Received: 17 June 2021 | Revised: 26 June 2021 | Accepted: 29 June 2021

DOI: 10.1002/rmv.2275

REVIEW

WILEY

Long noncoding RNAs in respiratory viruses: A review

Mina Mobini Kesheh[1] | Shahab Mahmoudvand[2,3] | Somayeh Shokri[2,3]

[1]Department of Virology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

[2]Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

[3]Department of Virology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Correspondence
Somayeh Shokri, Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz 6135715794, Iran.
Email: Shokri.so@ajums.ac.ir

Abstract

Long noncoding RNAs (lncRNAs) are defined as RNA molecules longer than 200 nucleotides that can regulate gene expression at the transcriptional or post-transcriptional levels. Both human lncRNAs and lncRNAs encoded by viruses can modulate the expression of host genes which are critical for viral replication, latency, activation of signalling pathways, cytokine and chemokine production, RNAi processing, expression of interferons (IFNs) and interferon-stimulated genes (ISGs). Studies on lncRNAs as key regulators of host-virus interactions may give new insights into therapeutic strategies for the treatment of related diseases. This current review focuses on the role of lncRNAs, and their interactions with respiratory viruses including influenza A virus (IAV), respiratory syncytial virus (RSV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

KEYWORDS
IAV, long noncoding RNAs, respiratory viruses, RSV, SARS-CoV-2

1 | INTRODUCTION

Viruses are obligate intracellular pathogens that can directly interact with cellular DNAs, RNAs and proteins.[1] Therefore, viruses rewire host gene expression processes or metabolic pathways to facilitate their replication.[2] Cellular long noncoding RNAs (lncRNAs) play important roles in the regulation of biological functions and gene expression.[3]

In viral infection, cellular LncRNAs act as a double-edged sword in innate immunity.[4] In other words, lncRNAs can promote virus replication and escape from antiviral immunity and on the other hand can prevent virus replication.[5] Additionally, viruses generate many lncRNAs to resist cellular antiviral activity in infected cells.[6] Below, we review function or effects of lncRNAs involved in suppression and/or progression of respiratory viral infections as well as regulation of innate immune response to them.

Abbreviations: Ad2, adenovirus type 2; ARDS, acute respiratory distress syndrome; BARTs, BamHI-A rightwards transcripts; BHLF1, BamHI H leftward reading frame 1; BMDCs, bone marrow-derived dendritic cells; BST2, bone marrow stromal cell antigen 2; CARDs, caspase recruitment domains; CBP, CREB-binding protein; CCL5, C-C motif chemokine ligand 5; cGAS, cyclic-GMP-AMP (cGAMP) synthase; CTD, C-terminal domain; CXCL10, C-X-C motif chemokine ligand 10; EBV, Epstein–Barr virus; EGOT, Eosinophil granule ontogeny transcript; ERK, extracellular signal-regulated kinases; FasL, Fas ligand; FOXO3A, forkhead Box O3A; HAdV, human adenovirus; HEXIM1, hexamethylene bis-acetamide-inducible protein 1; hnRNP U, heterogeneous nuclear ribonucleoprotein U; IAV, influenza A virus; IBV, Avian infectious bronchitis virus; IE, immediate-early; IFI44L, interferon induced protein 44 like; IFIT1, interferon induced protein with tetratricopeptide repeats 1; IFITM3, interferon induced transmembrane protein 3; IFN-β, interferon beta; IGFBP7-AS1, insulin-like growth factor binding protein 7-antisense 1; IL-6, interleukin 6; IRF1, interferon regulatory factor 1; IRF3, interferon regulatory factor 3; IRGs, immune response genes; ISGs, interferon-stimulated genes; lncRNA ISR, interferon-stimulated lncRNA; lncRNAs, long noncoding RNAs; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MAPK, mitogen-activated protein kinase; MBL, mannose-binding lectin; MEG3, maternally expressed gene 3; Mx1, MX dynamin like GTPase 1; MxA, Myxovirus resistance protein 1; MYC, MYC proto-oncogene, BHLH transcription factor; ncRNAs, noncoding RNAs; NDV, Newcastle disease virus; NEAT1, nuclear paraspeckle assembly transcript 1; NEAT2, nuclear-enriched abundant transcript 2; NF-κB, nuclear factor kappa B; NRAV, negative regulator of antiviral response; OAS1, 2-5′ oligoadenylate synthetase 1; PAAN, PA-associated noncoding RNA; PAMPs, pathogen-associated molecular patterns; PI3K, phosphatidylinositol 3-kinase; PKR, protein kinase R; PRMs, pattern recognition molecules; PSMB8-AS1, PSMB8 antisense RNA 1; PTP1B, protein tyrosine phosphatase 1B; RdRp, RNA-dependent RNA polymerase; RIG-1, retinoic acid-inducible gene I; RNase A, endonuclease A; RSAD2, radical S-adenosyl methionine domain containing 2; RSV, respiratory syncytial virus; SARS-CoVs, severe acute respiratory syndrome coronaviruses; SeV, Sendai virus; SFPQ, splicing factor proline and glutamine rich; ssDBPs, single-stranded DNA binding proteins; STAT1, signal transducer and activator of transcription 1; STING, stimulator of interferon genes; TBXL1, transcriptional coactivator T-box protein 1; TLR4, toll-like receptor 4; TNF-α, tumour necrosis factor-α; TPRG1L, tumour protein P63 regulated 1 like; TRIM25, tripartite motif containing 25; VIN, virus inducible lincRNA; VSV, vesicular stomatitis virus.

2 | LONG NONCODING RNAs

Noncoding RNAs (ncRNAs) are functional RNA molecules that are transcribed from mammalian genomic DNA but are unable to encode proteins.[7] The ncRNAs are classified into two major groups including small ncRNAs (~20 to 200 nucleotides) and long ncRNAs (200 nucleotides to ~100 kilobases).[8,9] These noncoding elements constitute nearly 80% of the human genome.[10] MicroRNAs (miRNAs) are one of the small single-stranded ncRNAs (18–25 nucleotides in length) that regulate around 60% of human protein-coding genes.[11,12] These molecules play an important role in regulating a great number of biological processes such as development, differentiation, growth, metabolism, stress response, angiogenesis, apoptosis and immune response.[13–15] The miRNAs inhibit transcription and protein synthesis by binding to the 3′ untranslated region (3′UTR) of messenger RNAs (mRNAs).[16] 5′UTR and the coding regions of mRNA are the sites other than 3′UTR that have the potential to interact with miRNAs, giving rise to translational suppression or target gene degradation.[17,18]

LncRNAs are a new class of noncoding RNAs that has emerged as novel players in the regulation of gene expression.[19,20] Unlike miRNAs, which primarily rely on base complementarity to interact with their target RNAs, lncRNAs employ diverse mechanisms for regulating biological processes.[21] LncRNAs can regulate gene expression at the level of transcription, RNA processing, or translation, so lncRNA subcellular localisation provides important clues to its potential mode of action.[22] Recently, it has been reported that lncRNAs play important roles during viral infections and subsequently the antiviral immune response.[23–26] Table 1 and Figures 1 and 2 show lncRNAs involved in immune responses and respiratory viral replication.

2.1 | LncRNA effects on cell signalling related to innate immunity following influenza A virus (IAV) infection

IAVs are important veterinary and human health pathogens that are present worldwide.[27,28] After 1918 IAV pandemic (H1N1) with 500 million infected cases and at least 50 million death, influenza pandemics occurred again in 1957 (H2N2), 1968 (H3N2), 1977 (H1N1) and 2009 (H1N1).[29,30] In IAV infection, the expression of thousands of lncRNAs is altered in host cells.[23]

2.1.1 | lncRNAs that prevent IAV replication

In vitro and in vivo models showed that after IAV infection especially in lung cells, according to corresponding retinoic acid-inducible gene I (RIG-I)-dependent signalling pathway and following interferon beta (IFN-β) induction, the level of interferon-stimulated lncRNA (lncRNA ISR) increased and it was able to suppress viral replication.[31,32]

ISG20 belongs to the 3′–5′ exonuclease super family that displays effective antiviral activity against several RNA viruses, including IAV. ISG20 inhibits the replication of IAV by interacting with viral NP protein and inhibiting viral polymerase activity.[33–35] Translation of ISG20 can be regulated by binding miRNA-326 (miR-326) to 3′UTR of ISG20 mRNAs. In this regard, Chai et al.[23] showed that IAV increases the expression of an interferon-inducible lncRNA termed lnc-ISG20. The lnc-ISG20 showed an inhibitory role on IAV replication by binding to miR-326 to enhance ISG20 protein levels.

Zhao et al.[36] analysed the dataset transcriptome of blood immune cells of patients with IAV infection. After recovery, a novel lncRNA, named IVRPIE was detected that was involved in antiviral innate immunity. Lnc-IVRPIE was remarkably upregulated during IAV infection. The enforced IVRPIE expression and the suppressed IVRPIE expression were significantly inhibited and promoted by IAV replication, respectively. In vitro data demonstrated that this lncRNA performed its antiviral activity by enhancing IFNβ1 and several interferon-stimulated genes (ISGs) such as interferon regulatory factor 1 (IRF1), interferon induced protein with tetratricopeptide repeats 1 (IFIT1), IFIT3, MX dynamin like GTPase 1 (Mx1), ISG15 and interferon induced protein 44 like (IFI44L). Their results demonstrated that IVRPIE establishes a critical role in host innate defence by the positive regulator of IFN β1and ISG expression during the IAV infection.[36]

Tripartite motif containing 25 (TRIM25) mediates K63-linked ubiquitination of the cytosolic pattern recognition receptor RIG-I which is an essential step for initiation of the intracellular antiviral response.[37,38] At the early stage of RNA virus infections such as IAV and vesicular stomatitis virus (VSV), a lncRNA called Lnc-zc3h7a by binding to TRIM25 and the helicase domain of activated RIG-1 leads to stabilising TRIM25-activated RIG-I complex. While RIG-I is not activated by lnc-zc3h7a and this lncRNA only binds to the domain which is exposed after RIG-I activation. The produced level of type 1 IFNs and interleukin 6 (IL-6) in serum was significantly less in lnc-zc3h7a−/− mice compared to lnc-zc3h7a+/+ mice as a result of a response to these RNA viruses.[39,40]

The lncRNAs can remotely regulate antiviral genes by relocating or competitively binding to gene repressors.[41] Splicing factor proline and glutamine rich (SFPQ), also known as PSF (PTB-associated splicing factor), is a multifunctional nuclear protein first identified as a splicing factor, that is implicated in many aspects of nuclear functions including RNA transport, apoptosis and DNA repair, transcriptional regulation and maintenance of genome stability.[42,43] Imamura et al.[44] showed that SFPQ bound to its SFPQ-binding motif on IL-8 promoter, led to repressed IL-8 gene expression in naive cells. During IAV infection, increased expression of nuclear paraspeckle assembly transcript 1 (NEAT1) leads SFPQ to relocate from its promoter and recruit into the paraspeckles (a type of subnuclear bodies built on the long noncoding RNA NEAT1). Therefore, transcriptional activation of the antiviral gene IL-8 was increased. As a result, NEAT1 induction followed by excess formation of paraspeckles caused to transcribe more IL-8 mRNAs. Also SFPQ is also an essential factor for influenza virus mRNA polyadenylation.[44,45]

Barriocanal et al.[46] reported that lnc-ISG15 and lnc-BST2/BISPR as IFN-stimulated lncRNAs increased in infected cells by mutant IAV

TABLE 1 A list of lncRNAs and their functions which are involved in immunity responses and respiratory viral replication

Virus	lncRNA	Function	Localisation
IAV	ISR	Reduction of viral replication through RIG-1-dependent signalling pathway	Nucleus
	ISG20	Increase the expression of ISG20 by binding to miR-326 to decrease its inhibition of ISG20 translation led to reduce the viral replication	Cytoplasm
	PSMB8-AS1	Its expression is induced by different strains of IAV and it is required for influenza virus replication	Nucleus
	IVRPIE	Antiviral activity by enhancing IFNβ1 and several ISGs expression	Nucleus
	ISG15	Antiviral activity via probable induction of PAMPs pathway	Nucleus
	BST2/BISPR	Antiviral activity via probable induction of JAK/STAT pathway. Also, it enhanced BST2 mRNA levels to produce tetherin protein, an inhibitor of viral release	Nucleus
	IPAN	Induces directly by IAV to assist viral replication by forming IPAN/PB1 complex to prevent viral RNA polymerase complex degradation	Cytoplasm
	lncRNA-155	By inhibition the expression of protein tyrosine phosphatase 1B (PTP1B) increases IFN-β and several critical ISG products	Found in nucleus more than cytoplasm
	ACOD1	By interacting with GOT2 promotes viral replication in a metabolic pathway	Cytoplasm
	PAAN	By interacting with viral RNP complex (BP1, BP2, NP and PA) is required for only influenza A virus replication and transcription	Cytoplasm
	VIN	By stabilising single stranded RNAs and protection of them against endonucleases is required for influenza virus replication	Nucleus
	EGOT	By controlling the levels of the TBXL1 and ISGs promotes viral replication	Nucleus
	AVAN	A positive regulator of the antiviral innate immunity by induction of type I interferon and ISGs	Nucleus/cytoplasm
IAV VSV	zc3h7a	Antiviral activity via TRIM25 mediates K63-linked ubiquitination of RIG-1 signalling pathway	Cytoplasm
IAV	NEAT1	-Antiviral activity by forming more paraspeckles	Nucleus/Cytoplasm
Ad2		-By interaction of IRF1, IRF4, STAT1, STAT3, STAT5A could contribute to antiviral response	
SARS-CoV-2		-By interaction of hnRNP U altered the histone modifications of target genes	
HBoV			
IAV SeV	Lsm3b	Negative feedback regulation by self-recognition of RNAs involved in downstream RIG-1 signalling	Cytoplasm
IAV SeV	lnc-MxA	By binding to INF-β promoter and forms RNA-DNA triplexes acts as a negative regulator	Nucleus
IAV	NRAV	-By losing its suppressor effect on transcription, initial transcription of interferon-stimulated genes triggered	Cytoplasm
RSV		-Its low level was corelated with Rab5c protein caused to reduce in viral entry and intracellular transmission	
Ad2		-It interacted with miR-509-3p to reduce cell growth during infection	
SARS-CoV-2	MEG3	-Its protective role in airway epithelial cells by suppressing TLR-4 dependent NF-κB and MAPK signalling	Nucleus
		-By increasing MEG3 in the late phase caused accumulation of p-53 may prevent cell growth	
		-By interaction of hnRNP U altered the histone modifications of target genes	
IBV	MANBAL and POMT2	Reduce possible viral receptor and maybe involved in mannose binding lectin signalling	Cytoplasm

(Continues)

TABLE 1 (Continued)

Virus	lncRNA	Function	Localisation
SeV	ATV	Raised viral titre by disrupting RIG-1-mediated signalling	Cytoplasm
	EPS	Its inhibitory effect on IRGs expression was suppressed as soon as viral entry	Nucleus
	ENST00000565297	It acts as a positive regulator in INF-1 signalling	Nucleus
RSV	PVT1	-By binding to miR-2031 increases entry of quiescent cells into the G1/S phase of the cell cycle	Nucleus
	n337374	-Inhibition of DCs maturation through downregulation of CD86 and pERK1/2 resulted in reduction of asthmatic symptoms due to RSV-infected DCs	
SARS-CoV-2	MALAT1	-Negative regulator of antiviral type I IFN production	Nucleus
		-By absorption of miR-146a-5p and miR-142-3p repress their anti-inflammatory function	
		-By interaction of IRF1, IRF4, STAT1, STAT3, STAT5A could contribute to antiviral response	
		-By interaction of hnRNP U altered the histone modifications of target genes	
Ad5	VAI and VAII	-Interference of VARNAI and RNAII with Dicer activity increased viral replication	Cytoplasm
		-VA RNA I binds to PKR and inhibits its function	

(PR81NS1) to prevent viral replication. The expression of lncBST2/BISPR and lnc-ISG15 are significantly dependent on JAK/STAT pathways and pathogen-associated molecular patterns (PAMPs), respectively.[25] Further studies are required to better understand this induction. Moreover, they observed that reduction of lnc-BST2/BISPR expression leads to decreased bone marrow stromal cell antigen 2 (BST2) mRNA levels which encode tetherin protein, an inhibitor of viral release.[46,47]

Negative regulator of antiviral response (NRAV) is an intronic antisense lncRNA that is identified as a controlling virus infection.[48,49] Ouyang et al.[50] reported that during IAV infection, NRAV was significantly downregulated. In fact, overexpression of NRAV lncRNA enhances IAV replication by suppressing the expression of several key ISGs such as IFIT2, IFIT3, interferon induced transmembrane protein 3 (IFITM3) and Myxovirus resistance protein 1 (MxA). These results indicate that NRAV is a key regulator of antiviral innate immunity.[50]

RIG-I is composed of two N-terminal caspase recruitment domains (CARDs), a DExD/H-helicase domain and a C-terminal domain (CTD).[51] When viral infection occurs viral RNAs bind to CTD that is thought to induce conformational changes to expose the CARDs. Lnc-Lsm3b is another lncRNA that binds to RIG-I-triggered antiviral signalling cascades and prevents downstream signalling by binding to helicase and CTD of RIG-I.[52] The results of Jiang et al.[52] study showed that upregulated lncRNA has a negative role in producing IFN-β and IL-6 at the late stage of IAV infection in mice, but not human cells. These data support the concept that in IAV infection, lnc-Lsm3b produced after elevated levels of inflammatory cytokines can cause cell death as well as tissue damage.[53] Also, lnc-Lsm3b can modulate immune response to the virus in a time-dependent manner. In the other words, lnc-Lsm3b directly competes with viral RNA for the binding of CTD of RIG-I.[52]

More et al. showed that the lncRNA PSMB8 antisense RNA 1 (PSMB8-AS1) expression was induced by different strains of influenza virus and type I IFN. After the PSMB8-AS1 repression using CRISPR interference, viral mRNA and protein levels reduced and led to decreased influenza virus infection and synthesis. Probably, PSMB8-AS1 has the binding site for regulating miRNAs, such as miR-382-3p.[54] The upregulation of PSMB8-AS1 can modulate the secretion of IL-6 and tumour necrosis factor (TNF) α, two pivotal proinflammatory cytokines.[55] It is concluded that lnc-PSMB8-AS1 can be used as a novel host factor for developing antiviral therapy against influenza virus infection.[56]

By using both in vitro (several cell lines) and in vivo (mouse model) experiments, Maarouf et al.[57] demonstrated that lncRNA-155 expression is greatly induced during IAV infection and has significant effects on virus replication and virulence. In fact, the overexpression of lncRNA-155 suppressed viral replication. In infected cells, lncRNA-155 stimulated innate immune response to IAV through regulating the expression of protein tyrosine phosphatase 1B (PTP1B).[48] This protein is a key negative regulator of type I IFN signalling pathway.[58] The PTP1B inhibition by lncRNA-155 leads to higher production of IFN-β and several critical ISGs. LncRNA-155 knockdown leads to in a significant downregulation of IFN-β and Mx1 mRNA levels and higher susceptibility to IAV infection.[57]

Nuclear lncRNA-antivirus and activate neutrophil (AVAN) binds to the promoter of forkhead box O3A (FOXO3A) and regulates it positively. FOXO3A suppresses Fas Ligand (FasL) in apoptosis

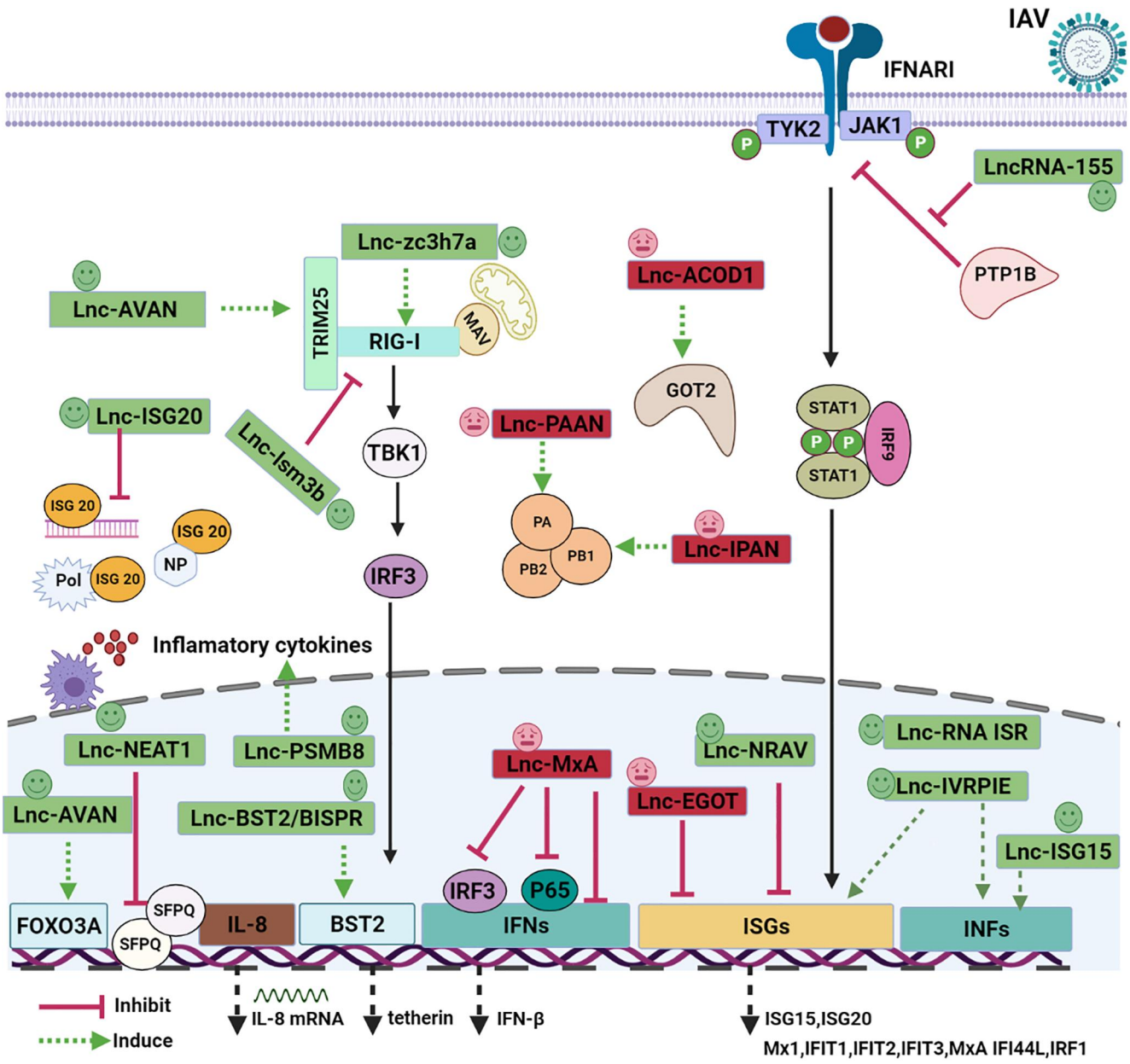

FIGURE 1 Schematic diagram of the roles of lncRNAs during influenza virus infection. Most lncRNAs regulate the host immune response against influenza virus at different steps to inhibit (green) or promote (red) the virus infection. Refer to the text for more details

pathway which concludes in neutrophil survival and elicits a cascade of neutrophil chemotaxis. Also, in cytoplasm, lnc-AVAN directly binds to TRIM25 and triggers cascades of Type 1 IFN responses. Lai et al.[59] demonstrated lnc-AVAN is upregulated upon IAV infection and limits the viral replication through activation of innate immunity.

2.1.2 | lncRNAs that promote IAV replication

The influenza RNA-dependent RNA polymerase (RdRp) is a trimeric complex comprising three subunits; P1 (or PB1), P2 (or PA) and P3 (or PB2). PB1 is the catalytic core of the polymerase complex responsible for the polymerase activity.[60] Wang et al.[61] identified an IFN-independent lncRNA called as IPAN that is hijacked by IAV for stabilising PB1 protein and promoting viral replication. In fact, this lncRNA forms the IPAN/PB1 complex and prevents virus degradation by the host immune system.

In IAV-infected cells, the expression of lnc-ACOD1 is not induced by IFN-I or interferon regulatory factor 3 (IRF3) factor. Instead, nuclear factor kappa B (NF-κB) via binding p65/RelA subunit to promoter of lncRNA-ACOD1 has role in its induction. Upregulation of lnc-ACOD1 in human cells (A549) after IAV infection indicated its vital role for viral replication. As well as this, lncRNA increases DNA or RNA viral replication through a probable general mechanism in human or mouse. A 225-nucleotide region in 5′end of the lnc-ACOD1 interacts with GOT2, an aspartate aminotransferase

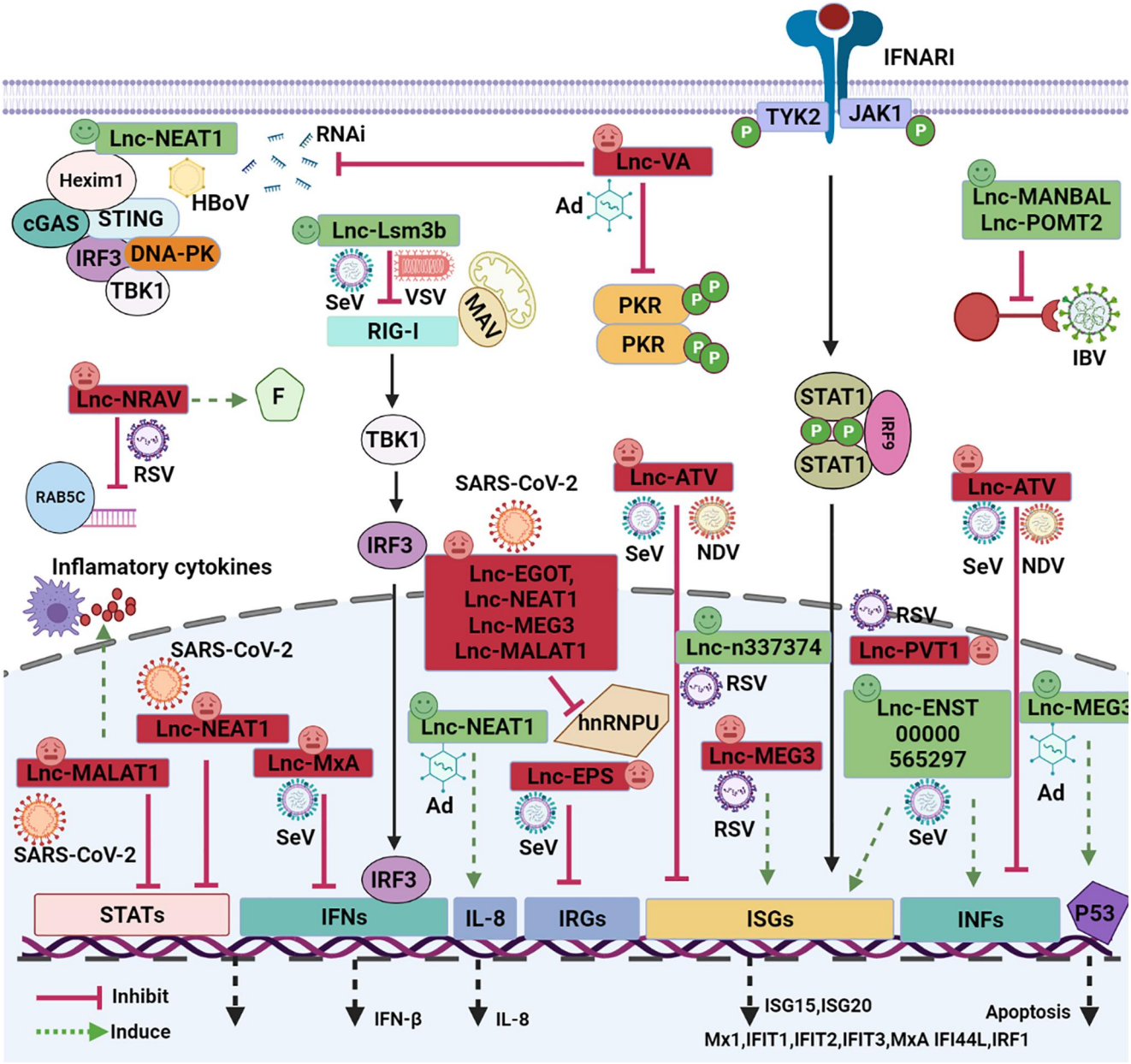

FIGURE 2 Schematic diagram of the roles of lncRNAs during respiratory viral infection. Most lncRNAs regulate the host immune response at different steps to inhibit (green) or promote (red) the virus infection. Refer to the text for more details

that converts oxaloacetate and L-glutamate into L-aspartate and α-ketoglutarate in the cytoplasm. GOT2 knockdown reduces the lnc-ACOD1 activity and subsequently, reduces viral replication. Wang et al.[62] suggested the importance of lnc-ACOD1 on viral replication in a metabolic pathway.

Another lncRNA by independent-IFN expression is lnc-PAAN (PA-associated noncoding RNA) which is induced by only IAV infection, not other viruses and is required for IAV transcription and replication. Lnc-PAAN interacts with components of the RNP complex; BP1, BP2, NP by preferable association with PA proteins and promotes the assembly of viral RNA polymerase. As a result, reduction of lnc-PAAN impairs the activity of viral RdRp and prevents the viral replication.[63]

Based on in silico prediction, the secondary structure of an lncRNA called virus inducible lincRNA (VIN) revealed insensitivity to endonuclease A (RNase A) digestion and this supported the idea that VIN has a functional role in other cellular components. This lncRNA is localised to the host cell nucleus and may be implicated in post-transcriptional control, and chromatin remodelling. Winterling et al.[64] demonstrated that VIN is induced already after infection by diverse IAV strains like H1N1, H3N2 and H7N7 but not with influenza B virus (IBV). The induction of VIN is not affected by all viruses, treatment with RNA mimics or the Type I IFN response. Indeed, it is induced only by specific viruses and correlated with their virulence. Identification of significant decrease of viral titres in VIN knockdown cells supported its effect in the IAV lifecycle.[53,64] These studies

provide novel insights into the role of lncRNAs in interacting the host immune system with IAV.

Li et al.[65] indicated that lnc-MxA by interfering with the enrichment of IRF3 and p65 at the IFN-β promoter facilitates IAV replication due to inhibition of INF-β activation. Also lnc-MxA binds to INF-β promoter and forms RNA-DNA triplexes. While, lnc-MxA knockdown leads to arise the mRNA levels of INF-β and other ISGs like MxA, IFITM1, IFITM3 and ISG15. Influenza virus may induce a robust immune response as a cytokine storm, while lnc-MxA as a negative regulator may help the cell return to homeostasis.[53,65]

Eosinophil granule ontogeny transcript (EGOT) lncRNA is induced after infection with RNA viruses, RNA mimics and by the activation of different stress-response pathways, including NF-κB, protein kinase R (PKR) and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT).[48,66,67] Increased expression of EGOT is observed in IAV infection and it may promote viral replication by controlling the levels of the transcriptional coactivator T-Box protein 1 (TBXL1) and ISGs leading to blocking the IFN antiviral response.[48,53,68] Inhibition of EGOT leads to increased levels of several ISGs and to decreased viral replication.

2.2 | Sendai virus (SeV)

SeV, or murine parainfluenza virus type 1, typically infects the respiratory tract of rodents.[69] Upon SeV infection, level of lncRNA ENST00000565297 was upregulated, subsequently transcription of IFNβ1, IFN-α1, ISG56, C-X-C motif chemokine ligand 10 (CXCL10) and IL-6 would be increased. Therefore, this SeV-induced lncRNA was reported as a positive regulator in defence against this virus.[70] Also, lnc-MxA, MxA mRNAs and lnc-Lsm3b were significantly increased in SeV-infected cells. Lnc-MxA facilitates the replication of SeV by interfering with the activation of IFN-β transcription,[65] while lnc-Lsm3b acts as a decoy for RIG-I and prevents downstream signalling; therefore, lnc-Lsm3b can restrict late antiviral response to SeV-infected mice in a feedback manner to maintain immune homeostasis.[52]

Lnc-EPS is expressed in macrophages and dendritic cells in resting state or absence of activation signals. It is introduced as a negative regulator in inflammatory response in these cells. Indeed, lnc-EPS downregulates immune response genes (IRGs) expression by binding to regulatory regions of IFIT2, RSAD2 (radical S-adenosyl methionine domain containing 2), 2′–5′ oligoadenylate synthetase 1 (OAS1) and some cytokine/chemokine genes such as CXCL10, CCL5 (C-C motif chemokine ligand 5) and IL-6.[71] Expression of lnc-EPS after entry of SeV is suppressed in bone marrow-derived macrophages to initiate innate immunity cells activity.[72]

LncATV, a human specific lncRNA, was relatively highly expressed in human monocytes, erythroleukemia cells and hepatoma cells. LncATV was upregulated upon Type I and III IFN stimulations and virus infection. RIG-I antiviral signalling and IFN effective pathway were inhibited by overexpressed lncATV.[73] Lnc-ATV promoted the replication of Newcastle disease virus (NDV) and SeV through disrupting the production of Type I IFN and ISGs.[74] This finding reveals that lncATV acts as a restricting innate immune response.

2.3 | Respiratory syncytial virus (RSV)

RSV is a respiratory virus that causes serious and complicated outcomes in infants, and the elderly.[75,76] RAB5C, as a direct target of miR-509, is an intracellular transporter protein and involved in vesicular traffic which may be used for viral entry and intracellular transmission. Lnc-NRAV regulated RAB5C expression through binding miR-509-3p.[77] In this regard, Li et al.[77] found that NRAV promoted RSV proliferation by upregulation of gene levels especially F protein, enhancing expression of RAB5C via sponging miR-509-3p, and accelerating intracellular vesicle transport. This results suggesting that RSV propagation was inhibited by silencing lnc-NRAV.

Maternally expressed gene 3 (MEG3), an lncRNA, is expressed in many normal tissues and has been shown to function as a tumour suppressor in numerous human cancer.[78] The expression level of plasma MEG3 has a significantly negative correlation with the level of each inflammatory cytokine.[79] Tao et al. indicated that in nasopharyngeal samples and BEAS-2B cells, the level of MEG3 was reduced following RSV infection and mRNA level of toll-like receptor 4 (TLR4), TNF-α and IL-8 raised was increased. TLR-4 was able to activate NF-κB and p38 mitogen activated protein kinase (MAPK) signalling in the early RSV response.[80,81] Overall, overexpression of lnc-MEG3 had a protective role against the activation of inflammatory cytokine in human airway epithelial cells.

RSV can induce asthma exacerbation in children and make them sensitive for asthma later in life. In an asthmatic mouse model, increase in lnc-n337374 led to relieve the symptoms of asthma. Generally, RSV infection causes maturation dendritic cells (DCs) and suggested that lnc-n337374 inhibited DCs maturation by down-regulation of CD86 and pERK1/2.[82]

Plasmacytoma variant translocation 1 (PVT1) is an lncRNA that has been found in a variety of cancers.[83] Yu et al.[84] indicated that lnc-PVT1 is involved in the function of α-asarone in treating RSV-induced asthma. Lnc-PVT1 was identified as a molecular sponge of miR-203a.[85] The miR-203a targets the 3′-untranslated region of E2F transcription factor 3 (E2F3), a positive regulator, that be involved in DNA replication by stimulating the entry of quiescent cells into the G1/S phase of the cell cycle.[86,87] Therefore, down regulation of lnc-PVT1 has positive effect on the treatment of RSV infection.

2.4 | Avian infectious bronchitis virus (IBV)

The first line of host defence mechanism is innate immunity.[88] In the innate immune system, pathogens are recognised by pattern recognition molecules (PRMs), including lectins. Mannose-binding lectin (MBL; also referred to as mannan-binding lectin and mannose-binding protein), is a pattern recognition innate immune molecule

and involved in the protection of the host against viral infections.[89,90] IBV is a contagious avian coronavirus that can infect respiratory tract of chicken and in poultry industry is a major problem.[91] Zhang et al.[92] showed that chicken MBL by the interaction to S1 spike protein of IBV plays a role in innate and the adaptive immune response. In avian bone marrow-derived dendritic cells (BMDCs) infected with IBV, levels of two lncRNAs MANBAL and POMT2 were downregulated. Both lncRNAs were associated with mannose, a possible receptor for viral entry.[93]

2.5 | Severe acute respiratory syndrome coronavirus (SARS-CoV)

SARS is a viral respiratory illness caused by SARS-associated coronaviruses (SARS-CoVs). SARS-CoV was first identified at the end of February 2003 that emerged in Guangdong Province in China and spread to many parts of the world. The SARS epidemic caused a total of 8422 infections and 919 deaths globally (CFR: 9.6%).[94,95]

One study by Peng et al.[96] in four mouse strains infected by SARS-CoV revealed differentially induced-infection expression of approximately 500 lncRNAs. From 37 selected lncRNAs, 43% of them were similar to influenza virus A/PR/8/34 infected mouse embryonic fibroblasts cells lncRNA pattern. Based on bioinformatic analysis, controlling gene expression by binding to chromatin-modifying complexes and transcriptional genes were proposed the most putative functions. Also, by applying gene functional annotation tools, lncRNA loci showed certain upregulated and downregulated regions of chromosomes 6/12 and 11, respectively.[96]

Also, Josset et al.[97] identified 5329 differentially expressed lncRNAs in eight mouse strains after IAV RP8 and SARS-CoV MA15 infection. To determine these lncRNAs and related functions, module-based, rank-based annotations and functional analysis tools were utilised. Among 5329 lncRNAs, 2059 were predicted as ISGs and 976 had at least one transcriptional factor binding motifs in their promoter. The lncRNAs expression was mainly dependent on mouse strain and virus. According to their analysis, around 60% of lncRNAs showed decreased expression after infection. Downregulation of lung-specific lncRNA introduced a possible factor for pulmonary cell death due to respiratory viral infection or immune cell infiltration.[97] These results implied that the lncRNAs could affect the host antiviral defence to SARS-CoV infection and probable pathogenic outcomes.

2.6 | Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

At the end of 2019, a new coronavirus named as SARS-CoV-2 emerged in Wuhan, China.[98] SARS-CoV-2 is the seventh coronavirus which has led to human disease and is still a major public health issue. As of 20 June, 2021, the WHO has reported that there are more than 177 million confirmed cases globally with more than 3.8 million deaths.[99]

Reduced levels of Type I/III interferon response have been observed in animal models, different tissues from coronavirus disease 2019 (Covid-19) patients and infected cells with SARS-CoV-2.[68] In contrast, increased levels of Type I IFN genes in Covid-19 patients and SARS-CoV-2 infected organoid have been observed. Differences in results may be related to use of different cell types, mixture of cell types or sampling at different times of the disease.[100] It is interesting to know that in strength and duration of IFN signalling, ISGs act as negative regulators.[101] In this regard, elevated expression of ISGs has been reported in Covid-19 patients.[100,102] Then, the level of IFNs decreases. In SARS-CoV-2-infected cells from the in silico analysis, several lncRNAs (TP53TG1, EGOT, EPB41L4A-AS1, HIF1A-AS2, LINC00174, LINC00473, LINC00662, MALAT1, MEG3, MEG9, RMRP, ZNF674-AS1, LINC00842, NEAT1) altered the histone modifications of target genes with interaction of heterogeneous nuclear ribonucleoprotein U (hnRNP U).[68] Zhao et al.[36] showed positive role of hnRNP U in IFNβ1, IRF1, IFIT1, IFIT3, Mx1, ISG15 and IFI44L expression.

LncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), also named as nuclear-enriched abundant transcript 2 (NEAT2), is a highly conserved ncRNA and acts as a negative regulator of antiviral type I IFN production.[103] Recently, an interesting study based on in silico analysis showed that expression of 20 lncRNAs was increased and four lncRNAs like PART1, TP53TG1 was decreased in SARS-CoV-2-infected cells. Among increased lncRNA, NEAT1 and MALAT1 interact with IRF1, IRF4, signal transducer and activator of transcription 1 (STAT1), STAT3, STAT5A and MYC proto-oncogene, BHLH transcription factor (MYC) could contribute to antiviral response to SARS-CoV-2 infection.[68] Concordant with these findings, recent data revealed that overexpression of MALAT1 and NEAT1 were reported in bronchoalveolar lavage fluid of Covid-19 patients and human bronchial epithelial cells (NHBE) in response to SARS-CoV-2 infection.[102,104] Based on above reports, it has been proposed that use of exogenous IFN to stimulate antiviral immunity might be successful for treating SARS-CoV-2 infection. Recent studies have shown that SARS-CoV-2 was sensitive to IFN-I inhaled interferon pretreatment in vero cells.[105,106] Also a randomised controlled trial (RCT) showed exogenous use of inhaled interferon beta-1a be effective in for treating SARS-CoV-2 infection.[107]

Apart from the role of MALAT1 in reduction of IFN signalling, this lncRNA could absorb miR-146a-5p and miR-142-3p to repress their anti-inflammatory function and its overexpression, promoting inflammatory response.[103] Recent studies have shown that exaggerated inflammatory responses and inflammatory cytokine storm leads to acute respiratory distress syndrome (ARDS) aggravation and even death. As listed in Table 2, lncRNAs are implicated in inflammatory cytokine storm and inflammatory complex including IL-6, TNF-α and NLRP3 inflammasome.[108,109] In patients that infected by SARS-CoV-2, lncRNAs through inflammatory pathways including TLR signal transduction and NF-κB signalling pathway, leading to host autoimmunity.[110]

Specific lncRNAs can be potential candidates to treat Covid-19. A recent study described that four lncRNAs (H19, Hotair, Fendrr and

LINC05) directly interact with spike transcript (mRNA) and viral genome.[111] Targeting these lncRNAs involved in innate immune responses could affect the silencing function of miRNAs to provide another treatment strategy for Covid-19.

2.7 | Adenoviruses

Human adenovirus (HAdV) are an important cause of mild upper respiratory symptoms and they can also infect lower respiratory tract, causing pneumonia and bronchitis.[112] The life cycle of adenovirus can be divided into two phases, an early and a late phase, which are separated by viral DNA replication. The early phase covers the regulation of the cell cycle and suppression of the cellular antiviral response, whereas the late phase covers making gene products that are related to production and assembly of capsid proteins.[113] In human primary lung fibroblast cells (IMR-90) infected by adenovirus type 2 (Ad2), NEAT1 upregulated moderately during early genes expression as an antiviral response, while its expression was diminished at 36 h postinfection when late genes expression occurs (late phase). Hence, NEAT1 prevent virus production through the expression of antiviral genes including cytokines such as IL-8.[114,115]

Ad2 by increasing MEG3 in the late phase caused accumulation of P53, a protein involved in cellular apoptosis, may prevent cell growth induced by adenovirus. Indeed, MEG3 acts as a host antiviral response.[114] Although NEAT1 and MEG3 can prevent reproduction but adenoviruses deregulated lncRNAs in the late phase of infection that involved in growth, structure, apoptosis and wound healing in the early phase, cell proliferation in the intermediate phase and protein synthesis, modification and transport in the late phase to optimise their reproduction.[114]

PKR is an interferon-inducible serine-threonine protein kinase activated in infected cells as part of the antiviral response. Ad5 encodes two virus-associated (VA) RNAs, VAI and VAII. These VA RNAs are lncRNA that fold into a dsRNA with a well-conserved structure. VA RNA I binds to PKR and inhibits its function.[5,116] RNA interference (RNAi) with two key players, Dicer and Argonaute, act to digest viral RNAs.[117] The interference of VARNAI and RNAII with Dicer activity block the RNAi processing pathway.[5] Therefore, the increased viral replication may affect the severity of the disease.[117]

2.8 | Human bocavirus (HBoV)

HBoV is a respiratory pathogen with four genotype HBoV1-4 that can infect the upper and lower respiratory tract of children and infants. The virus has mechanisms to evade the host's immunity by interfering type I INFs.[118] Hexamethylene bis-acetamide-inducible protein 1 (Hexim1), a protein that inhibits the positive transcription elongation factor b (P-TEFb), acts as a tumour suppressor and is involved in the regulation of innate immunity. The lnc-NEAT1 by binding to Hexim1 forms the Hexim1-DNA-PK-paraspeckle components-ribonucleoprotein complex (HDP-RNP). These complexes interact with the proteins in cGAS-STING-IRF3 pathway which are mediated innate immunity responses. Silencing lnc-NEAT1 disrupts the HDP-RNP complex and decreases cytosolic DNA-dependent IFN production. In cells infected with HBoV, lnc-NEAT1 was downregulated.[119–121] Therefore, downregulation of lnc-NEAT1 promotes HBoV replication.

TABLE 2 The most significant lncRNAs associated with Covid-19 cytokine storm

lncRNA name	Cytokine target
NORAD	IL-6, IL-10, CSF3, TNFα, CXCL10
RAD51-AS1	CCL2, TNFα, IL-6
lnrCXCR4	IL-10, CCL3
SBF2-AS1	IL-7
TUG1	CCL2
GAS5	TNFα
SNHG1	IL-10, CCL2
NRAV	CCL2, IL-10
BANCR	IL-2
DRAIC	IL-2
lnc-IL7R	IL-6
LNCSRLR	IL-6
LNC-LBCS	IL-6
SENCR	IL-6
STXBP5-AS1	CSF3
THRIL	TNFα
NRCP	TNFα
TMEVPG1	IFNγ
PRC1-AS1	IFNγ
MALAT1	CCL2
CDK6-AS1	CCL3
CASC15	TNFα

3 | CONCLUSION

LncRNAs are defined as nonprotein-coding transcripts longer than 200 nucleotides. Evidence have reveals the strong regulatory functions of lncRNAs as negative regulator to inhibit antiviral response and positive regulator to inhibit viral replication. LncRNAs from hosts or viruses are responsible for altered expression or activity of pivotal innate immune molecules. Several lncRNAs behave as inducers or inhibitors of the IFN response, transcription of ISGs, activation of JAK-STAT and NF-κB, cytokines and chemokines production, RNAi processing pathway and help to latency. The number of lncRNAs with experimentally verified function is limited. Therefore, detailed functional studies are still needed to define the functioning of lncRNAs

during the viral pathogenesis such as SARS-CoV-2 infection. Further characterisation of lncRNAs may provide new targets for antiviral interventions.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Somayeh Shokri designed the study. Mina Mobini Kesheh, Shahab Mahmoudvand and Somayeh Shokri wrote the first draft of the manuscript and critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in the cited reference.

ORCID

Somayeh Shokri https://orcid.org/0000-0003-4609-3110

REFERENCES

1. Robinson M, Schor S, Barouch-Bentov R, Einav S. Viral journeys on the intracellular highways. *Cell Mol Life Sci*. 2018;75:3693-3714.
2. Dias A, Bouvier D, Crépin T, et al. The cap-snatching endonuclease of influenza virus polymerase resides in the PA subunit. *Nature*. 2009;458:914-918.
3. Yi K, Zhang Y, Wang Y, et al. Long noncoding RNA and its role in virus infection and pathogenesis. *Front Biosci*. 2019;24:777-789.
4. Liu W, Ding C. Roles of LncRNAs in viral infections. *Front Cell Infect Microbiol*. 2017;7:205.
5. Ding Y-z, Zhang Z-w, Liu Y-l, Shi C-x, Zhang J, Zhang Y-g. Relationship of long noncoding RNA and viruses. *Genomics*. 2016;107:150-154.
6. Wang Z, Zhao Y, Zhang Y. Viral lncRNA: a regulatory molecule for controlling virus life cycle. *Noncoding RNA Res*. 2017;2:38-44.
7. Palazzo AF, Lee ES. Non-coding RNA: what is functional and what is junk? *Front Genet*. 2015;6:2.
8. Fang Y, Fullwood MJ. Roles, functions, and mechanisms of long non-coding RNAs in cancer. *Genom Proteom Bioinf*. 2016;14:42-54.
9. Ma L, Bajic VB, Zhang Z. On the classification of long non-coding RNAs. *RNA Biol*. 2013;10:925-933.
10. Srijyothi L, Ponne S, Prathama T, Ashok C, Baluchamy S. Roles of non-coding RNAs in transcriptional regulation. In *Transcriptional and Post-transcriptional Regulation*. IntechOpen; 2018:55.
11. Ying S-Y, Chang DC, Lin S-L. The microRNA (miRNA): overview of the RNA genes that modulate gene function. *Mol Biotechnol*. 2008;38:257-268.
12. Catalanotto C, Cogoni C, Zardo G. MicroRNA in control of gene expression: an overview of nuclear functions. *Int J Mol Sci*. 2016;17:1712.
13. Zou Z, Gong W-X, Huang K, Sun X-M, Jin M-L. Regulation of influenza virus infection by microRNAs. *J Integr Agr*. 2019;18:1421-1427.
14. Zheng B, Zhou J, Wang H. Host microRNAs and exosomes that modulate influenza virus infection. *Virus Res*. 2020;279:197885.
15. Keshavarz M, Dianat-Moghadam H, Sofiani VH, et al. miRNA-based strategy for modulation of influenza A virus infection. *Epigenomics*. 2018;10:829-844.
16. O'Brien J, Hayder H, Zayed Y, Peng C. Overview of MicroRNA biogenesis, mechanisms of actions, and circulation. *Front Endocrinol*. 2018;9:402.
17. Forman JJ, Legesse-Miller A, Coller HA. A search for conserved sequences in coding regions reveals that the let-7 microRNA targets Dicer within its coding sequence. *Proc Natl Acad Sci USA*. 2008;105:14879-14884.
18. Zhang J, Zhou W, Liu Y, Liu T, Li C, Wang L. Oncogenic role of microRNA-532-5p in human colorectal cancer via targeting of the 5'UTR of RUNX3. *Oncol Lett*. 2018;15:7215-7220.
19. Wang Z, Zheng Y. lncRNAs regulate innate immune responses and their roles in macrophage polarization. *Mediat Inflamm*. 2018;2018:8050956.
20. Murphy MB, Medvedev AE. Long noncoding RNAs as regulators of Toll-like receptor signaling and innate immunity. *J Leukoc Biol*. 2016;99:839-850.
21. Atianand MK, Caffrey DR, Fitzgerald KA. Immunobiology of long noncoding RNAs. *Annu Rev Immunol*. 2017;35:177-198.
22. Elling R, Chan J, Fitzgerald KA. Emerging role of long noncoding RNAs as regulators of innate immune cell development and inflammatory gene expression. *Eur J Immunol*. 2016;46:504-512.
23. Chai W, Li J, Shangguan Q, et al. Lnc-ISG20 inhibits influenza A virus replication by enhancing ISG20 expression. *J Virol*. 2018;92:e00539.
24. Nourbakhsh M, Sharifi R, Ghorbanhosseini SS, et al. Evaluation of plasma TRB3 and sestrin 2 levels in obese and normal-weight children. *Child Obes*. 2017;13:409-414.
25. Ouyang J, Hu J, Chen JL. lncRNAs regulate the innate immune response to viral infection. *Wiley Interdiscip Rev RNA*. 2016;7:129-143.
26. Zhang Y, Cao X. Long noncoding RNAs in innate immunity. *Cell Mol Immunol*. 2016;13:138-147.
27. Laconi A, Fortin A, Bedendo G, et al. Detection of avian influenza virus: a comparative study of the in silico and in vitro performances of current RT-qPCR assays. *Sci Rep*. 2020;10:8441.
28. Yamaji R, Saad MD, Davis CT, et al. Pandemic potential of highly pathogenic avian influenza clade 2.3.4.4 A(H5) viruses. *Rev Med Virol*. 2020;30:e2099.
29. *1918 Pandemic (H1N1 Virus), CDC 2019*. Accessed March 20, 2019. https://www.cdc.gov/flu/pandemic-resources/1918-pandemic-h1n1.html
30. Kilbourne ED. Influenza pandemics of the 20th century. *Emerg Infect Dis*. 2006;12:9-14.
31. Pan Q, Zhao Z, Liao Y, et al. Identification of an interferon-stimulated long noncoding RNA (LncRNA ISR) involved in regulation of influenza A virus replication. *Int J Mol Sci*. 2019;20:5118.
32. Ginn L, La Montagna M, Wu Q, Shi L. Diverse roles of long non-coding RNAs in viral diseases. *Rev Med Virol*. 2020. https://doi.org/10.1002/rmv.2198
33. Qu H, Li J, Yang L, Sun L, Liu W, He H. Influenza A Virus-induced expression of ISG20 inhibits viral replication by interacting with nucleoprotein. *Virus Gene*. 2016;52:759-767.
34. McKellar J, Rebendenne A, Wencker M, Moncorgé O, Goujon C. Mammalian and avian host cell influenza A restriction factors. *Viruses*. 2021;13:522.
35. Weiss CM, Trobaugh DW, Sun C, et al. The interferon-induced exonuclease ISG20 exerts antiviral activity through upregulation of type I interferon response proteins. *mSphere*. 2018;3:e00209.
36. Zhao L, Xia M, Wang K, et al. A long non-coding RNA IVRPIE promotes host antiviral immune responses through regulating interferon β1 and ISG expression. *Front Microbiol*. 2020;11:260.

37. Martín-Vicente M, Medrano LM, Resino S, García-Sastre A, Martínez I. TRIM25 in the regulation of the antiviral innate immunity. *Front Immunol*. 2017;8:1187.
38. Yang W, Gu Z, Zhang H, Hu H. To TRIM the immunity: from innate to adaptive immunity. *Front Immunol*. 2020;11:02157.
39. Lin H, Jiang M, Liu L, et al. The long noncoding RNA Lnczc3h7a promotes a TRIM25-mediated RIG-I antiviral innate immune response. *Nat Immunol*. 2019;20:812-823.
40. Choudhury NR, Heikel G, Michlewski G. TRIM25 and its emerging RNA-binding roles in antiviral defense. *WIREs RNA*. 2020;11:e1588.
41. Statello L, Guo C-J, Chen L-L, Huarte M. Gene regulation by long non-coding RNAs and its biological functions. *Nat Rev Mol Cell Biol*. 2021;22:96-118.
42. Pellarin I, Dall'Acqua A, Gambelli A, et al. Splicing factor proline- and glutamine-rich (SFPQ) protein regulates platinum response in ovarian cancer-modulating SRSF2 activity. *Oncogene*. 2020;39:4390-4403.
43. Lim YW, James D, Huang J, Lee M. The emerging role of the RNA-binding protein SFPQ in neuronal function and neurodegeneration. *Int J Mol Sci*. 2020;21:7151.
44. Imamura K, Imamachi N, Akizuki G, et al. Long noncoding RNA NEAT1-dependent SFPQ relocation from promoter region to paraspeckle mediates IL8 expression upon immune stimuli. *Mol Cell*. 2014;53:393-406.
45. Wang Y, Chen L-L. Organization and function of paraspeckles. *Essays Biochem*. 2020;64:875-882.
46. Barriocanal M, Carnero E, Segura V, Fortes P. Long non-coding RNA BST2/BISPR is induced by IFN and regulates the expression of the antiviral factor tetherin. *Front Immunol*. 2015;5:655.
47. Sharma A, Lal SK. Is tetherin a true antiviral: the influenza a virus controversy. *Rev Med Virol*. 2019;29:e2036.
48. Suarez B, Prats-Mari L, Unfried JP, Fortes P. LncRNAs in the type I interferon antiviral response. *Int J Mol Sci*. 2020;21:6447.
49. Liu S, Liu X, Li J, et al. Long noncoding RNAs: novel regulators of virus-host interactions. *Rev Med Virol*. 2019;29:e2046.
50. Ouyang J, Zhu X, Chen Y, et al. NRAV, a long noncoding RNA, modulates antiviral responses through suppression of interferon-stimulated gene transcription. *Cell Host Microbe*. 2014;16:616-626.
51. Onomoto K, Onoguchi K, Yoneyama M. Regulation of RIG-I-like receptor-mediated signaling: interaction between host and viral factors. *Cell Mol Immunol*. 2021;18:539-555.
52. Jiang M, Zhang S, Yang Z, et al. Self-recognition of an inducible host lncRNA by RIG-I feedback restricts innate immune response. *Cell*. 2018;173:906-919.
53. Wang J, Cen S. Roles of lncRNAs in influenza virus infection. *Emerg Microb Infect*. 2020;9:1407-1414.
54. Zhang H, Zhu C, He Z, Chen S, Li L, Sun C. LncRNA PSMB8-AS1 contributes to pancreatic cancer progression via modulating miR-382-3p/STAT1/PD-L1 axis. *J Exp Clin Canc Res*. 2020;39:179.
55. Servaas NH, Mariotti B, van der Kroef M, et al. Characterization of long non-coding RNAs in systemic sclerosis monocytes: a potential role for PSMB8-AS1 in altered cytokine secretion. *Int J Mol Sci*. 2021;22:4365.
56. More S, Zhu Z, Lin K, et al. Long non-coding RNA PSMB8-AS1 regulates influenza virus replication. *RNA Biol*. 2019;16:340-353.
57. Maarouf M, Chen B, Chen Y, et al. Identification of lncRNA-155 encoded by MIR155HG as a novel regulator of innate immunity against influenza A virus infection. *Cell Microbiol*. 2019;21:e13036.
58. Carbone CJ, Zheng H, Bhattacharya S, et al. Protein tyrosine phosphatase 1B is a key regulator of IFNAR1 endocytosis and a target for antiviral therapies. *Proc Natl Acad Sci USA*. 2012;109:19226-19231.
59. Lai C, Liu L, Liu Q, et al. Long noncoding RNA AVAN promotes antiviral innate immunity by interacting with TRIM25 and enhancing the transcription of FOXO3a. *Cell Death Differ*. 2021. https://doi.org/10.1038/s41418-021-00791-2
60. Guu TSY, Dong L, Wittung-Stafshede P, Tao YJ. Mapping the domain structure of the influenza A virus polymerase acidic protein (PA) and its interaction with the basic protein 1 (PB1) subunit. *Virology*. 2008;379:135-142.
61. Wang J, Zhang Y, Li Q, et al. Influenza virus exploits an interferon-independent lncRNA to preserve viral RNA synthesis through stabilizing viral RNA polymerase PB1. *Cell Rep*. 2019;27:3295-3304.
62. Wang P, Xu J, Wang Y, Cao X. An interferon-independent lncRNA promotes viral replication by modulating cellular metabolism. *Science*. 2017;358:1051-1055.
63. Wang J, Wang Y, Zhou R, et al. Host long noncoding RNA lncRNA-PAAN regulates the replication of influenza A virus. *Viruses*. 2018;10:330.
64. Winterling C, Koch M, Koeppel M, Garcia-Alcalde F, Karlas A, Meyer TF. Evidence for a crucial role of a host non-coding RNA in influenza A virus replication. *RNA Biol*. 2014;11:66-75.
65. Li X, Guo G, Lu M, et al. Long noncoding RNA lnc-MxA inhibits beta interferon transcription by forming RNA-DNA triplexes at its promoter. *J Virol*. 2019;93:e00786.
66. Carnero E, Barriocanal M, Prior C, et al. Long noncoding RNA EGOT negatively affects the antiviral response and favors HCV replication. *EMBO Rep*. 2016;17:1013-1028.
67. Qiu L, Wang T, Tang Q, Li G, Wu P, Chen K. Long non-coding RNAs: regulators of viral infection and the interferon antiviral response. *Front Microbiol*. 2018;9:1621.
68. Laha S, Saha C, Dutta S, et al. Silico analysis of altered expression of long non-coding RNA in SARS-CoV-2 infected cells and their possible regulation by STAT1, STAT3 and interferon regulatory factors. *Heliyon*. 2021;7:e06395.
69. Park A, Hong P, Won ST, et al. Sendai virus, an RNA virus with no risk of genomic integration, delivers CRISPR/Cas9 for efficient gene editing. *Mol Ther Methods Clin Dev*. 2016;3:16057.
70. Wu H, Yao R-R, Yu S-S, et al. Transcriptome analysis identifies the potential roles of long non-coding RNAs during parainfluenza virus infection. *FEBS Lett*. 2018;592:2444-2457.
71. Bocchetti M, Scrima M, Melisi F, et al. LncRNAs and immunity: coding the immune system with noncoding oligonucleotides. *Int J Mol Sci*. 2021;22:1741.
72. Atianand MK, Hu W, Satpathy AT, et al. A long noncoding RNA lincRNA-EPS acts as a transcriptional brake to restrain inflammation. *Cell*. 2016;165:1672-1685.
73. Fan J, Cheng M, Chi X, Liu X, Yang W. A human long non-coding RNA LncATV promotes virus replication through restricting RIG-I-mediated innate immunity. *Front Immunol*. 2019;10:1711.
74. Rehwinkel J, Gack MU. RIG-I-like receptors: their regulation and roles in RNA sensing. *Nat Rev Immunol*. 2020;20:537-551.
75. Hogan AC, Caya C, Papenburg J. Rapid and simple molecular tests for the detection of respiratory syncytial virus: a review. *Expert Rev Mol Diagn*. 2018;18:617-629.
76. Pangesti KNA, Abd El Ghany M, Walsh MG, Kesson AM, Hill-Cawthorne GA. Molecular epidemiology of respiratory syncytial virus. *Rev Med Virol*. 2018;28:103-116.
77. Li J, Li M, Wang X, et al. Long noncoding RNA NRAV promotes respiratory syncytial virus replication by targeting the MicroRNA miR-509-3p/rab5c Axis to regulate vesicle transportation. *J Virol*. 2020;94:e00113-00120.
78. Yu F, Geng W, Dong P, Huang Z, Zheng J. LncRNA-MEG3 inhibits activation of hepatic stellate cells through SMO protein and miR-212. *Cell Death Dis*. 2018;9:1014.
79. Shao HF, Li ZZ, Zheng XF, et al. Research on the correlation of changes in plasma lncRNA MEG3 with change in inflammatory

factors and prognosis in patients with traumatic brain injury. *Eur Rev Med Pharmacol Sci*. 2019;23:4341-4347.
80. Tao X-W, Zeng L-K, Wang H-Z, Liu H-C. LncRNA MEG3 ameliorates respiratory syncytial virus infection by suppressing TLR4 signaling. *Mol Med Rep*. 2018;17:4138-4144.
81. Wu W, Choi E-J, Lee I, Lee YS, Bao X. Non-coding RNAs and their role in respiratory syncytial virus (RSV) and human metapneumovirus (hMPV) infections. *Viruses*. 2020;12:345.
82. Sun S, Yao M, Yuan L, Qiao J. Long-chain non-coding RNA n337374 relieves symptoms of respiratory syncytial virus-induced asthma by inhibiting dendritic cell maturation via the CD86 and ERK pathway. *Allergol Immunopathol*. 2021;49:100-107.
83. Wu H, Wei M, Jiang X, et al. lncRNA PVT1 promotes tumorigenesis of colorectal cancer by stabilizing miR-16-5p and interacting with the VEGFA/VEGFR1/AKT Axis. *Mol Ther Nucleic Acids*. 2020;20:438-450.
84. Yu X, Zhe Z, Tang B, et al. α-Asarone suppresses the proliferation and migration of ASMCs through targeting the lncRNA-PVT1/miR-203a/E2F3 signal pathway in RSV-infected rats. *Acta Biochim Biophys Sin*. 2017;49:598-608.
85. Yang M, Zhang L, Wang X, Zhou Y, Wu S. Down-regulation of miR-203a by lncRNA PVT1 in multiple myeloma promotes cell proliferation. *Arch Med Sci*. 2018;14:1333-1339.
86. Wu L, Wan S, Li J, et al. Expression and prognostic value of E2F3 transcription factor in non-small cell lung cancer. *Oncology lett*. 2021;21:1-12.
87. Zhu X, Wei Y, Dong J. Long noncoding RNAs in the regulation of asthma: current research and clinical implications. *Front Pharmacol*. 2020;11:532849.
88. Warrington R, Watson W, Kim HL, Antonetti FR. An introduction to immunology and immunopathology. *Allergy Asthma Clin Immunol*. 2011;7:1-8.
89. Garred P, Larsen F, Seyfarth J, Fujita R, Madsen HO. Mannose-binding lectin and its genetic variants. *Gene Immun*. 2006;7:85-94.
90. Gupta A, Gupta GS. Status of mannose-binding lectin (MBL) and complement system in COVID-19 patients and therapeutic applications of antiviral plant MBLs. *Mol Cell Biochem*. 2021. https://doi.org/10.1007/s11010-021-04107-3
91. Chen L, Xiang B, Hong Y, et al. Phylogenetic analysis of infectious bronchitis virus circulating in southern China in 2016–2017 and evaluation of an attenuated strain as a vaccine candidate. *Arch Virol*. 2021;166:73-81.
92. Zhang W, Bouwman KM, van Beurden SJ, et al. Chicken mannose binding lectin has antiviral activity towards infectious bronchitis virus. *Virology*. 2017;509:252-259.
93. Lin J, Wang Z, Wang J, Yang Q. Microarray analysis of infectious bronchitis virus infection of chicken primary dendritic cells. *BMC Genom*. 2019;20:557.
94. Shokri S, Mahmoudvand S, Taherkhani R, Farshadpour F. Modulation of the immune response by Middle East respiratory syndrome coronavirus. *J Cell Physiol*. 2019;234:2143-2151.
95. Yang Y, Peng F, Wang R, et al. The deadly coronaviruses: the 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. *J Autoimmun*. 2020;109:102434.
96. Peng X, Gralinski L, Armour CD, et al. Unique signatures of long noncoding RNA expression in response to virus infection and altered innate immune signaling. *mBio*. 2010;1:e00206-e00210.
97. Josset L, Tchitchek N, Gralinski LE, et al. Annotation of long non-coding RNAs expressed in collaborative cross founder mice in response to respiratory virus infection reveals a new class of interferon-stimulated transcripts. *RNA Biol*. 2014;11:875-890.
98. Mahmoudvand S, Shokri S. Interactions between SARS coronavirus 2 papain-like protease and immune system: a potential drug target for the treatment of COVID-19. *Scand J Immunol*. 2021:e13044. https://doi.org/10.11111/sji.13044
99. Weekly Epidemiological Update. 2021. https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---22-june-2021
100. Lee JS, Park S, Jeong HW, et al. Immunophenotyping of COVID-19 and influenza highlights the role of type I interferons in development of severe COVID-19. *Sci Immunol*. 2020;5:eabd1554.
101. Carnero E, Barriocanal M, Segura V, et al. Type I interferon regulates the expression of long non-coding RNAs. *Front Immunol*. 2014;5:548.
102. Xiong Y, Liu Y, Cao L, et al. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. *Emerg Microb Infect*. 2020;9:761-770.
103. Tang H, Gao Y, Li Z, et al. The noncoding and coding transcriptional landscape of the peripheral immune response in patients with COVID-19. *Clin Transl Med*. 2020;10:e200.
104. Vishnubalaji R, Shaath H, Alajez NM. Protein coding and long noncoding RNA (lncRNA) transcriptional landscape in SARS-CoV-2 infected bronchial epithelial cells highlight a role for interferon and inflammatory response. *Genes*. 2020;11:760.
105. Lokugamage KG, Hage A, de Vries M, et al. Type I interferon susceptibility distinguishes SARS-CoV-2 from SARS-CoV. *J Virol*. 2020;94:e01410-e01420.
106. Mantlo E, Bukreyeva N, Maruyama J, Paessler S, Huang C. Antiviral activities of type I interferons to SARS-CoV-2 infection. *Antivir Res*. 2020;179:104811.
107. Monk PD, Marsden RJ, Tear VJ, et al. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Respir Med*. 2021;9:196-206.
108. Paniri A, Akhavan-Niaki H. Emerging role of IL-6 and NLRP3 inflammasome as potential therapeutic targets to combat COVID-19: role of lncRNAs in cytokine storm modulation. *Life Sci*. 2020;257:118114.
109. Morenikeji OB, Bernard K, Strutton E, Wallace M, Thomas BN. Evolutionarily conserved long non-coding RNA regulates gene expression in cytokine storm during COVID-19. *Front Bioeng Biotechnol*. 2021;8:582953.
110. Wu Y, Zhao T, Deng R, Xia X, Li B, Wang X. A study of differential circRNA and lncRNA expressions in COVID-19-infected peripheral blood. *Sci Rep*. 2021;11:7991.
111. Natarelli L, Parca L, Mazza T, Weber C, Virgili F, Fratantonio D. MicroRNAs and long non-coding RNAs as potential candidates to target specific motifs of SARS-CoV-2. *Noncoding RNA*. 2021;7:14.
112. Mahmoudvand S, Kord M, Pirbonyeh N, Moattari A, Shokri S, Zomorodian K. Molecular detection of adenoviruses in the sinus tissues of patient by nested-PCR in Shiraz, Southwest Iran. *Int J Med Lab*. 2019;6:192-198.
113. Kulanayake S, Tikoo SK. Adenovirus core proteins: structure and function. *Viruses*. 2021;13:388.
114. Zhao H, Chen M, Lind SB, Pettersson U. Distinct temporal changes in host cell lncRNA expression during the course of an adenovirus infection. *Virology*. 2016;492:242-250.
115. Ahmed W, Liu Z-F. Long non-coding RNAs: novel players in regulation of immune response upon herpesvirus infection. *Front Immunol*. 2018;9:761.
116. Aparicio O, Carnero E, Abad X, et al. Adenovirus VA RNA-derived miRNAs target cellular genes involved in cell growth, gene expression and DNA repair. *Nucleic Acids Res*. 2010;38:750-763.
117. Andika IB, Kondo H, Suzuki N. Dicer functions transcriptionally and posttranscriptionally in a multilayer antiviral defense. *Proc Natl Acad Sci USA*. 2019;116:2274-2281.

118. Bhat R, Almajhdi FN. Induction of immune responses and immune evasion by human bocavirus. *Int Arch Allergy Immunol*. 2021. https://doi.org/10.1159/000514688
119. Morchikh M, Cribier A, Raffel R, et al. HEXIM1 and NEAT1 long non-coding RNA form a multi-subunit complex that regulates DNA-mediated innate immune response. *Mol Cell*. 2017;67:387-399.
120. Schildgen V, Pieper M, Khalfaoui S, Arnold WH, Schildgen O. Human bocavirus infection of permanent cells differentiated to air-liquid interface cultures activates transcription of pathways involved in tumorigenesis. *Cancers*. 2018;10:410.
121. Bensaude O. HEXIM1 has different functions within different RNA-protein complexes. *Mol Cell*. 2017;67:357-359.

How to cite this article: Kesheh MM, Mahmoudvand S, Shokri S. Long noncoding RNAs in respiratory viruses: a review. *Rev Med Virol*. 2022;32(2):e2275. https://doi.org/10.1002/rmv.2275