Viral lncRNA: A regulatory molecule for controlling virus life cycle

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1. Introduction

Viruses are important infectious agents that interfere with the molecular process of gene expression in the host cell. Therefore, an understanding of the mechanisms by which viruses adapt to the host cellular environment and enhance the expression of specific viral genes that control pathogenicity will provide basic information concerning cellular processes during viral infection. Although the majority of factors that are known to regulate the viral life cycle are proteins, a growing number of long non-coding RNAs (lncRNAs) have been verified to function in these processes [1]. Historically, genes of non-coding RNAs have been regarded as “junk DNA”. However, this type of long non-coding transcript has recently risen to prominence as a surprisingly versatile regulator of gene expression. The functional diversity of the mere handful of validated lncRNAs indicates the vast regulatory potential of these silent biomolecules.

During viral infection, viruses generate lncRNAs to facilitate virus-induced cytopathicity and pathogenicity [2]. Additionally, host lncRNA expression is profoundly influenced by viral infections. For example, 4729 lncRNAs are upregulated and 6588 are downregulated during human foamy virus (HFV) infection of H293 cells [3]. Additionally, researchers discovered 504 differentially regulated lncRNAs in a whole transcriptome analysis of SARS-CoV-infected mouse lung tissue [4], and more than 4800 lncRNAs were differentially expressed in rhabdomyosarcoma cells infected with enterovirus 71 [5]. These findings suggest that widespread differential expression of lncRNAs occurs in response to viral infection and the potential roles of these dysregulated lncRNAs in the viral life cycle.

In this review, we describe the biological roles of lncRNAs generated by viruses and induced during the viral life cycle (Fig. 1) and discuss the potential usefulness of lncRNAs as therapeutic targets. This review shows that viruses have evolved a unique strategy to facilitate their life cycle via generating or inducing lncRNA production, which may have important consequences for the application of clinical approaches for the treatment of viral diseases.

2. Enhancing viral gene expression

Once a virus reaches the appropriate cell compartment, the viral genome must direct the expression of “early” proteins, which will
enable genome replication, and “late” proteins, which are used to package the viral genome and assemble the capsid. In cells infected with the dengue or kunjin viruses, subgenomic flavivirus RNA (sfRNA), which is a lncRNA that is incompletely degraded from the viral genomic RNA presumably by the cellular 5’-3’ exoribonuclease XRN1, inhibits XRN1 activity and alters host mRNA stability. This effect may assist the stabilization of viral transcripts and disrupt the regulation of host cell gene expression [6].

For DNA viruses, polyadenylated nuclear (PAN) RNA, which is a lncRNA encoded by the Kaposi’s sarcoma-associated herpesvirus (KSHV) genome, can transcriptionally activate KSHV gene expression by physically interacting with the KSHV genome [7]. Alternatively, PAN RNA can relieve gene suppression by acting as a molecular scaffold for chromatin modifying enzymes to remove the H3K27me3 mark [8], which is required for the production of late viral proteins, by binding to the host poly(A)-binding protein C1 (PABPC1) to regulate mRNA stability and translation efficiency [9]. Moreover, adenovirus virus-associated RNA (VARNA) I is involved in the selective translation of viral mRNA and the shut-off of host cell protein synthesis by inhibiting the cleavage of double-stranded RNA and the inactivation of DAI, which is an elf-2 kinase known to be a suppressor of protein translation initiation [10,11]. In addition to lncRNAs encoded by viral genomes, NEAT1 (nuclear enriched abundant transcript 1) is a cellular lncRNA that functions as a scaffold for paraspeckle formation [12–14] and is induced by viral infection [15–17]. Recently, we found that NEAT1 binds to viral genes and increases viral gene expression and viral replication [18].

3. Promoting viral replication

Many viruses must continually replicate to maintain themselves. Generally, DNA viruses replicate their genomes directly to DNA, whereas RNA viruses replicate their genomes directly to RNA. However, some DNA viruses copy their genomes via an RNA intermediate, and some RNA viruses copy their genomes via a DNA intermediate. sfRNA has been shown to regulate viral gene expression and is required for efficient viral replication and cytopathicity in cells infected with West Nile virus Kunjin (WNV KUN)
40

and yellow fever virus [20]. In contrast, sRNA plays a negative role in viral replication and translation in cells infected with Japanese encephalitis virus [21]. Furthermore, KSHV PAN RNA associates with the demethylases UTX and JMJD3 to activate lytic replication through a physical interaction with the viral genome [22].

4. Promoting viral assembly and boosting virion release

As part of the viral life cycle, the genome packaging and virion release processes are initiated by tethering of viral proteins by the viral genome into new infective progeny viruses within the infected cell. In moloney murine leukemia virus (MLV)-infected cells, the mY1 and mY3 RNAs, which are non-coding RNA polymerase III transcripts that are normally complexed with the Ro60 and La proteins in host cells, are selected for encapsidation and assist with viral RNA biogenesis and quality control [23]. Additionally, sRNA has been shown to be essential for ensuring specific genome packaging in many flaviviruses. For instance, in WNV KUN-infected cells, the plaque size and virus growth in mammalian and mosquito cells correlated with the generation and amount of full-length sRNA, showing that the production of abundant amounts of full-length sRNA was essential for efficient viral packaging and virion release [2]. Furthermore, in Japanese encephalitis virus (JEV)-infected cells, sRNA promote the packaging and release of virions for the next infectious cycle by shutting down both antigen synthesis and JEV translation [21]. In our study, we found that the herpes simplex virus-1 (HSV-1) glycoprotein density and intensity were much lower in NEAT1-knockdown HeLa cells than in the control cells, suggesting that NEAT1 influenced HSV-1 virion release [18].

5. Maintaining viral latency

Some viruses undergo a lysogenic cycle where the viral genome is incorporated into a specific location in the host’s chromosome by genetic recombination. Thus, the viral genome is replicated whenever the host divides. In most situations, the concerted effort of the innate and adaptive responses is effective in eliminating the pathogen. However, in some cases, the acute resolution of infection is incomplete and viral persistence results. Herpes simplex virus, Heliobius zea nudivirus 1 (HzNV-1), adenovirus virus and Theiler’s virus are hallmark examples of infections that develop lifelong viral persistence by “hiding” from the immune response. In contrast to the many viral translated and induced proteins involved in maintaining persistent infections by direct inhibition of T cell responses and/or by down-regulating antigen recognition molecules [24,25], some IncRNAs have been shown to be responsible for derailing the immune response to permit viral persistence. Tmevpg1, which is a long intergenic non-coding RNA, controls persistent infection with Theiler’s virus by positively regulating IFN-gamma expression; this process is dependent on Stat4 and T-bet, which are the two transcription factors that drive the Th1 differentiation program [26–28].

Additionally, some non-coding genes can act as bi-functional factors to promote viral entry or the maintenance of a latent state. The non-coding gene Pag1 blocks the HzNV-1 gene hhi to establish viral latency by encoding two miRNAs that target and degrade the hhi1 transcript, which is a stimulator of apoptosis [29,30]. PAF1, which is another non-coding transcript encoded by pag1, has also been verified to be involved in persistent infection in cells. However, whether PAF1 is directly responsible for the establishment of persistent infection or only enhances this process is unknown [31]. For HSV-1, the latency-associated non-coding transcript (LAT) is the only viral gene that is expressed during latent infection in neurons. In these cells, LAT exerts its anti-apoptotic effect [32] and blocks the function of early genes to maintain latency by proceeding into and functioning as a microRNA (miR-LAT) that down-regulates transforming growth factor-beta 1 and SMAD3 expression [33]. Moreover, adenovirus virus-associated RNAs (VA RNAs) are processed into small RNAs that are expressed at high levels and may be associated with the ability of this virus to efficiently establish a persistent infection [34]. One VA RNA-derived small RNAs (mivaRNA), mivaRNA-138 can inhibit cell apoptosis by targeting and binding TIA-1, which is a well-characterized factor that activates apoptosis [35,36]. Importantly, mRNAs associated with viral replication are essentially unaffected by these small non-coding RNAs [37].

6. Assisting viral-induced cellular transformation

Viral transformation most commonly refers to the virus-induced malignant transformation of an animal cell in a body or cell culture and can impose characteristically determinable features upon a cell. Typical phenotypic changes include a high saturation density, anchorage-independent growth, loss of contact inhibition, loss of orientated growth, immortalization, and disruption of the cell’s cytoskeleton, which are favorable for the viral life cycle. Currently, viruses drive cellular transformation through their ability to alter cellular gene expression, signaling pathways, and the cell cycle [38]. A study on the regulatory roles of Kaposi’s sarcoma-associated herpes-virus PAN RNA on viral and cellular gene expression showed that PAN RNA could maintain cellular transformation by affecting cellular gene expression, resulting in an enhanced growth phenotype, higher cell densities, and increased survival [7]. In Epstein-Barr virus (EBV)-associated carcinogenesis, EBV-miR-BART6-3p inhibited EBV-associated cancer cell migration and invasion by targeting and downregulating the IncRNA LOC553103 [39]. The Epstein-Barr early RNAs (EBERs) are two abundantly expressed and virally encoded IncRNAs in latently EBV-infected cells. A recent study of the in vivo effects of EBERs in cellular gene expression demonstrated that the EBERs regulated a variety of host cell genes, including deaminase, protein kinase, cell adhesion, regulation of apoptosis, and receptor signaling [40]. Moreover, EBER-1 enhanced host cell protein synthesis by blocking the activation of the double-stranded RNA-dependent eukaryotic initiation factor 2α (eIF-2α) protein kinase DAI (p68) [41]. EBERs have also been shown to impact the growth potential of Burkitt’s lymphoma (BL) cells by mediating the stable relocalization of L22 from the nucleoli to the nucleoplasm [42] and inducing interleukin-10, which is a growth factor for virally infected cells [43]. These findings contribute to the potential ability of EBERs to establish or maintain a transformed phenotype in EBV-associated nasopharyngeal carcinoma [44] and in EBV-infected NIH 3T3 cells [45]. However, EBER-2 but not EBER-1 plays a critical role in viral-induced growth transformation in EBV-infected B cells [46].

7. Imparting resistance to the antiviral immune responses

The intracellular antiviral immune response in host cells provides essential protection against virus infection. The innate immune response can be triggered by the interaction between host cell pathogen recognition receptors and viral surface proteins and the presence of viral products, such as nucleic acids, in the host cell. However, some IncRNA generated by viruses have shown their roles in imparting resistance to the antiviral immune responses (Table 1). As the predominant antiviral response against invading viruses, RNA interference (RNAi) is an intracellular process that is induced by double-stranded RNA (dsRNA) that results in the cleavage of both cellular and viral mRNAs into small interfering
Activated PKR is autophosphorylated; in turn, PKR phosphorylates interferons (IFNs), which can be triggered by the presence of certain viruses [54]. Dicer, an RNase that cleaves long dsRNA, is essential for the completion of the viral life cycle and is required for the stabilization of the mitochondrial membrane potential and the prevention of metabolic dysfunction, which are critical players in gene regulation and molecular pathways [55, 56]. Another study showed that the replacement of constitutive IFN expression by hybridization with PKR and abrogating its activity [49]. Additionally, the adenosine-activated VAI RNA and VAI RNA can attenuate the viral pathway by directly inhibiting PKR activity [50, 51] and functioning as competitive substrates to sqelch Dicer and interfere with its activity [52]. Another RNA encoded by the West Nile and dengue viruses (sfRNA) not only efficiently suppressed siRNA- and miRNA-induced RNAi pathways in both mammalian and insect cells partially by disturbing dsRNA cleavage [53] but also interfered with the RNAi pathway by inhibiting the RNase Dicer [54].

In addition to the RNAi pathway, antiviral substances, such as interferons (IFNs), can be triggered by the presence of certain viruses. The roles of these antiviral substances are to protect adjacent cells from infection and activate T cell-mediated immunity by initiating apoptosis and autophagy [55, 56]. To dissect the mechanisms by which viruses perturb the IFN signaling pathway, Schuessler A et al. showed that sfRNA derived from West Nile virus contributed to viral evasion of the type I interferon-mediated antiviral response by blunting the increase in IFN expression provoked by viral infection [57]. Furthermore, another study showed that sfRNA played a role against host cell antiviral responses by preventing the cells from undergoing apoptosis and thus contributed to viral persistence by obstructing interferon production, nuclear translocation and IFR-3 activation, which is a key factor in the induction of early antiviral responses [58]. These effects of sfRNA may protect latently infected host cells from the anti-viral action of IFNs.

Moreover, virus-infected cells may initiate apoptosis to prevent the spread of infection to other cells. As a countermeasure, human cytomegalovirus encodes Beta 2.7, which is the most abundantly transcribed early gene, to prevent the host cell stress response and apoptosis by binding to components of the mitochondrial respiratory chain complex; (reduced nicotinamide adenine dinucleotide-ubiquinone oxido-reductase). This interaction is also important for the stabilization of the mitochondrial membrane potential and mitochondrial ATP production and the prevention of metabolic dysfunction, which are essential for the completion of the viral life cycle [59]. The psoriasis susceptibility-related RNA gene induced by stress (PRINS) is an lncRNA overexpressed by herpes simplex viral infection [60]; upregulated PRINS can decrease cell apoptosis by regulating the anti-apoptotic G1P3 protein [61].

In addition to the innate antiviral response, an important outcome of viral infection is the development of a virus-specific immune response triggered by viral antigens. Accumulating evidence suggests that lncRNAs are important regulators of the differentiation and functions of T cells, which orchestrate the adaptive immune responses [62, 63] and have been implicated in antigen receptor diversification [64]. Thus, lncRNAs are likely to play a role in regulating antiviral adaptive immunity.

8. Discussion

It is becoming apparent that lncRNAs can perform vital roles in the control of a variety of processes by regulating gene expression. Recently, more than 20% of lncRNAs were found to contain one or more Alu elements, which are critical players in gene regulation and molecular pathways [65, 66]. A study showed that Alu sequences embedded in both lncRNAs and miRNAs played crucial roles in targeted miRNA decay via short imperfect base pairing. This imperfect base pairing may extend the potential ability of lncRNAs to regulate protein synthesis [67], although tens of thousands of human lncRNAs have not been shown to direct protein synthesis. Moreover, the NEAT1 lncRNA, which is up-regulated in virus-infected cells, has been demonstrated to mediate the nuclear retention process [68], which may help explain the essential roles played by lncRNAs in viral life cycles following accumulation in the nucleus [69]. Furthermore, thousands of lncRNAs have been found to regulate gene expression by binding PRC2, and additional lncRNAs are bound by other chromatin-modifying complexes [70]. As a mediator of gene expression, lncRNAs can generate small ncRNAs less than 200 nts in length, such as tRNAs and miRNAs, to enlarge their regulatory power. MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) is a lncRNA that is specifically retained in the nucleus [71] and has been found to be involved in not only the assembly, modification and/or storage of the pre-miRNA processing machinery [72] but also the generation of a short tRNA-like ncRNA [MALAT1-associated small cytoplasmic RNA (mascRNA)] through cleavage by RNase P and RNase Z. After processing, the long MALAT1 transcript remains in the nucleus, whereas mascRNA is exported to the cytoplasm [73]. This regulatory mechanism may allow cytoplasmic components to sense the differential MALAT1 expression in the nucleus and may be involved in translational regulation by serving as a tRNA mimic. As another example, H19 appears to be a bi-functional RNA acting as both an lncRNA and a miRNA precursor that is subsequently processed into miR-675 by cleavage by the RNase III enzymes Drosha and Dicer [74]. Although H19 and miR-675 are regarded as a tumor suppressor and an oncogene, respectively [75], the mechanism by which H19 exerts its functions through the generation of miRNAs raises the possibility that some other lncRNAs might also perform their biological roles by giving rise to miRNAs.

In addition to functioning as a small ncRNA precursor, growing evidence has demonstrated that lncRNAs may function as “miRNA sponges” with diverse and far-reaching effects. HULC, which is a highly up-regulated lncRNA in liver cancer, contains a motif with a sequence targeted by miR-372. HULC has been reported to initiate a cascade of molecular events to increase chromatin accessibility for general transcription by recruiting miR-372 and attenuating its chromatin modification activity [76]. Recently, Wang et al. illustrated that the lncRNA linc-RoR functioned as a key competing

| Name             | Source (Name, Family name, Classification) | Function                                                                 |
|------------------|-------------------------------------------|-------------------------------------------------------------------------|
| EBER1 and EBER2  | Epstein-Barr virus, Herpesviraideae, dsDNA | Binding PKR and abrogating its activity                                 |
| VAI RNA and VAI RNA | Human adenovirus, Adenoviridae, dsDNA | Inhibiting PKR activation; Interfering with the activity of Dicer       |
| sfRNA            | West Nile, Flaviviridae, ssRNA             | Disturbing dsRNA cleavage; Inhibiting the RNase Dicer                   |
| sfRNA            | Dengue viruses, Flaviviridae, ssRNA       | Disturbing dsRNA cleavage; Inhibiting the RNase Dicer                   |
| sfRNA            | Japanese encephalitis virus, Flaviviridae, ssRNA | Preventing host cells from apoptosis; Obstructing interferon production, nuclear translocation and IFR-3 activation |
| sfRNA            | Human cytomegalovirus, Herpesviraideae, dsDNA | Preventing the host cell stress response, apoptosis and metabolic dysfunction |

DsRNA: double-stranded RNA; ssRNA: single-stranded RNA.
endogenous RNA by preventing core transcription factors (TFs) from functioning in miRNA-mediated suppression and maintaining embryonic stem cell self-renewal and differentiation by targeting and antagonizing miR-145, which is a repressor of the translation of the core TF mRNAs [77]. To investigate the regulatory interactions between RNA classes, the interaction network between lncRNAs, miRNAs and mRNAs has been well-characterized computationally and experimentally [78,79]. Systematic transcriptome-wide analysis of the multiple classes of RNAs suggests widespread regulatory roles for lncRNAs and indicates the potential ability of lncRNAs to act as important mediators of various biological processes. Through deep-sequencing technology, lncRNAs have been reported to play crucial roles in viral infection processes. Moreover, lncRNAs may act as a “bridge” that interlinks two types of viruses. For instance, in human parvovirus B19 (B19V)-infected cells, the adenoviral VA I RNA stimulates B19V capsid protein expression most likely by inhibiting the dsRNA-induced activation of PKR through competition for the PKR RNA-binding domain [80]. In HIV subtype E-infected pediatric patients, EBERs are co-expressed with the HIV core protein p24, which plays an important role in the interaction with host proteins during HIV-1 adsorption, membrane fusion, and entry, in surgical lung biopsies [81]. Therefore, lncRNAs may be a better target for viral intervention strategies due to their active regulatory roles in facilitating the host environment for viruses. A study reported that the ribosomal protein L22 might be able to buffer cells against the ability of EBER-1 to induce cellular transformation and impart resistance to the antiviral immune response by competitively binding EBER-1 [82]. High-level expression of viral EBER-1 can lead to the resistance of cells to physiological stresses and pro-apoptotic stimuli and can confer aspects of the transformed phenotype, resulting in outright tumorigenicity in some cases [46,83]. Moreover, the COX-2 inhibitor etodolac induced apoptosis via a Bcl-2-regulated pathway through inhibition of EBER expression [84]. These findings indicated the potential usefulness of lncRNAs as targets for viral intervention strategies, which could have therapeutic implications for the application of clinical approaches for the treatment of viral diseases. Currently, many gene therapeutic approaches in clinical trials are promising, such as small interfering RNAs, antisense oligonucleotides, ribozymes, etc. However, the major drawback of these approaches is that their function lacks persistence. Recently, the clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 system have the advantage of affecting interested gene permanently [85] and many viruses have been proven to be sensitive to this system [86–91]. Therefore, targeting lncRNA involved in viral life cycle with (CRISPR)-Cas9 technology may have better therapeutic utility for control of virus infection.

In this review, we have thoroughly described the biological roles of lncRNAs in enhancing viral gene expression, promoting viral replication and genome packaging, boosting virion release, maintaining viral latency, assisting viral transformation, and antagonizing the host antiviral innate immune response. More importantly, in view of their regulatory roles, lncRNAs have been regarded as targets to block the facilitation of viral infection. Since the viral life cycle and the mechanism of the host antiviral response are clearer, targeting lncRNAs for prophylactic or therapeutic ends is an attractive alternative. With further advances in our understanding of the molecular details that govern the viral life cycle and immune response, this review hopefully revealed information that will help expand viral intervention strategies.

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