



# Viral long non-coding RNA regulates virus life-cycle and pathogenicity

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## Abstract

Viral infection is still a serious global health problem that kills hundreds of thousands of people annually. Understanding the mechanism by which virus replicates, packages, and infects the host cells can provide new strategies to control viral infection. Long non-coding RNAs (lncRNAs) have been identified as critical regulators involved in viral infection process and antiviral response. A lot of host lncRNAs have been identified and shown to be involved in antiviral immune response during viral infection. However, our knowledge about lncRNAs expressed by viruses is still at its infancy. lncRNAs expressed by viruses are involved in the whole viral life cycle, including promoting genome replication, regulating gene expression, involvement in genome packaging, assembling new viruses and releasing virions to the host cells. Furthermore, they enhance the pathogenicity of viral infections by down-regulating the host cell's antiviral immune response and maintain the viral latency through a refined procedure of genome integration. This review focuses on the regulatory roles of viral lncRNA in the life-cycle and pathogenicity of viruses. It gives an insight into the viral lncRNAs that can be utilized as therapeutic targets against viral diseases, and future researches aimed to identify and explore new viral lncRNAs and the mechanisms of their involvement in viral infection is encouraged.

**Keywords** lncRNA · Viral infection · Viral life cycle · Viral pathogenicity

## Introduction

Viral infection is still a major global concern that causes various of infectious diseases and kills hundreds of thousands of people annually. Take SARS-CoV-2 (Coronavirus disease 2019, the causative agent of COVID-19) as an example, it is a single-stranded, positive RNA virus, broken out in 2019 and still has hundreds of thousands of new cases every day, posing huge threats to human health and causing economic crisis around the globe[1]. It is therefore crucial to understand the process and the mechanism by which viruses infect the host cells and discover new strategies for the treatment of the infectious diseases they cause.

High throughput analyses reveal that the majority of the genome is transcribed into RNAs, but less than 2% of them are translated into proteins[2–6]. Therefore, most transcripts are non-coding RNAs (ncRNAs) [4–6]. In recent years, a large number of ncRNAs have been found to have regulatory functions in various physiological and pathological processes. According to their length, regulatory ncRNAs are classified into short non-coding RNAs (<200 nt) and long non-coding RNAs (lncRNAs, >200 nt). Short non-coding RNAs include microRNAs (miRNAs), small interfering RNAs (siRNAs), and piwiRNAs (piRNAs)[4, 6, 7]. lncRNAs are the products of RNA polymerase II or III, and are often 5'-capped, 3'-polyadenylated and spliced[3, 8, 9]. Based on the locations in the genome, lncRNAs are divided into antisense, sense, bidirectional, intergenic, and intronic ones[9]. Compared with mRNA, the expression of lncRNA is much lower and shows cell- and tissue-specificity[10, 11]. Recently, lncRNAs have been identified as critical regulators in several biological processes including gene expression, chromatin modification, cell apoptosis, cell

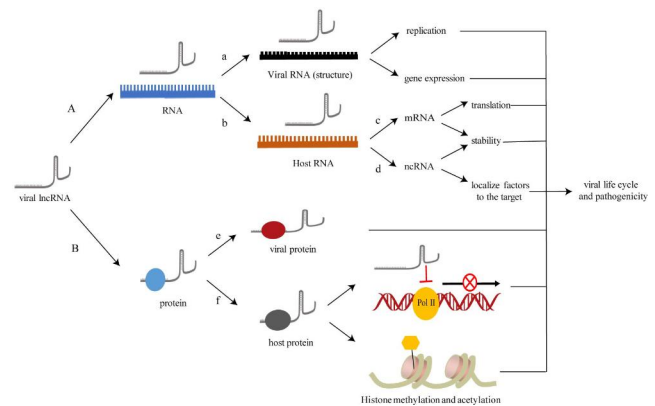
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differentiation and so on[12–14]. LncRNAs are also found to be involved in viral infection process and the host antiviral response[15–20].

At the earliest, studies on the roles of lncRNAs in viral infection mainly focused on the host cellular lncRNAs which were found to be involved in promoting cellular immune response and antiviral response. Most of them regulate the virus-host interaction by activating the production of IFNs (interferons) and cytokines, the expression of ISGs (IFN-stimulated genes) and the PRR-associated (pattern recognition receptor-associated) signaling. Some are associated with the activation of the expression of transcription factors, such as NF- $\kappa$ B (nuclear factor  $\kappa$ -light-chain-enhancer of activated B cells)[8, 12, 18, 20–24]. Some cellular lncRNAs can also be hijacked by viruses to facilitate their replication and gene expression[25–29]. For example, VIN (virus inducible lincRNA) was reported to be hijacked by IAV (influenza A virus) to guarantee its propagation, because the silence of nucleus-located VIN significantly decreased the virus replication and viral gene express[30].

Later, transcriptome analysis revealed that both cellular lncRNAs and viral lncRNAs were altered in their expression levels after viral infection[30–32]. And lots of evidence showed that viral lncRNAs are also important regulators during viral infection[19, 33–36]. For example, PAN RNA (polyadenylated nuclear RNA) expressed by KSHV (Kaposi's sarcoma-associated herpesvirus) represses the expression of several host immune regulators and modulates their own life cycle[37–39]. ncRNAs can fold to their specific three-dimensional structures which are essential for their interaction with proteins or other transcription products, and these interactions are critical for their regulatory roles (Fig. 1)[20, 35, 40, 41]. For example, RNA sequences of stem loops except 618–872 in NRAV is essential for controlling IAV replication[27]. A putative loop E motif in RNase L ciRNA (RNase L competitive inhibitor RNA) is necessary for its ability to inhibit ribonuclease L, however, mutations of bases within this loop resulted in a loss of this ability[42]. Viral lncRNAs operate in a similar manner, they may interact with other molecules of nucleic acids through base pairing to destroy the structures or stabilities of the targets. Meanwhile, the interaction between viral lncRNAs and cellular RNAs can localize some specific proteins close to the targets[43–45]. Viral lncRNA may also interact with several kinds of proteins, including chromatin modifying factors, transcription factors, factors for RNA processing, proteins for RNA stability, et cetera, to affect the antiviral response[20, 41, 46]. Although most reports focused on the interaction between viral lncRNAs with host transcripts and proteins, the cases of interactions between viral lncRNAs with viral proteins and viral genomic RNA also exist. For example, the binding of KSHV PAN RNA to several KSHV



**Figure 1** A model describes the mechanisms by which viral lncRNA may function in their life cycle and pathogenicity. The binding of viral lncRNAs with proteins or other transcripts are necessary for their functions in life cycle and pathogenicity. (A) Viral lncRNA may bind to viral RNA (a) or host cellular RNA (b). For host RNA, they may bind to target mRNA (c) or target non-coding RNA (d). (B) Viral lncRNAs can bind with viral proteins (e) or host proteins (f). The structure of viral lncRNA is important for their binding to proteins or RNAs.

proteins can modulate the viral gene expression[37, 47, 48]. Another example is LMT1 (low-molecular-weight tristetra 1), a 5'-terminal long non-coding RNA which was produced by CTV (Citrus tristeza virus). LMT1 can bind CTV p33 protein and contribute to the viral persistence in the host for the whole tree life[49].

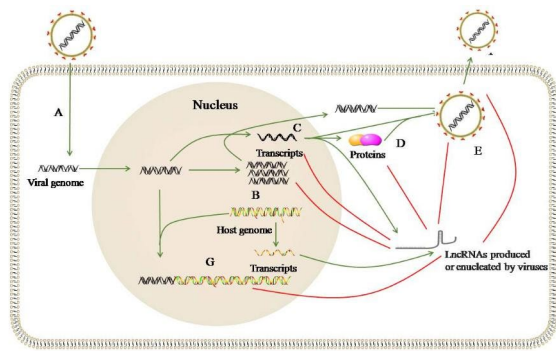
In subsequent sections, we will focus on describing lncRNAs expressed by viruses and their roles in viral life cycle and pathogenicity.

## Viral lncRNAs are involved in regulating viral life cycles

Once virus enters the host cell membrane, they release their genome into the cytoplasm. Some of the viral genome will utilize the cellular machinery to replicate, translate to viral proteins, and then assemble to new infective viruses. Finally the virions are released and infect other host cells. Additionally, a part of the viral genome will integrate into the host chromosome to maintain the viral latency[46]. lncRNAs generated by viruses participate in all these processes (Fig. 2).

## Viral lncRNAs promote viral replication

A lot of evidence show that viral lncRNAs can promote viral replication. The viral lncRNAs that are involved in viral replication are listed in Table 1. The first described viral lncRNA is viroid. Its genome is a circular and single stranded RNA, possessing no protein coding capacity. However, viroid can replicate autonomously[20, 50, 51]. lncRNA PAN is



**Figure 2** The roles of viral lncRNAs in virus life cycle[33]. Virus was recognized by receptors of the host cell surface and viral genome was released in host cells (A). Viral lncRNAs function throughout the life cycles by enhancing replication (B), transcription (C), translation (D), genome packaging (E), and virion releasing (F). Some viral genome may integrate into the host genome, and replicates while host genome replicates (G).

the most abundant lncRNA generated by KSHV and it is involved in almost every stage of viral infection, including activating viral replication, regulating gene expression, pluripotency and host-virus interaction[39, 48]. PAN can bind the promoter of demethylases JMJD3 and UTX to promote viral replication[37, 38, 47]. T1.5 is another KSHV-encoded lncRNA which is generated at the early stage of infection and has also been reported to be required for viral replication[34, 52]. SfrRNA (Subgenomic flavivirus RNA) is the digestion product of the genome of the genus Flavivirus by host 5′-3′ exonuclease[35, 40, 44, 45, 53–55]. SfrRNAs are necessary for replication and pathogenicity of YFV (yellow fever virus) and WNV (West Nile Virus)[53, 54]. However, they repress the replication and gene expression of JEV (Japanese encephalitis virus)[55]. BHLF1, an EBV (Epstein-Barr Virus) encoded lncRNA, positively affects the initiation of viral replication[34, 56]. LncRNA2.7 of HCMV (Human cytomegalovirus) is highly expressed at the early stages of infection and can interact with complex I to inhibit translocation of GRIM-19 to maintain the mitochondrial membrane potential, leading to the production of ATP for the virus[57, 58]. Some host lncRNAs can also promote viral replication. For example, lncRNA-PAAN enhances IAV replication by promoting the formation of functional RNA-dependent RNA polymerase[25].

### Viral lncRNAs regulate gene expression

lncRNAs transcribed by viruses can regulate not only the expression of their own genes but also the expression of host genes. Usually, lncRNAs regulate gene expression by altering the transcription and degradation of target RNA.

**Table 1** Functions of viral lncRNAs in viral replication

Sources	lncRNA	Functions	References
Viroid	Viroid	Replicate autonomously	[28, 51, 52]
KSHV	PAN RNA	Binding the promoter of demethylases JMJD3 and UTX to promote viral replication	[46–48, 53, 54]
KSHV	T1.5	Required for viral replication	[42, 55]
YFV WNV JEV	SfrRNA	Promoting replication and pathogenicity of YFV and WNV KUN;Repress replication and gene expression of Japanese JEV	[43, 56–61]
EBV	BHLF1	Promote the initiation of viral replication	[42, 62]
EBV	oriPts	Modulates the paraspeckle-based antiviral immune response, viral DNA replication and lytic gene expression during reactivation	[84]
HCMV	LncRNA2.7	Interact with complex I to inhibit translocation of GRIM-19 to maintain the mitochondrial membrane potential, leading to the production of ATP for virus	[63, 64]

### Viral lncRNAs regulate gene expression by controlling transcription

Regulation of gene expression by lncRNAs majorly occurs at the transcriptional level, and may lead to the alteration of early-to-late or latent-to-lytic infection[20]. For example, PAN of KSHV can bind the promoter of LANA (latency associated nuclear antigen) and then abolish the negative roles of LANA on lytic genes[59, 60]. PAN can regulate the expression of viral and cellular factors which are necessary for chromatin remodeling by removing repressive marks and adding positive ones[37, 38, 47, 48]. PAN interacts with the promoter of Rta, JMJD3 and UTX to decrease the H3K27 trimethylation, and bind the active methyltransferase MLL2[37, 38]. PAN can also function as a negative regulator by binding polycomb repressive complex 2 (PRC2) [38]. EBER2 (EBV encoded small RNA 2) represses the expression of genes located at the terminal repeats of the latent EBV genome and promotes viral lytic replication by recruiting paired box protein 5 (PAX5) to the EBV DNA[20, 34, 36, 61]. For HIV (human immunodeficiency virus), their gene expression is also suppressed by the antisense HIV transcripts through their interaction with DNMT3a, EZH2

and HDAC1[62, 63]. Besides, viral lncRNAs can also regulate the expression of host genes related to immune and antiviral response. Adenovirus VARNA (virus-associated RNA) was reported to participate in regulating translation of both viral genes and cellular genes by inactivating an eIF-2 kinase DAI[33, 64, 65]. VAI RNA is required for the translation of viral mRNAs at late stages after infection[65, 66]. PAN of KSHV can interact with the transcription factor IRF4 and then inhibit expression of cellular genes including immune responsive and antiviral responsive genes[47]. Interestingly, a newly identified viral lncRNA BocaSR in HBoV1 (Human bocavirus 1) is required for the role of HBoV1 in helping the DNA replication of another virus AAV2 (adeno-associated virus 2)[67].

### Viral lncRNAs regulate gene expression by altering RNA stability

lncRNAs can also regulate gene expression by altering RNA degradation through targeting the activity of exonuclease or through RNAi pathway[20]. For example, double strand RNA viroids can be processed by RNAi machinery to generate lots of siRNAs which can change the expression of host genes[68]. sfRNA is the incomplete digestion product of Xrn1 from Flavivirus genome[55, 69]. However, sfRNA inversely inhibits the activity of Xrn1 and in turn changes the stability of cellular mRNA. By repressing the 5' to 3' exonuclease activity of Xrn1, unstable transcripts are accumulated and a lot of cellular genes including growth factors, cytokines, oncogens are deregulated[40, 70, 71]. Furthermore, sfRNA also can target RNAi pathway by suppressing Dicer[72, 73]. Adenovirus VARNA can be digested to several viral microRNAs by RNAi machinery[74], however, these miRNAs are not required for viral replication but are involved in regulating viral and cellular gene expression[19, 74, 75].

### Viral lncRNAs regulate virus assembly and release

When the new viral genomes and proteins are enough prepared within the host cells, they must be packaged, assembled and then released. Viral lncRNAs are also involved in these processes. HBoV1 is not only required for AAV2 replication but also for the packaging of AAV2 genome and formation of progeny virions[67]. lncRNA BocaSR of HBoV1 participates in such processes[67]. sfRNA in JEV was reported to be present in the late stages of the viral replication cycle and to be a *trans*-acting riboswitch that inhibits translation of host antigenomic and JAV genes, but promotes genomic RNA synthesis, packaging and virion release[40, 55]. Moreover, the full length of sfRNA in WNV was found to be abundant in the infected cells and necessary

for their genome package and new virus assembly[54, 55]. Silencing expression of PAN in KSHV and RRV (the related Rhesus macaque rhadinovirus) both led to down-regulation of late lytic viral genes and reduction of progeny virions from the infected cells, indicating that PAN promotes virion release[37–39, 47, 48].

These findings therefore show that lncRNAs generated by viruses are likely to be involved in the regulation of the whole course of viral life cycle, including the viral genome replication, gene expression, assembly and release of virions.

### Viral lncRNAs contribute to viral pathogenicity

Viral lncRNA plays important role in exerting the viral protective and resistance to host cellular antiviral response. They contribute to both viral persistence and acute infections.

### Viral lncRNAs contribute to viral persistent infections

Some viral genome is integrated into the host chromosome, and replicates while the host genome replicates. Usually, the immune system can eliminate this pathogen. However, in some situations, the acute resolution of infection is not complete and viral persistence occurs. Some viral lncRNAs were reported to be involved in controlling the immune response to maintain the viral persistence[7, 46]. lncRNAs can also help viral persistent infections by controlling the cellular response system. As mentioned above, sfRNA can inhibit expression of Xrn1 to stabilize mRNAs of some cytokines and generate a cytokine storm related to the viral infections[20, 69–71]. TLR3 can sense EBERs to cause immunopathological diseases[20]. Tmepvg1 regulates the persistent infection of Theiler's virus by up-regulating expression of  $\gamma$ -IFN[76, 77]. PAT1 (persistence-associated transcript 1) of Hz-1 virus is the product of *pag1*, which is necessary for the persistent Hz-1 viral infection in the infected cells[78]. 3 LATs (latency-associated transcripts) of HSV are expressed during their latent viral infection[79]. lncRNA ASP of HIV can recruit PRC2 to the 5' LTR of HIV-1 to suppress the H3K27 trimethylation and establish the latency of HIV-1[46, 80]. The binding of CTV LMT1 with CTV p33 may help CTV to persist in the host for the whole tree life, and when arrive at sufficient titers to be transmitted to a new host[49].

## Viral lncRNAs contribute to resistance to antiviral immune responses

The antiviral immune responses will be triggered to protect against viral infection. Therefore, to successfully cause infection in a host, viruses must overcome the host antiviral immune responses. lncRNAs produced by viruses are reported to be involved in these processes. Numerous examples exist. PAN expressed by KSHV inhibits the expression of a lot of immune factors (IL-4, IL-8, IFN-16, IFN- $\gamma$  and RNase L) by binding to the host transcriptional factors, such as PU.1, H1/ H2A and SSBPs[47, 81]. Meanwhile, PAN can also decrease the expression of many host antiviral genes through activation of PRC2 (Polycomb Repressive Complex 2)[38]. sRNA of WNV resists the host antiviral response by inhibiting apoptosis, decreasing IFN production, nuclear translocation and IRF-3 activation[72, 73]. DENV-2 sRNA of DENV-2 inhibits the expression of many critical interferons-stimulated genes (ISGs), such as PKR and IFITM2 by targeting the host RNA-binding proteins[82]. PR-2B sRNA of DENV-2 destabilizes RIG-1 leading to a decrease in the formation of IFN and other antiviral responses by binding TRIM25 (E3 ubiquitin ligase) to prevent its deubiquitylation[83]. lncRNA oriPts of EBV modulates the paraspeckle-based antiviral immune response, viral DNA replication, and lytic gene expression during reactivation[84]. RNase L ciRNA produced by Group C enteroviruses (GCE) inhibits the function of the ISG RNase L[85]. CTV LMT1 was reported to play a role in modulating plant antiviral response by limiting the production of reactive oxygen species (ROS)[49]. VA RNA prevents the phosphorylation of eIF2 (translation initiation factor 2) through inhibiting the host PKR signaling and resists the antiviral response of the host cell[86]. However, in some situations, viral lncRNAs are responsible for immune activation by viruses. They may induce the Toll-like receptor 3 (TLR3) signaling, resulting in the production of IFN-1 and some other proinflammatory cytokines. For instance, RIG-1 is activated by EBERs and VA RNAs, leading to the production of IFN[65, 87, 88]. VA RNAs can also promote the formation of OAS, and then activate RNase L to degrade ssRNAs (single strand RNAs), resulting in additive activation of RIG-1 and IFN response[89]. While secreted EBERs can activate TLR3 pathway to produce several inflammatory cytokines[87, 88]. The activation of innate immunity by viral lncRNAs may account for immunopathologic diseases caused by viruses.

As discussed above, viral lncRNAs may be involved in regulating the antiviral immune response and in the maintenance of the latency for persistent infection through the integration of the viral genome into the host chromosome.

## Summary and future prospects

It is now well known to all that lncRNAs play numerous regulatory roles in a wide range of cellular physiological and pathological process. Lots of evidences indicate that lncRNAs are also involved in the process of viral infection, including the host antiviral immune responses and the survival of viruses. Here, we summarize that lncRNAs expressed by viruses also play important roles in viral infection. First, viral lncRNAs can regulate viral life cycles, they can promote genome replication, regulate gene expression, assist in genome packaging, new viral assembly and release virions to infect other cells of the host. Second, viral lncRNAs can affect the pathogenicity by down-regulating the host cell's antiviral immune response and in maintaining the viral latency through a refined procedure of genome integration for persistent infection.

Although there are great achievements in this field of lncRNA, many challenges remain to be addressed. First, most of the investigations into the roles of lncRNAs in viral infection come from host lncRNAs. The reports about viral lncRNAs are still limited. Therefore, more researches targeted towards the identification of new viral lncRNAs, especially the functional ones are encouraged. Second, the roles and the mechanisms of viral lncRNAs in viral infection need to be further investigated. Elucidation of viral lncRNAs is still in its infancy and will undoubtedly be an increasingly important research area for years to come. Finally, further studies are needed to determine the applicability of viral lncRNAs as both therapeutic targets and diagnostic biomarkers. When using lncRNAs as therapeutic targets, strategies can aim to prevent the formation of secondary structures or hold back the interaction between lncRNAs with those transcripts, because the secondary structures of viral lncRNAs and their binding to transcripts are critical for their roles in viral infection[20, 85]. Meanwhile, the role of specific lncRNA must be taken into account when utilizing these lncRNAs as targets. For latency-inducing lncRNAs, small interfering RNA (siRNA), short hairpin RNA (shRNA), or anti-sense oligonucleotide (ASO) can be used to decrease their expression level by post-transcriptional degradation. Promoter blockade or CRISPR-Cas-based gene editing can be utilized to silence the expression of viral lncRNAs. There are also some viral lncRNAs that may be unfavorable for viral infection[90, 91]. Therefore, synthetic lncRNAs can be delivered to up-regulate the expression of these unfavorable viral lncRNAs. Vectors, liposomes and nanoparticles can be used as the delivery vehicles[91]. On the other aspects, the unique viral lncRNAs in early infection can be explored as new diagnostic biomarkers for viral infection. In addition, it is necessary to develop new sensitive lncRNA detection methods.

Using the present COVID-19 which is still spreading globally and causing major health challenges in the human population as an instance[1]. Numerous studies have been carried out on the mechanism of pathogenicity of SARS-CoV-2 and possible therapeutic strategies to overcome the disease. Non-coding RNAs were found to also be involved in SARS-CoV-2 infection. Most of the reports focused on the change of the host cellular miRNAs which may be required for their replication and assembly or be important for antiviral immune response. MiRNAs expressed by SARS-CoV-2 can also affect their pathogenicity by down-regulating the host cells' immune response[1]. Till now, little is known about lncRNAs generated by SARS-CoV-2. Therefore, discovery of lncRNAs expressed by SARS-CoV-2 and the exploration of their roles and mechanisms of action in SARS-CoV-2 infection are novel fields which may provide better understandings into the treatment of SARS-CoV-2 infection.

In conclusion, this review gives an insight into the involvement of viral lncRNAs in virus life cycle and pathogenicity. It also pointed out the utilization of viral lncRNAs as therapeutic targets and prognostic biomarkers for the treatment of viral diseases and future studies aimed at moving these findings from the laboratory through the clinical table to the patients are strongly advocated for.

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## Declarations

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