of numerous lncRNAs remain to be further explored. With a deeper understanding of host and virally encoded lncRNAs and the regulatory mechanisms involved in the innate antiviral immune response they impact upon, this will likely provide new druggable targets and therapeutic strategies for the treatment of infectious disease.

CONFLICT OF INTEREST

The authors have no competing interest.

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