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, IκB 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; MDAS, melanoma differentiation-associated gene 5; miRNA, microRNA; NADPH, nicotinamide adenine dinucleotide phosphate; ncRNAs, noncoding RNAs; NEMO, NF-κB 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
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. 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. In 2002, a large-scale discovery of lncRNAs was achieved by sequence analyses of 60,770 mouse full-length complementary DNAs (cDNAs). As of November 2018, approximately 16,066 human lncRNAs and nearly 29,566 transcripts have been released by GenCode (Version 29). 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. 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. 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. These host and virally encoded lncRNAs regulate infections through various regulatory mechanisms, such as participating in innate immune responses and altering cellular metabolic pathways. 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, and can be either polyadenylated or nonpolyadenylated (ie, are bimorphic). 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. 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. According to the positional relationship between lncRNAs and their target genes on the chromosome, lncRNAs can be classified into five groups: (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). 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, with small ncRNAs and lncRNAs now known to account for an estimated 20% to 42% of ncRNAs. 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 RNAs of their target genes. 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. 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 modifications; (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 mRNA; (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 transcription; (5) lncRNA binds to a specific protein, altering the activity or cytoplasmic localization of the protein; (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 classes; and finally (7) lncRNAs can be transcribed as the precursors of small molecule RNAs, such as miRNAs and piwi-interacting RNAs (piRNAs). 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...
molecules, molecular sponges, and scaffolds.\textsuperscript{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.\textsuperscript{28,29,41,42} In the past decade, IncRNA 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 IncRNAs in the context of innate antiviral immunity.

2 | DIFFERENTIAL EXPRESSION OF LncRNAs

2.1 | Viral infection and differential expression of IncRNAs

Virus infection elicits changes in the expression of cellular IncRNAs. By means of gene chip analyses, Winterling and colleagues revealed 17 differentially expressed IncRNAs in human alveolar epithelial cells (A549) infected with influenza virus A/WSN/33 (H1N1).\textsuperscript{43} Subsequently, using high-throughput sequencing, numerous research groups identified thousands of differentially expressed IncRNAs following viral infection. In order to systematically study the regulatory effects of the neurotropic enterovirus A71 (EVA71) infection on IncRNAs, Yin et al performed a comprehensive analysis of EVA71-infected rhabdomyosarcoma (RD) cells and observed differential expression of greater than 4800 IncRNAs.\textsuperscript{44} Similarly, Meng et al identified 8541 differentially expressed IncRNAs in EVA71-infected human peripheral blood mononuclear cells.\textsuperscript{45} Also, using the RNA sequencing (RNA-Seq) technique, Shi et al identified a total of 760 and 1210 IncRNAs that were upregulated and downregulated, respectively, in RD cells infected with Coxackievirus A16 (CVA16). Interestingly, there was an apparent bias in the IncRNA class differentially regulated upon CVA16 infection as approximately 43.6% and 22.3% were intergenic and sense IncRNAs, respectively, demonstrating a significant enrichment upon viral infection of the former IncRNA class.\textsuperscript{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 IncRNAs had significant changes.\textsuperscript{47} In addition, other viral families, such as Zika virus,\textsuperscript{48} hepatitis B virus (HBV),\textsuperscript{49-51} and hepatitis C virus,\textsuperscript{52} have been shown upon host infection to lead to differential expression of host IncRNAs compared with uninfected controls. Therefore, the differential expression of IncRNAs 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 IncRNAs to modulate the host immune response. For example, human cytomegalovirus (HCMV) encodes a 2.7 kb IncRNA, $\beta_2.7$, which protects viral RNAs from degradation by the host nuclease A,\textsuperscript{53} $\beta_2.7$ inhibits the induction of stress responses and apoptosis in infected cells, which facilitates HCMV replication.\textsuperscript{9} Gammaherpesviruses transcribe their own structurally and functionally intricate IncRNAs, which modulate cellular and viral gene expression to maintain viral latency or to induce lytic reactivation.\textsuperscript{54} In addition, a 3.91 kb IncRNA M3-04 generated by gammaherpesviruses regulates viral replication in mice by interacting with antisense miRNAs and the latency gene M2.\textsuperscript{55} Other herpesviruses also encode multiple functional IncRNAs, such as the Epstein-Barr virus encoding ncRNA, BamH I-A rightward transcripts,\textsuperscript{56} Kaposi’s sarcoma-associated herpesvirus (KSHV) encoding UCA1,\textsuperscript{57} and herpesvirus saimiri encoding U-rich RNAs.\textsuperscript{58} Additionally, the 3’-untranslated region (UTR) of the flavivirus RNA genome is capable of transcribing an active IncRNA, termed the subgenomic flavivirus RNA (sRNA), 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.\textsuperscript{10,59} Therefore, viral infection
can induce differential expression of a series of IncRNAs in cells, suggesting that IncRNAs may play important functional roles in viral infection.

2.2 Cytokines and differential expression of IncRNAs

Cytokines play an essential role in regulating the development, maturation, and differentiation of nonspecific innate immune cells. IncRNAs are found to be deregulated upon viral infection or following interferon (IFN) treatment, and some IncRNAs can modulate viral infection in an IFN-dependent manner.60 To investigate whether IFN regulates the transcription of IncRNAs, 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 IncRNAs ISR2, ISR8, and ISR12.51 Similarly, treatment of Huh7 cells by IFN-α or type III IFN-λ induced an upregulation of the expression of IncRNAs BST2 and ISG15. Inhibition experiments showed that IncRNA 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 IncRNA Lethe, which responds to NF-κB stimulation and reduces inflammation.63 The IncRNA NKILA which is induced by proinflammatory cytokines binds to NF-κB/IkB and directly masks the phosphorylation motifs of IkB, thereby inhibiting IKK-induced IkB phosphorylation and downstream NF-κB activation, and thereby preventing excessive activation of the NF-κB pathway in epithelial cells.64 Therefore, the inductive effect of cytokines is closely related to and modulated by the differential expression of host IncRNAs.

2.3 Metabolites and differential expression of IncRNAs

Metabolites not only function within cellular metabolic pathways but have also been implicated in the regulation and differential expression of IncRNAs. The specific β3-adrenergic receptor agonist, CL-316,243, induces the differentiation of brown adipocytes, and a total of 21 differentially expressed IncRNAs have been detected in both cellular and adipose tissues.65 This has led to the identification of the IncRNA 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, IncRNA 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 IncRNA 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, IncRNA PCGEM1 affects glutamine metabolism at the transcriptional level. Taken together, IncRNA PCGEM1 is a key transcriptional regulator of cellular metabolic pathways.

In the process of viral infection, IncRNAs can act as mediators to link viral infection to innate immunity and cellular metabolism. IncRNAs 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 IncRNAs elicited by virus infection often leads to disturbance of homeostasis, resulting in disease.67 IncRNAs 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 IncRNAs

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-κB.71,72 The IncRNAs Lethe and Inc-Lsm3b have been shown to bind directly to immunosensors and block downstream signaling of the innate immune pathway (Table 1). The IncRNA Lethe competitively binds with and blocks NF-κB from binding to specific promoter regions of its target genes, thereby preventing a cascade of signal transduction events.63 The IFN-inducible, host-derived IncRNA, Inc-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, Inc-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 Inc-Lsm3b upon RNA virus stimulation. Taken together, these findings implicate Inc-Lsm3b as a potent negative regulator of innate RIG-I signaling pathway upon RNA virus infections.73
| IncRNAs | Name | Stimuli | Functions/Mechanisms | Refs. |
|---------|------|---------|----------------------|-------|
| **PRR-related signal transduction** | Lethe | TNF-α | IncRNA Lethe competitively binds with NF-κB and inhibits the interaction between NF-κB and the promotor, thereby preventing downstream signal transduction. | Rapicavoli et al.63 |
| | Lsm3b | VSV | Binding of Inc-Lsm3b 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** | lincRNA-Cox2 | Pam3CSK4, LPS | lincRNA-Cox2 interacts with hnRNPA/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 |
| | NeST | Theiler’s virus | NeST 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 |
| | NRAV | IAV | NRAV inhibits the transcriptional initiation of antiviral genes by affecting the histone modifications of MxA and IFITM3 (H3K4me3 and H3K27me3). | Ouyang et al.77 |
| | Aspro5 | HIV | Aspro5 recruits a variety of histone modification enzymes to form a heterochromatic structure inhibiting the transcriptional activity of the viral promoter. | Saayman et al.78 |
| **Transcriptional level** | NRON | HIV | A complex of the lincRNA NRON, 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.76 |
| | NEAT1 | HIV | NEAT1 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 |
| | lincRNA-EPS | LPS | lincRNA-EPS controls nucleosome localization and inhibits IRG transcription by interacting with heterogeneous nuclear ribonucleoprotein L. | Atianand et al.79 |
| | sfRNA | Flaviviruses | sfRNA prevents the activation of the IFN-β promoter and the initiation of transcription by inhibiting the phosphorylation of IRF3. | Pijlman et al.80 and Chang et al.81 |
| | sfRNA | Dengue virus | sfRNA binds to the host RNA binding protein and CAPRIN1 and inhibits the transcription of IFITM2 and PKR; sfRNA also binds to the ubiquitin ligase TRIM25 and negatively regulates RIG-I expression. | Manokaran et al.82 and Bidet et al.83 |
| **Posttranscriptional level** | NEAT1 | HIV | NEAT1 inhibits nuclear export of HIV-1 mRNAs and reduces replication efficiency in viral cells. | Zhang et al.84 |
| | ISG20 | Sendai virus; IAV; poly I:C | Acts as a competitive endogenous RNA (ceRNA) of ISG20 mRNA, IncRNA ISG20 binds to mRNA-326, releasing its transcriptional repression of ISG20 mRNA, and activates the innate immune response. | Chal et al.85 |
| **Metabolic level** | ACOD1 | VSV | ACOD1 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 |
3.2 | IncRNAs 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 IncRNAs can regulate gene expression at the epigenetic level through chromatin remodeling pathways.29,89 For example, lipopolysaccharide (LPS) or the synthetic triacylated lipopeptide Pam3CKS4 can induce formation of a lincRNA-Cox2 and SWI/SNF complex which modulates the assembly of NF-κB 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 hnRNPA3 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 IncRNA-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 lncRNA 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 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-κB 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.
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. 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 Salmonona 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. 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. 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.

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. On the other hand, lncRNAs can also recruit transcription factors to promoters and enhancers to initiate transcription of innate immune genes. 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. 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-1β concentration in dendritic cells.

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 hnRNPU, which activates transcription factor 2 (ATF2) to promote the transcription of ISG effectors. 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). In addition, by reducing or increasing the abundance of lncRNA NRON (an inhibitor of NFAT) through the early viral protein Vpu and the late protein Vpr, respectively, the function of NFAT is controlled to achieve a subtle balance between HIV proliferation and cell death.

In addition, some lncRNAs, such as the lncRNA THRIL (linc-1992), NEAT1, and lncRNA-EPS, can indirectly regulate the transcription of immune-related genes. TNF-α is a critical cytokine that activates NF-kB-mediated inflammatory responses. THRIL forms a complex with hnRNPL, which in turn activates the TNF-α transcription by binding to the TNF-α promoter. 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. In the cytoplasm, NEAT1 interacts with the NONO protein to promote the formation of paraspeckles in the nucleus. Paraspeckles are subnuclear structures, termed ribonucleoprotein 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).

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.

Interestingly, certain virus-encoded lncRNAs with transcriptional regulatory functions play important roles in host-virus interactions. The flavivirus-encoded lncRNA, sfRNA, is highly conserved in the 3′-UTR of the flavivirus genome. 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.

Dengue virus serotype 2 (DENV2)-induced sfRNA inhibits the transcription of IFITM2 and the double-stranded RNA-dependent protein.
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. 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 H3K27 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 (Aβ 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 Aβ 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).111 lincRNA-p21 acts as an inhibitor and reduces the translation efficiency of its target gene by pairing with the target mRNA.111
IncRNA 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. In A549 cells treated with poly(I:C) and Sendai virus, IncRNA ISG20, acting as a competitive endogenous RNA (ceRNA), competes with miR-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). Similarly, IncRNA-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.

3.5 | IncRNAs 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. HNF4α is a nuclear receptor that serves as a master regulator of hepatocyte differentiation by function in the activation of glycolysis in hepatocytes, inhibition of apoptosis of host cells, and promotion of flavivirus hepatitis C replication. It has also been revealed by lipidomics that fatty acid and lipid mediators are critical in the replication of IAV in A549 cells. The involvement of IncRNAs in cellular metabolism plays a crucial role in innate immunity induced by viral infection. Wang et al found that deletion of IncRNA ACOD1 greatly attenuates VSV infection mediated by the IFN-I/IRF3-independent pathway. In addition, the IncRNA ACOD1 elevates the catalytic activity of glutamicoxaloacetic 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). Taken together, these studies reveal a new regulatory mechanism of IncRNAs through which host metabolism, rather than classical innate immune pathways, is regulated to promote viral genomic replication and virus proliferation.

4 | SUMMARY AND PROSPECTS

IncRNAs 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 IncRNAs promote immune responses following a self-recognition mode. Acting as a potent molecular decoy, the inducible “self” IncRNA 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 IncRNAs 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, IncRNAs 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 IncRNAs in antiviral regulation. Although many breakthroughs have been achieved towards the understanding of IncRNA-mediated innate immune responses, the study of IncRNAs is only in its infancy when compared with other ncRNAs, such as microRNAs. IFN-I-independent IncRNAs 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. This mechanism adds a further layer of complexity to the regulatory networks previously established in viral infection. The connection between IncRNAs, 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 IncRNAs remain to be further explored. With a deeper understanding of host and virally encoded IncRNAs 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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