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REVIEW

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Diverse roles of long non-coding RNAs in viral diseases

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Summary

Viral infection leads to large alterations in the host transcriptome and stimulates an antiviral host immune response involving numerous proteins and signalling pathways. Long non-coding RNAs (lncRNAs) have emerged as important regulators during viral infection. Emerging data demonstrates that lncRNAs play essential roles at the host pathogen interface modulating viral infection by either antiviral response at distinct level including pathogen recognition receptors or by epigenetic, transcriptional, and post-transcriptional effects. Furthermore, differentially expressed lncRNAs may be employed as prognostic and diagnostic biomarkers for viral diseases. Here, we summarize the current knowledge of lncRNAs and their functions in viral infections with a specific focus on host-virus responses. In addition, the potential implications of lncRNAs in severe acute respiratory syndrome coronavirus 2 will be discussed.

1 | INTRODUCTION

Human history is replete with viral disease outbreaks that have devastated society and entire populations.[1,2] In recent history, there have been growing incidents of viral infectious diseases that have spread among different geographic regions and caused severe fatality thus representing a dramatic threat to the public health. For example, an epidemic of the severe acute respiratory syndrome (SARS-CoV) in 2003, the 2009 H1N1 influenza, the 2013–2016 Ebola virus in Africa, the Zika crisis in America and beyond in 2016 all caused global epidemics.[3-6] Finally, the still ongoing pandemic of coronavirus disease 2019 (Covid-19) emerged in December of 2019, in Wuhan, in the Hubei Province of China, and spread rapidly to over 200 countries and territories.[7] Covid-19 is triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a member of the coronavirus family which also includes SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV).[7] There were 46 million verified patients of Covid-19 globally with 1.2 million deaths recorded by the World Health Organization (WHO) by 1 November 2020. This pandemic has highlighted the severity of viral diseases at a global level and indicates that further study is required to better manage their spread and treatment.

Although viruses and their mechanisms of infection are generally diverse, there are obligatory steps in viral infection for a virus to exert pathogenic effects. Firstly, the virus must gain entry to the host and hijack host-cell machinery for viral replication: cell entry,

Abbreviations: ceRNAs, competitive endogenous RNAs; Covid-19, coronavirus disease 2019; EZH2, enhancer of zeste homologue 2; H3K27me3, trimethylation of histone H3 on lysine 27; lncRNA, long non-coding RNA; PRC2, polycomb repressive complex 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TLRs, toll-like receptors; TNF, Tumour necrosis factor; SFPQ, splicing factor proline/glutamine-rich.

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replication of genetic material, expression of viral proteins, assembly of viral particles, and cell exit.[8,9] In order to spread within the host, the virus needs to evade the host immune response and surpass barriers to spread through an extracellular system consisting of interstitial fluid, lymph, and blood to distant tissues and organs.[10] The next stage is host shedding, where the virus exits and infects a new host. Finally, the host adaptive immune response is important in clearing the virus. However, some viruses can also become latent, remaining dormant in the cell and cause persistent infections which can increase the risk of shedding and viral spread, as well as a chronic disease.[8] Although the general mechanisms for viral infection are known, the detailed mechanisms in individual disease and the full role of host factors in the viral response is not fully understood.

According to the Encyclopedia of DNA Elements (ENCODE) project, which is the most extensive attempt yet to explore transcription in the human genome, protein-coding genes account for only 2%–3% of the total human genome.[11] In the past decade, advances in transcriptome sequencing have established that more than 90% of the human genome is transcribed and that the majority of transcriptional products are Long non-coding RNAs (lncRNAs). LncRNAs are a subset of RNAs ranging from 200 to 100, 000 nt in length and do not encode proteins. Most lncRNAs are transcribed by RNA polymerase II, are capped at the 5′ end and contain a poly-adenylated tail at the 3′ end, similarly to mRNAs. They are classified as sense, antisense, bidirectional, intronic, and intergenic lncRNAs based on their position relative to protein-coding genes.[12,13] The human genome encodes thousands of lncRNAs that were previously considered 'dark matter' or 'junk DNA' in the genome.[14] The list of annotated and functionally studied lncRNAs has expanded exponentially and it has been well established that these lncRNAs play essential roles in various biological processes, and their dysregulations have been linked to human diseases, including viral diseases.[15-18]

Increasing studies indicate that viruses may regulate host and/or viral gene expression through lncRNAs to maintain virus latency and replication.[19-21] Modern advances in high throughput sequencing techniques identified that a large number of lncRNAs are involved in viral infections and immunological processes. Having a more detailed understanding of the connection between lncRNAs and viruses would offer a novel perspective and may direct potential strategies for antiviral therapy to reduce the worldwide burden of viral diseases. In this review, we will summarize the role of lncRNAs in viral infection, their underlying mechanisms and discuss the role of lncRNAs in virus-related disease.

2 | MOLECULAR MECHANISMS OF LncRNAs

Recent studies have shown that lncRNAs are important regulatory molecules in various biological and pathological processes and the function of lncRNAs is largely reflected by their subcellular location.[12] The established mechanisms can be broadly grouped into eight distinct categories (Figure 1). (1) Firstly, lncRNAs can regulate chromatin modifications. For example, Rinn et al., reported that lncRNA HOTAIR directly interacts with polycomb repressive complex 2 (PRC2) and further modulates PRC2-mediated chromatin silencing.[22] (2) LncRNAs can induce chromosome looping to regulate gene expression. Xiang et al., observed that lncRNA CCAT1-L, transcribed from a locus 515 kb upstream of MYC, co-operates with the MYC transcriptional repressor CTCF to induce chromatin looping and regulate MYC transcription.[23] (3) LncRNAs can also act as transcriptional regulators. It has been reported that lncRNA MeXis is involved in LXR-dependent transcriptional regulation by recruiting the transcriptional coactivator DDX17 to the promoter of Abca1, which is critical for cholesterol efflux regulation.[24] (4) LncRNAs have also been implicated in RNA processing events such as alternative splicing. The heterogeneous nuclear ribonucleoprotein E1 (hnRNP E1) binds to exon 12 of protein phosphatase 1 regulatory subunit 10 (PPP1R10, also known as PNUTS) and results in an alternative spliced isoform of lncRNA PNUTS. Alternative spliced lncRNA PNUTS competitively binds to hsa-miR-205 and increases ZEB1 expression, which leads to epithelial-mesenchymal transition (EMT) and tumour development.[25] (5) Furthermore, by acting as subcellular structures lncRNAs could serve as decoy, scaffold, guide, and enhancer molecules to control protein and RNA interactions to regulate gene expression.[26] (6) As well as at a transcriptional level, lncRNAs can interact with proteins to regulate post-transcriptional processes and important signalling cascades.[12] (7) LncRNAs can also act as competitive endogenous RNAs (ceRNAs) to soak up or 'sponge' microRNAs (miRNAs) preventing the inhibitory effect of the miRNAs on their target genes. For example, Wang et al., reported that lncRNA NRF could bind hsa-miR-873 and upregulate its target RIPK1/RIPK3 and increase necrosis.[27] (8) Finally, lncRNAs could modulate mRNA stability and translation in the cytoplasm and participate in the regulation of cell-dependent processes such as cell apoptosis, migration/invasion and cell growth.[28,29] Therefore, lncRNAs can function in many cellular processes through a variety of different mechanisms. Herein, we will summarize the fundamental mechanisms of lncRNAs in viral diseases.

3 | LncRNA DYSREGULATION DURING VIRAL INFECTION

With the established high throughput sequencing technology, scientists have discovered that viral infection causes comprehensive alternations in the host cell transcriptome, including a large number of lncRNAs.[30-32] Peng and colleagues identified that 504 annotated and 1406 unannotated lncRNAs in mice and mouse embryonic fibroblasts are significantly modulated during infection with SARS-CoV virus. In addition, the authors found that dysregulated lncRNAs are associated with pathogenic prognosis and identified that the innate immune response influences the expression of lncRNAs.[30] Chen et al., reported a total number of 6188 dysregulated lncRNA associated with porcine endemic diarrhoea virus (PEDV) viral infection, further supporting the potential roles of lncRNA in viral

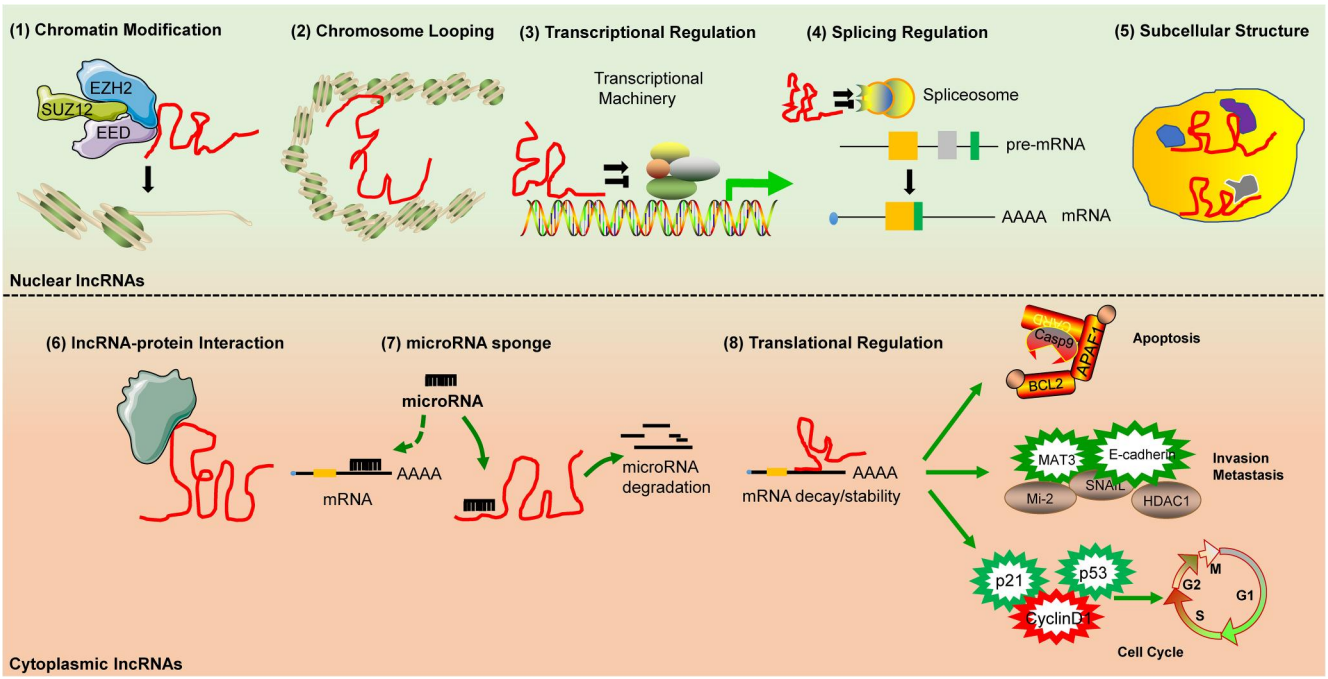

FIGURE 1 The General Molecular Mechanisms of lncRNAs. Nuclear lncRNAs can regulate gene transcription by recruiting chromatin modifying complex (1), modulating chromosome looping (2), regulating or binding to transcription factors (3), participating in pre-mRNA alternative splicing (4), acting as decoy, enhancer, scaffold or guide to control gene interaction or expression (5). Cytoplasmic lncRNAs control gene expression by interacting with protein (6), serving as sponge of miRNAs (7), and promoting or inhibiting mRNA stability (8). lncRNAs, Long non-coding RNAs

diseases.[31] Using genome-wide sequencing, Zhang and colleagues found that 25 lncRNAs are involved in Hepatitis C virus (HCV) induced hepatocellular carcinoma (HCC). Similarly, Hu et al., characterized 149 differentially expressed lncRNAs in human neural progenitor cells upon Zika viral infection, suggesting that subsets of lncRNAs may be involved in particular diseases and may offer valuable insight into disease-specific therapeutic strategies.[33] Recently, Meng et al., showed that 8541 lncRNAs are dysregulated following infection of enterovirus 71 (EV71) in human peripheral blood mononuclear cells. Furthermore, 10 of the lncRNAs were examined in EV71-infected mild, severe and healthy cases, and could be used as biomarkers to distinguish mild and severe patients to aid in earlier diagnosis.[34] Therefore, lncRNAs are differentially expressed in various viral diseases, suggesting they may play a role in viral pathology and could be promising therapeutic and diagnostic targets. Table 1 reports a list of lncRNAs differentially expressed during several viral infections.

4 | VIRAL-ENCODED LncRNAs

Viral infection not only alters host endogenous lncRNA levels but also manipulates the host genome to express viral lncRNAs that are critical for viral infection and pathogenesis. Table 2 shows some critical lncRNAs that are produced by viral infection such as polyadenylated nuclear (PAN) RNA and subgenomic flaviviral RNA (sfRNA). PAN RNA is encoded by the Kaposi sarcoma-associated herpes virus (KSHV) and was first discovered as a novel abundant 1.2 kb RNA that is transcribed by RNA polymerase II.[35] Rossetto and colleagues showed that PAN RNA prevents the repressive histone marker trimethylation of histone H3 on lysine 27 (H3K27me3) binding at the ORF50 promoter, activating KSHV gene expression. They also presented that PAN RNA binds to PRC2 to regulate the cell cycle and inflammatory cytokines.[35,36] In addition, PAN RNA is able to enhance the stability of viral transcripts by interacting with ORF57 in the nucleus to prevent transcript degradation and facilitate nuclear mRNA export and increase cytoplasmic mRNA levels.

The flaviviruses are a group of single-strand positive-sense RNA viruses including yellow fever virus, dengue virus, and West Nile virus, which cause worldwide health threats.[37] sfRNA is generated from the 3'untranslated region (3′UTR) of RNA genome through an incomplete degradation of genomic RNA by the virus 5′-3′ exoribonuclease XRN1. The stem-loop structure in the 3′UTR, which is resistant to nuclease XRN1 degradation, promotes the formation of sfRNA.[38,39] Fragile X mental retardation protein (FMRP), a known cellular mRNA translational repressor, has been reported as a negative regulator against viral infection. SfRNA directly interacts with FMRP and antagonizes its function and upregulates FMRP target genes in cell culture and mice.[40] Pijlman et al., also demonstrated that the production of sfRNA enhances viral pathogenicity.[41] Therefore, the expression of viral lncRNAs, as well as differentially

TABLE 1 Differentially regulated lncRNAs during viral infection

lncRNA	Virus	Expression	Target	Function and mechanism	Reference
lncRNA Dreh	HBV	Down	Vimentin	Inhibit vimentin expression, repress HBV-related HCC growth and metastasis in *vitro* and in vivo.	110
lncRNA NRON	HIV	Down	Tat	Directly facilitate Tat to CUL4B and PSMD11, thus promoting Tat stabilization; suppress viral transcription through Tat.	111
lncRNA#32	EMCV	Down	ATF2	LncRNA#32 binds to ATF2 and regulates ISG expression, regulates EMCV viral replication.	20
LncRNA SEMA6A-As1	HBV-related HCC	Down		Low expression of SEMA6A-As1 is associated with poor prognosis in HBV-related HCC.	112
LncRNA zc3h7a	VSV	Up	TRIM25	Mediate TRIM25-mediated K63-linked ubiquitination of RIG-I and downstream signalling, silencing of lncRNA zc3h7a impairs RIG-I signalling and antiviral response.	113
lncRNA RP11-288L9.4	HCV	Up	IF16	Activate the histone modification on IFI6 promoter, affect antiviral innate immunity and HCV infection.	114
lncRNA MALAT1	HIV-1	Up	PRC2	Interact with EZH2, release EZH2 from binding with HIV-1 LTR promoter thus abolishing epigenetic silencing of HIV-1 transcription.	81
LncRNA NRAV	IAV	Up	IFITM3, MxA	Promote IAV replication, negatively regulate ISGs such as IFITM3 and MxA.	82
lncRNA NEAT1	IV, HSV, HIV	Up	IL8, SFPQ	Relocation of SFPQ from IL8 promoter to paraspeckle, active IL8; promote the HIV replication.	76,77
lncRNA Morrbid	LCMV	Up	BCL2L11	Control CD8 T cell expansion and survival by BCL2L11, modulate the PI3K-AKT signalling.	67
lncRNA EGOT	HCV	Up	NF-κB	Active NF-κB pathway and promote HCV replication.	61
lncRNA MADC2-As1	HSV	Up	Hsp90α	The interaction between MADC2-As1 and Hsp90α facilitates the nuclear transport of viral tegument protein VP16.	115
lncRNA UCA1	OVV	Up	miR-18a/182, CDC42	Inhibit miR-18a and miR-182, thereby facilitating CDC42 expression, which in turn regulates OVV cell to cell spread.	116
lncRNA TSPOAP1	IAV	Up	NF-κB	Promote IAV virus replication, negatively regulate ISGs expression.	53

Abbreviations: lncRNAs, Long non-coding RNAs; LCMV, lymphocytic choriomeningitis virus; OVV, oncolytic vaccinia virus; PRC, polycomb repressive complex 2; SFPQ, splicing factor proline/glutamine-rich; HCC, hepatocellular carcinoma; VSV, vesicular stomatitis virus; LTR, long terminal repeat.

expressed host lncRNAs, are important in viral gene expression and the viral response.

5 | LncRNAs IN VIRAL REPLICATION

To produce a successful infection, viruses must interfere with host cells to facilitate viral replication.[42,43] Recent efforts have revealed the essential function of lncRNAs in viral cell cycle and proliferation.[44-46] Wang et al., showed that the expression of lncRNA-ACOD1 is induced by multiple viruses including vesicular stomatitis virus (VSV), vaccinia virus (VACV) and herpes simplex virus type 1 (HSV1) through activation of NF-κB signalling. Ectopic lncRNA-ACOD1 promoted viral replication in human and mouse cells by directly interacting with the metabolic enzyme glutamic-oxaloacetic transaminase 2 (GOT2) and enhancing its enzymatic activity in the cytoplasm. In addition, restored GOT2 rescued viral replication, which suggests that lncRNA-ACOD1 mediates viral replication through GOT2.[47-50] LncRNAs ISR, PAAN and TSPOAP1 could modulate IFN signalling and facilitate IAV replication, suggesting the importance of lncRNAs in viral replication.[51-53] Furthermore, as IFN signalling is key in the viral immune response, it suggests crosstalk between viral replication and the immune response.

6 | LncRNAs IN ANTIVIRAL IMMUNITY

6.1 | LncRNAs and immune response

The host immune response is important in the defence against viral infection and causes proinflammatory activation and an antiviral response.[54,55] Pathogen recognition receptors (PRRs), such as toll-like receptors (TLRs) recognize pathogen-associated molecular patterns (PAMPs) on viruses upon viral infection to trigger the innate

TABLE 2 Viral encoded lncRNAs

lncRNA	Virus	Pheno-type	Reference
PAN RNA	KSHV	PAN RNA interacts with demethylases JUJD3, UTX and the histone methyltransferase MLL2. The interaction results in a decrease of H3K27me3 mark at the ORF50 promoter and therefore controlling KSHV transcription; PAN RNA binds to PRC2 and modulates inflammation, cell cycle and immune response.	117,36
sfRNA	Flavivirus, Zika	A production from flaviviral genome; interacts with XRN1 and DEAD/H-box helicase ME31B and determines flavivirus and Zika viral replication.	118,38
Lat	HSV-1, HSV-2	Lat binds to CTCF factor and retains a specific chromatin structure; promotes reactivation of HSV.	119,120
β2.7	HCMV	Anti-apoptotic by interacting and stabilizing mitochondrial complex I; reducing ROS production.	121,122
5.0 kb RNA	HCMV	Highly AT-rich in sequence; a stable intron expressed during HCMV infection; not required for cell proliferation upon viral infection.	123,73
7.2 kb RNA	MCMV	Highly conservation among cytomegaloviruses, an orthologue of RNA 5.0 kb RNA; a stable and live-lived intron; enhance the processes from the acute to a persistent phase of infection.	124-126
EBERs	EBV	Interact with PKR and inhibit its phosphorylation, counteract INFα-induced apoptosis; induce IL-10 transcription and confer clonability; maintain EBV latency by the induction of AKT expression.	127-129

Abbreviations: EBERs, EBV-encoded non-coding RNAs; EBV, Epstein-Barr virus; HCMV, human cytomegalovirus; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; H3K27me3, trimethylation of histone H3 on lysine 27; KSHV, Kaposi sarcoma-associated herpes virus; lncRNAs, Long non-coding RNAs; MCMV, murine cytomegalovirus; PAN RNA, polyadenylated nuclear RNA; PRC2, polycomb repressive complex 2; ROS, Reactive Oxygen Species; SFPQ, splicing factor proline/glutamine-rich; sfRNA, subgenomic flaviviral RNA

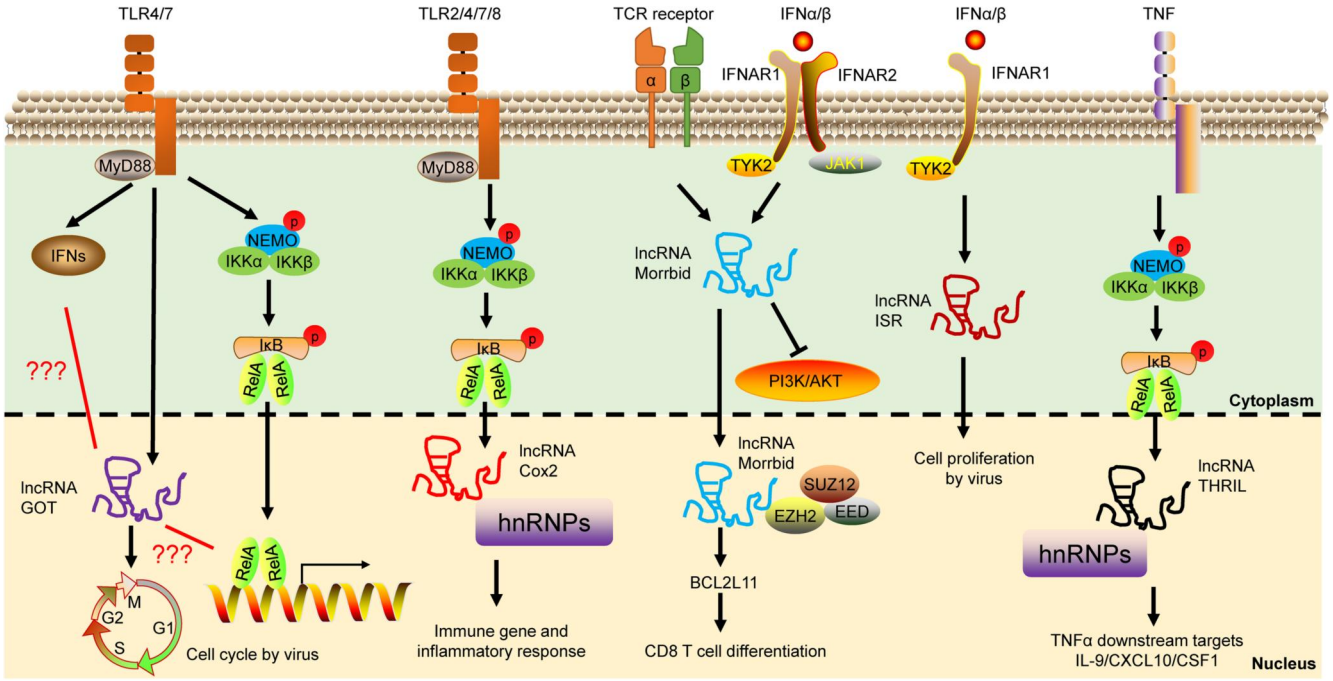

FIGURE 2 LncRNAs regulate host innate immune response. From left to right: TLR4 and TLR7-induced lncRNA GOT promotes host viral replication. TLRs-upregulated LncRNA Cox2 binds to hnRNPs and thereby controlling immune genes and immune response. LncRNA Morrbid regulates PI3K/AKT pathway and BCL2L11 through the interaction with PRC2 complex. The-type I IFN receptor, IFNAR1, synergically increases lncRNA ISR expression which promotes viral replication. TNFα induces lncRNA THRIL via NF-κB. THRIL binds to hnRNPs and contributes to TNFα and other cytokines expression. lncRNAs, Long non-coding RNAs; TLR, toll-like receptors; GOT, glutamic-oxaloacetic transaminase; hnRNP, heterogeneous nuclear ribonucleoprotein E1; PRC, polycomb repressive complex 2; ISR, interferon-stimulated lncRNA, TNF, tumour necrosis factor

immune response.[56,57] The extensive knowledge of TLRs helps us to better understand the mechanism of the innate immune response in chronic viral infections.[58-60] RNA-seq or microarray-based approaches have identified that lncRNAs are associated with TLR-relevant antiviral immune responses. For example, Carnero et al., found that TLR4/TLR7-induced lncRNA EGOT enhances viral replication and antagonizes the antiviral response (Figure 2).[61] Furthermore, given the essential function of TLR4 and TLR7 in host immunity and their crosstalk with transduction signalling pathways such as NF-κB and IFN pathways,[62-64] it suggests that lncRNA EGOT may be involved in various processes during viral infection. It has also been reported that a TLR2 ligand, Pam_3CSK_4, transcriptionally induces numerous protein-coding genes and 62 lncRNAs which are involved in innate immunity. LncRNA Cox2 is one of the most significantly upregulated lncRNAs and it is proximal to the protein-coding gene Cox2. Other TLRs like TLR4/7/8 can also stimulate lncRNA Cox2 expression. LncRNA Cox2 interacts with hnRNP-A/B and A2/B1 in cytosolic and nuclear compartments to regulate immune genes and inflammatory response (Figure 2).[65] Although the TLR induced viral response leads to the upregulation of lncRNAs that modulate the innate immune response, the precise downstream mechanisms of lncRNAs/TLRs in antiviral immune response have yet to be fully explored and further study is required.

Interferons are leading pro-inflammatory cytokines and immunomodulatory factors in antiviral immune response.[66] Kotzin recently showed that lncRNA Morrbid is induced by T-cell receptor (TCR) and type I IFN activation at the early stage of acute and chronic lymphocytic choriomeningitis virus infection. Upregulated lncRNA Morrbid modulates CD8 T cell differentiation and survival via repression of PI3K/AKT pathway and induction of pro-apoptotic gene BCL2L11.[67] They also verified that lncRNA Morrbid regulates BCL2L11 by controlling the enrichment of PRC2 complex at BCL2L11 promoter and thus, in cis, affect allele-specific BCL2L11 transcription (Figure 2).[68]

Another lncRNA, named as interferon-stimulated lncRNA (ISR), is effectively induced upon IAV infection in a mouse model by IFN signalling, where the induction of ISR by IFN is abolished in host deficient with IFNAR1, a type I IFN receptor. Ectopic lncRNA ISR reduces, whereas silencing of ISR promotes viral replication and ISR promoted the antiviral response (Figure 2). Therefore, interferon signalling is important in regulating lncRNAs that are involved in the antiviral response.

Tumour necrosis factor (TNF), an activator of NF-κB, is a key inflammatory cytokine and participant in the host defence against viral infection.[69] Li et al., established that lncRNA THRIL (linc1992), named as TNFα and hnRNPL related immunoregulatory lincRNA, is required for TNFα expression. THRIL directly interacts with hnRNPL and controls TNFα downstream targets (Figure 2). Other cytokines and chemokines such as IL-8, CXCL10 and CSF1, are induced by THRIL but the mechanisms are required to be explored.[70] Therefore, not only are lncRNAs induced by the viral immune response, they can also regulate key immune molecules, such as cytokines, to modulate the immune response.

6.2 | LncRNAs regulate immune response via transcriptional regulation

Emerging data have discovered that lncRNAs can transcriptionally regulate gene expression to modulate the immune viral response and viral replication.[19,71,72] Firstly, lncRNAs can recruit transcription factors (TFs), to activate or repress the transcription of innate immune genes such as IFN and ISGs.[73] Ma and colleagues showed that lncRNA NEAT1 is induced during the Hantaan virus (HTNV) infection. Induced NEAT1 relocates the SFPQ to paraspeckles and thus reversing its transcriptional inhibition of RIG-I and DDX60. Restored DDX60 promotes endogenous RIG-I expression and facilitates RIG-I induced IFN response. Therefore, NEAT1 can activate IFN signalling and modulate the innate immune response which gives negative feedback against HTNV viral infection (Figure 3a).[74] Furthermore, the formation of paraspeckles by a virus may serve to modulate host responses to viral infection and help establish latency.[75] Similarly, another group established that lncRNA NEAT1 is induced by IV and HSV infection leading to the excess formation of paraspeckles, as well as by TLR3-p38 pathway-triggered poly I:C that stimulates viral infection. Here, NEAT1 relocates SFPQ from the IL8 promoter to paraspeckles leading to the transcriptional activation of IL8 and activation of the innate immune response (Figure 3a).[76] On the other hand, HIV-induced NEAT1 could inhibit HIV production by increasing nucleus-to-cytoplasm export of instability element HIV RNAs into paraspeckles and further modulate HIV1 mRNAs.[77] Therefore, NEAT1 is a key lncRNA induced during viral infection and plays an important role in activating the innate immune response and modulating viral replication at the transcriptional and post-transcriptional level.

NF-κB is a critical TF in inflammatory and immune processes and can activate downstream of interferon signalling.[78] As well as TLR mediated upregulation, lncRNA EGOT was shown to be induced through NF-κB activation in liver cells treated with HCV, by the antiviral factor PKR. Ectopic NF-κB directly binds to lncRNA EGOT promoter region and transcriptionally enhances EGOT expression, while downregulation of EGOT is observed after treatment of IκB, an NF-κB suppressor. Silencing of EGOT increased the innate immune response and decreased viral replication following viral infection and ectopic expression lead to the repression of antiviral ISG genes. Therefore, despite being associated as an antiviral factor in HCV, PKR functions to promote viral replication by stimulating EGOT expression and inhibiting the antiviral response.[61] Similarly to EGOT, a pseudogene lncRNA Lethe is selectively triggered by NF-κB but acts as a negative regulator on NF-κB-dependent gene expression. As a decoy, Lethe directly interacts with the NF-κB subunit RelA-RelA homodimers and blocks its binding on the promoters of downstream genes, such as IL-6, IL-8 and SOD2, hindering the immune response (Figure 3b).[79] Furthermore, NF-κB was involved in IAV induced ISR expression, where ISR expression is reduced upon treatment with an NF-κB inhibitor in A549 cells or mice.[51] However, in contrast to EGOT and Lethe, ISR promoted the antiviral response and inhibited viral replication. Therefore, as NF-κB signalling can regulate lncRNAs

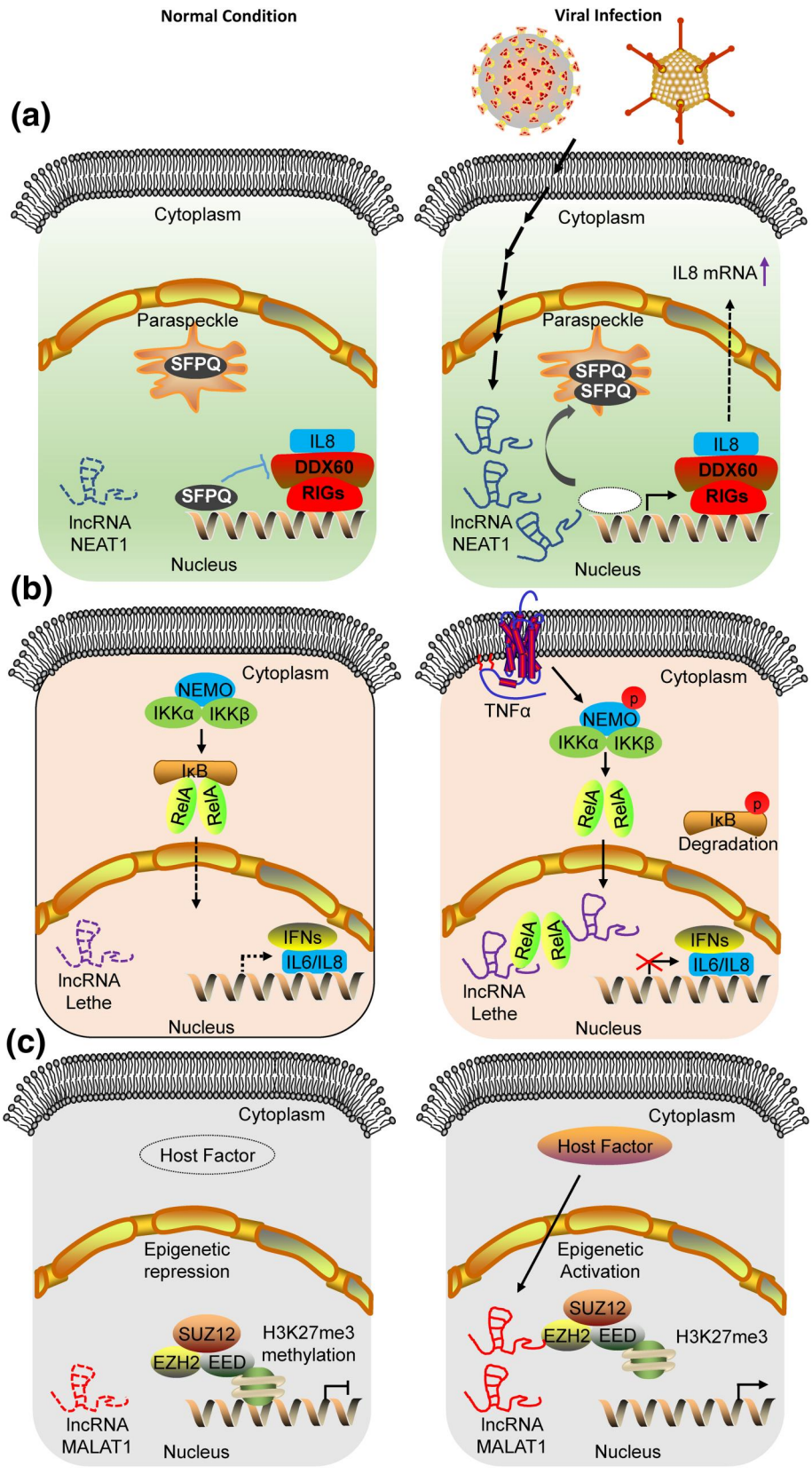

FIGURE 3 LncRNAs Transcriptional Regulation in Viral Infection. (a) Left: Under normal condition, lncRNA NETA1 is inactive, SFPQ transcriptional represses IL8, DDX60 and RIGs. Right: During viral infection, active NEAT1 relocates SFPQ to paraspeckle and therefore promotes the IL8, DDX60 and RIGs gene expression. (b) Left: Under normal condition, the lncRNA Lethe is low expressed. NF-κB signalling is not activated and RelA-RelA homodimer is not translocated in the nucleus. Right: NF-κB is activated by TNFα and the RelA-RelA homodimer translocates to the nucleus. NF-κB-induced lncRNA Lethe interacts with RelA and prevents the RelA-RelA homodimer binds to gene promoters thereby repressing gene expression. (c) Left: Under normal condition, lncRNA MALAT1 is inactive. EZH2 interacts with H3K27me3 and results in epigenetic repression. Right: MALAT1 is upregulated during HIV-1 infection. Ectopic MALAT1 binds to EZH2, relocates PRC2-H3K27me3 complex and contributes to HIV transcription. lncRNAs, Long non-coding RNAs; PRC, polycomb repressive complex 2; ISR, interferon-stimulated lncRNA, TNF, tumour necrosis factor; SFPQ; splicing factor proline/glutamine-rich, H3K27me3; trimethylation of histone H3 on lysine 27lncRNAs

that modulate viral replication and immune responses positively or negatively, further study is required to investigate the crosstalk between lncRNAs and NF-κB transcriptional regulation.

Increasing studies made over the past decade support the idea that lncRNAs control transcription via chromatin modification, and this may be a key method of lncRNA regulation in the antiviral response.[80] For example, HIV-1 induced lncRNA MALAT1 guides EZH2, a core component of PRC2, away from the promoter of HIV-1 long terminal repeat (LTR). This leads to the detachment of PRC2 mediated H3K27me3 and alleviates epigenetic repression on HIV-1 transcription. The re-activation of HIV-1 LTR-promoted transcription is essential for viral replication and latency (Figure 3c).[81] Ouyang et al., showed that lncRNA NRAV is upregulated by IAV, and silencing of NRAV suppresses IAV replication and viral production. NRAV also negatively regulates the initial transcription of multiple critical ISGs such as MxA and IFITM3 by modulating the enrichment of H3K4me3 (an active mark) and H3K27me3 (a repressive mark) on the transcription start sites of MxA and IFITM3, respectively. However, ZONAB, a binding protein of lncRNA NRAV, can significantly rescue the NRAV-mediated decrease in expression of MxA.[82] Therefore, there may be multiple mechanisms for regulation of IAV infection by NRAV and further study is required to elucidate the precise mechanisms.

7 | LncRNAs AND SARS-CoV-2

A novel coronavirus, officially named as SARS-CoV-2, has recently caused a large global outbreak and is still a major public health issue.[7] Two other pathogenic coronaviruses SARS-CoV and MERS-CoV caused zoonotic epidemic and local outbreaks in humans in 2003 and 2012, respectively.[3] However, the mechanism of coronavirus infection is poorly understood and the function of lncRNAs in coronavirus diseases has not been well studied. To our best knowledge, few reports have shown the functions of non-coding RNAs, in particular lncRNAs, in the coronavirus viral replication and immune response.

Vishnubalaji et al., recently reported that 18 lncRNAs are upregulated in SARS-CoV-2 infected bronchial epithelial cells but their roles in viral inflammatory response need to be investigated.[83] Peng et al., identified that approximately 500 lncRNAs are dysregulated during SARS-CoV infection. This is the first study demonstrating the differential expression of lncRNAs upon coronavirus infection. The differentially regulated lncRNAs are involved in the immune response and are able to regulate neighbouring protein-coding genes to regulate viral replication. In addition, these lncRNAs are also regulated by IAV, a virus which causes acute lung disease similar to SARS-CoV,[30] representing an opportunity to better understand SARS-CoV. Josset et al., reported similar results of dysregulated lncRNAs in mice upon infection with SARS-CoV and IAV.[84] Using RNA-seq, the authors identified 5295 dysregulated lncRNAs and many of these are associated with cell proliferation, the IFN response and proinflammatory pathways.[84] One of the top dysregulated lncRNAs is MALAT1, a key mediator and biomarker in lung cancer metastasis.[85] Given the fact that patients with non-small cell lung cancer (NSCLC) exhibit a higher incidence of Covid-19 and present with more severe symptoms and poorer outcomes,[86,87] the high expression of MALAT1 in NSCLC patients may antagonize the antiviral host response, and increase susceptibility to SARS-CoV-2 infection. However, further work is required to elucidate the exact role of MALAT1 in SARS-CoV-2. LncRNAs are also important mediators in animal coronaviruses. For example, differentially expressed lncRNAs affect transmissible gastroenteritis virus (TGEV)-induced inflammation through modulation of the NF-κB pathway.[88]

Virus binding and entry are the first steps of viral infection. Recent studies have underlined the molecular mechanisms of SARS-CoV and SARS-CoV-2 and reported that the angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase-4 (DPP4) are receptors that can facilitate viral entry into host cells.[89,90] After that, these receptors will be internalized and its membrane expression decreased, which results in local vascular leakage leading to the damage of lung tissues. ACE2 and DPP4 are associated with metabolic signals and pathways regulating inflammation and viral genome replication, and it has been suggested that lncRNAs may control COVID-19 through the regulation of these receptors. Ectopic ACE2 enhances the severity of the disease in mouse after SARS-CoV infection,[91] implying a potential strategy against COVID-19by blocking this receptor. Li and colleagues showed that lncRNA ALT1 directly interacts with ACE2 in HUVECs cells. ALT1 knockdown decreases ACE2 level thereby inhibiting cell proliferation via promotion of cyclin D1 ubiquitination.[92] Several studies have also addressed that lncRNAs control cell proliferation, autophagy, or colony formation through DPP4.[93-95] Furthermore, ACE2 and DPP4 are involved in multiple pathways such as VEGF, PI3K/AKT, and CXCR, which are important for viral replication.[96-98] Given the key functions of lncRNAs in these pathways and other biological processes, lncRNAs may function in coronavirus replication by modulating viral receptors such as ACE2 and DPP4. There is currently limited publication relevant to lncRNA/SARS-CoV-2 to the best of our knowledge. Therefore, further study of lncRNAs involved in SARS-CoV-2 will shed light on the precise molecular mechanisms in viral replication.

The pathophysiology of SARS-CoV-2 infection closely resembles that of SARS-CoV infection, with inflammatory responses strongly implicated in the resulting damage to the lung and airways.[99] After virus entry, host cells recognize PAMPs such as SARS-CoV-2 through PRRs, stimulate an innate immune response and produce proinflammatory cytokines and chemokines IL-6, IFN-$\alpha\beta$ and TNFs. Lei et al., recently reported that SARS-CoV-2 triggers the evasion of Type I IFNs responses by inhibiting IFN-β activation.[100] In agreement with that, Blanco-Melo et al., also observed that SARS-CoV-2 infection induces a limited IFN-I and III response juxtaposed to elevated chemokines and high expression of IL-6.[101] As discussed previously, lncRNAs are emerging as key modulators of gene expression in the immune system and they most likely participate in the antiviral responses to coronavirus by regulating the expression of cytokines and chemokines.[102,103] For example, Zhuang and colleagues report that lnc-DC modulates the immune response by inhibiting the

expression of TNFα, IL-6, IL-12 as well as increasing TLR-9/STAT3 signalling in dendritic cells upon HBV infection.[104] In addition, the double-stranded RNA-activated PKR is an important factor in modulating the antiviral response. Coronaviruses could antagonize the PKR-regulated antiviral response by preventing phosphorylation of the protein synthesis initiation factor eukaryotic initiation factor-2 alpha (eIF2α) and therefore facilitate virus replication.[105,106] It has been shown that lncRNA nc886 inhibits PKR-dependent signalling and induces $CD4^+$ T cell activation via the interaction with IFNγ and IL-2,[107] which suggests the potential functions of lncRNAs in the antiviral responses via different immune signalling pathway upon coronavirus infections.

Taken together, the potential roles of lncRNAs in SARS-CoV-2 indicate that therapies targeting the antiviral response through lncRNAs may become promising means to inhibit inflammation in Covid-19 diseases.

8 | CONCLUSION AND FUTURE PERSPECTIVES

One of the major surprises of the ENCODE project was the identification of numerous non-coding RNAs, in particular lncRNAs. Since then, lncRNAs have been widely described as versatile regulators in viral diseases, cancer development and other pathological conditions.

Firstly, a large number of lncRNAs become upregulated or downregulated after viral infection, implying their crucial functions in the host antiviral response. The differential expression level of lncRNAs also suggests their potential as prognostic biomarkers or implications for therapeutic diagnosis. Screening the serum of patients for lncRNA biomarkers may provide an early tool of diagnosis for viral disease progression. In addition to the dysregulation of host lncRNAs, the expression of viral lncRNAs is also of fundamental importance for viral infection.

Secondly, virus regulated lncRNAs can function as Yin and Yang regulators in various important stages of the immune response. There is increasing evidence showing that lncRNAs regulate essential cytokines and proinflammatory factors such as IFN or ISGs. The alterations of these innate immune molecules significantly affect the host antiviral reaction to enhance or alleviate viral infection and replication. TLR-regulated lncRNAs can also modulate viral replication via host cell machinery providing a new insight for lncRNA regulation upon viral infection other than via the direct effect on the innate immune response.

Thirdly, lncRNAs can modify the assembly of transcription or translation complexes by recruiting transcriptional factors or epigenetic modulators, such as NF-κB and PRC2, to modify gene expression which is involved in viral replication. As a result, endogenous lncRNAs can regulate mRNA stability and enhance the expression levels of innate immunity related genes. Furthermore, lncRNAs have been shown to act via different mechanisms to regulate viral replication. These observations provide strong evidence for the critical function of lncRNAs in controlling the antiviral response. Although many breakthroughs have been achieved towards the mechanisms of lncRNAs in viral diseases, their functions remain far beyond full understanding.

Lastly, the ongoing SARS-CoV-2 pandemic causes a significant threat to human health however, the biology and mechanism of pathogenicity are limited. Although little is known about SARS-CoV-2 antiviral response, information can most likely be extrapolated from SARS-CoV and MERS-CoV based mechanisms.[108,109] Type I and II IFNs responses, the production of cytokines and chemokines and the activations of key transcriptions factors like NF-κB and AP-1 may help SARS-CoV-2 to escape from the host immune surveillance and eventually enhance viral replication. The well-established functions of lncRNAs in these biological processes may offer a tool to further understand the antiviral innate immunity upon coronavirus infection.

Extensive evidence strongly supports the key roles of lncRNAs in transcription, replication, and immunity during the antiviral response. However, the function of virus regulated lncRNAs with experimentally verified functions remain to be further investigated. In conclusion, a more extensive comprehension gained on the roles of lncRNAs in viral diseases may help identify potential therapeutic strategies in the future.

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CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Lucy Ginn, Manuela La Montagna and Lei Shi, conceptualized the review, performed the literature search and wrote the manuscript. Qinghua Wu provided helpful recommendations and helped editing the manuscript. All authors read and approved the final manuscript. Lei Shi revised each step in the work and was responsible for the final revision.

DATA AVAILABLITIY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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