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Review article

Long noncoding RNAs and viral infections

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ABSTRACT

In this review, we focus on the roles of long noncoding RNAs (lncRNAs), including cellular and viral lncRNAs, in virus replication in infected cells. We survey the interactions and functions of several cellular lncRNAs such as *XIST*, *HOTAIR*, *NEAT1*, *BIC*, and several virus-encoded lncRNAs.

1. Introduction

A small portion (less than 2%) of the human genome is used to encode about 25,000 protein-encoding genes, while based on the findings from genome tiling arrays and RNA sequencing, >70% of the human genome is transcribed into RNAs, with the vast majority of these RNAs being devoid of obvious protein-coding capacity [1,2]. These numbers suggest that noncoding RNAs (ncRNAs) may not simply be effete materials, and they, like their protein counterparts, may play significant functional roles [3].

Operationally, ncRNAs can be grouped into small noncoding RNAs (sncRNAs) and long noncoding RNAs (lncRNAs) according to their length [4]. Within these two groups, there can be additional subclassifications of the moieties [5,6].

Of these two RNA groups, sncRNAs are transcripts that are <200 nt in length. Housekeeping RNAs, such as transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs) (5S, 5.8S), fall within this noncoding category [7]. The first characterized ncRNAs, tRNAs, serve as adaptors between messenger RNAs (mRNAs) and proteins for the elongation of polypeptide; rRNAs are essential elements for protein translation [8,9]. Other sncRNAs include small nucleolar RNAs and small nuclear (snRNAs) that play certain roles in rRNA modification and RNA splicing [10,11]. Besides these entities, sncRNAs also include three major types of regulatory RNAs: piwi-interacting RNAs (piRNAs), microRNAs (miRNAs), and small interfering RNAs (siRNAs) [12,13]. Of these regulatory RNAs, piRNAs are involved in the regulation of transposon activity and chromatin state in germline and somatic cells [14,15]; miRNAs and cell endogenous siRNAs contribute to RNA interference (RNAi) or post-transcriptional gene silencing [16]. Approximately 2000 miRNAs are encoded by the human genome [17,18]; miRNAs serve as guide RNAs in an RNA-induced silencing complex (RISC) to target mRNAs through imperfect complementarity leading to repression of translation or degradation of the mRNAs [19–21]. Similarly, cell endogenous siRNAs also participate with RISC proteins in silencing gene expression usually via perfect complementarity

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with mRNA targets [22]. The functional roles of sncRNAs have been reviewed extensively elsewhere [12,18,23–26]. This current review focuses on the still less well-studied counterpart of sncRNAs and lncRNAs, and their interactions with viruses.

2. Long noncoding RNAs

The lncRNAs are transcripts that are >200 nt in length [5]. This class of RNAs includes intergenic ncRNAs, pseudogene transcripts, and many antisense RNAs [5,6]. The majority of lncRNAs are transcribed by RNA polymerase II; they are 5′-capped, spliced, and polyadenylated, and are mRNA-like in many ways [27]. A small minority of lncRNAs are transcribed by RNA polymerase III; these include *7SK* and *7SL* [28,29]. The *21A* lncRNA is also an RNA Pol-III transcript, but it is not polyadenylated [30]. Additionally, several other features frequently define lncRNAs, such as epigenetic marks shared with protein-coding gene (H3K4me3 at the gene promoter and H3K36me3 throughout the gene body), splicing of multiple exons via canonical splice site motifs, regulation by transcription factors, and expression in a tissue-specific manner [6]. It is now increasingly understood that lncRNA sequences are abundant in the mammalian genome. To date, approximately 6700 lncRNAs have been identified in the human genome [31,32], and it is estimated that 7000–23,000 lncRNAs putatively exist in the human genome [33,34]. Whether many of these deduced lncRNAs are authentically expressed and serve functional roles remain to be demonstrated. As of November 2012, 194 lncRNAs have been recorded in the lncRNAdb, a database that archives lncRNAs reported in published literature [35].

3. Functions of lncRNAs

Accumulating data support the fact that lncRNAs contribute functions that affect many cellular processes [6,27,36,37]. Extant findings indicate contributions of lncRNAs to both transcriptional and post-transcriptional regulations [6,37]. Here, we discuss a few of the better characterized lncRNAs such as *XIST*, *HOTAIR*, *H19*, *HMGA1-p*, *MALAT1*, and *NEAT1* among others. Many of these RNAs are expressed during tumorigenesis or disease pathogenesis, or in different stages of embryonic stem cell differentiation [36].

4. Transcriptional regulation

Several lncRNAs play roles in transcriptional regulation. *XIST*, which was first discovered by searching cDNA libraries [38], is perhaps the most well-known lncRNA. A double-hairpin RNA motif in the RepA domain in *XIST* binds polycomb repressive complex 2 (PRC2), the complex that has been shown to be recruited by many lncRNAs to target genes [39] and that propagates function leading to X chromosome inactivation, as observed in some breast cancers [40–42]. Hypomethylation of *XIST* in lymphoma and male testicular germ-cell tumors has also been described, although their functional significance needs more study [6,43].

Another well-studied lncRNA is *HOTAIR*. The *HOTAIR* gene is located within the *HoxC* gene cluster on chromosome 12 [44]. The *HOTAIR* transcript represses the expression of genes in the *HoxD* gene cluster on chromosome 2. The 5′-domain of *HOTAIR* binds PRC2, while its 3′-domain interacts with the LSD1/CoRES/REST complex [44,45], leading to methylation of histone H3 lysine 27 and demethylation of lysine 4, and gene repression by chromatin remodeling [45]. Mechanistically, *HOTAIR* serves as a modular scaffold for assembling a multiprotein complex [45].

Separately, it has been demonstrated that lncRNAs can regulate gene expression by increasing enhancer activity [4]. *Evf-2*, a 3.8-kilobase (kb) alternatively spliced form of *Evf-1*, is transcribed from the highly conserved region between the *Dlx-5* and *Dlx-6* genes, members of the *Dlx/dll* homeodomain-containing protein family [46]. *Evf-2* specifically recruits DLX and MECP2 transcription factors to increase the transcriptional activity of the *Dlx-5/6* enhancer [47].

5. Post-transcriptional regulation

Recent studies have also provided insights into the post-transcriptional regulatory roles of lncRNAs. One view suggests that lncRNAs can be precursors of small RNAs, e.g., miRNAs [48]. *H19*, a 2.5-kb RNA polymerase II-dependent transcript, is an imprinting-associated lncRNA located on chromosome 11 [49]. The function of *H19* has remained elusive since its discovery over 20 years ago. Recently, *H19* has been reported to serve as the precursor of *miR-675*, which can act to moderate cell growth. The excision of *miR-675* from *H19* is under the control of the stress-response RNA-binding protein HuR; *miR-675* is specifically expressed in the placenta from time of gestation and may function to limit placental growth [50].

Emerging reports suggest that pseudogenes can play important roles in regulating coding gene expression. For example, *HMGA1-p*, the pseudogene of *HMGA1*, encodes a transcript that competes with the *HMGA1* 3′-UTR for a critical RNA stability factor; this competition triggers a significant decline in the stability of *HMGA1* mRNA [51]. In the case of *PTEN*, the transcribed pseudogene *PTENP1* competes for miRNA-binding sites with the authentic *PTEN* RNA, thereby regulating the cellular abundance of *PTEN* mRNA [52].

Recently, Gong and Maquat [53] described a new functional mechanism of lncRNAs. The half-STAU1-binding site RNA 1 *1/2-sbsRNA1* contains an Alu element that can base-pair with the Alu element in the 3′-UTR of *SERPINE1* mRNA and *FLJ21870* mRNA. This base-pairing between two Alu elements forms the binding site for Staufen 1 (STAU1) protein, which recognizes double-stranded RNA [54], resulting in STAU1-mediated mRNA decay [53].

The lncRNAs can also bind to cellular protein and modulate their localization and activity. One of the well-characterized examples is *MALAT1*, which regulates alternative splicing by modulating the phosphorylation of the serine/arginine splicing factors [55]. Another example is *NRON* (an ncRNA repressor of the nuclear factor of activated T cells), which is proposed to block specifically nuclear trafficking of transcription factor NFAT (the nuclear factor of activated T cells)

as an RNA component of a protein complex that acts to repress NFAT activity [56].

6. Structural lncRNAs

There is also evidence that lncRNAs contribute structural/scaffolding functions. The lncRNA *NEAT1*, also known as *MENε/β*, was reported recently to be essential for the formation and maintenance of the nuclear substructure paraspeckles [48,57–59]. Paraspeckles are found in the interchromatin space of a nucleus and serve as depots for RNA-binding proteins in the nucleus [60]. Similarly, the lncRNA *Xlsirts* is suggested to be necessary for maintaining the cytokeratin cytoskeleton in *Xenopus* oocytes [61,62].

7. Cellular lncRNAs in virus-infected cells

Viruses are parasites that interact with their hosts. Since the functions of lncRNAs are highly pleiotropic, ranging from gene regulation to sncRNA precursors [4] and from cell development to cancer growth [6,12], it is not surprising that lncRNAs may be involved in virus replication. Early studies of the relationship between ncRNAs and viruses mainly focused on sncRNAs, such as miRNAs [63,64], while the roles of lncRNAs were not well studied. However, there is emerging evidence that cellular lncRNA expression can be regulated by virus infection. Thus, whole transcriptome analyses showed that during an infection by severe acute respiratory syndrome coronavirus, approximately 500 annotated lncRNAs and 1000 nonannotated genomic regions are differentially expressed in lung samples, and 40% of these changes are similarly observed during influenza virus infection and interferon treatment, indicating that many lncRNAs may be involved in regulating the host response to virus infection [65]. A concordant interpretation was separately proposed based on findings that the expression patterns of eight mRNA-like lncRNAs in immune tissues of chickens were changed after Marek's disease virus infection, similarly suggesting that they may play a role in host immune response [66]. Another example is *PRINS* (psoriasis susceptibility-related RNA gene induced by stress), which is increased by herpes simplex virus infection [67]. Separately, we recently profiled 83 disease-related lncRNAs in HIV-1-infected T cells and identified several lncRNAs that were changed in both Jurkat and MT4 cells, e.g., *BIC*, *NEAT1*, and *PANDA* [68].Our findings are also consistent with the overall notion that some lncRNAs serve in host responses to viral infections. Finally, studies have found a non-protein-coding infection-specific gene family called *Pinci1*, which is upregulated by *Phytophthora infestans* infection, in potatoes [69].

Although the lncRNAs discussed above have differential expression in virus-infected cells, their specific functions in virus replication remain incompletely characterized. In the following, we will discuss briefly some examples of lncRNAs whose roles in viral life cycle and viral pathogenesis are beginning to be better understood (Fig. 1).

8. 7SL

The *7SL*, a 300-nt RNA transcribed by RNA Pol-III, is the architectural RNA component of the signal recognition particle (SRP) ribonucleoprotein complex [70,71], which is a universally conserved ribonucleoprotein that directs the traffic of proteins within the cell and allows them to be secreted [72]. In mammals, six SRP proteins, named SRP9, SRP14, SRP19, SRP54, SRP68, and SRP72, assemble on *7SL* and form SRPs [73,74].

The *7SL* was first detected in avian and murine oncogenic RNA virus particles and then was found to be packaged by a broad range of retroviruses [75,76]. Tian et al [77] showed that *7SL* RNA is more selectively packaged into HIV-1 virions than other abundant Pol-III-transcribed RNAs, such as *Y* RNAs, *7SK* RNA, *U6* snRNA, and cellular mRNAs. Interestingly, *7SL* has been suggested to participate as a cofactor in the innate antiviral function of host cytidine deaminases such as cytidine deaminases APOBEC3G (A3G) and APOBEC3F (A3F) [78,79]. Wang et al [78] demonstrated that A3G selectively interacts with *7SL* RNAs and both are incorporated into virions, while A3G mutants that reduce *7SL* RNA binding but maintain wild-type levels of mRNA and tRNA binding are packaged poorly and have impaired antiviral activity. Reducing *7SL* RNA packaging by overexpression of SRP19 proteins inhibits *7SL* RNA, and A3G and A3F virion packaging, and impairs their antiviral functions [78,79]. Moreover, virion packaging of both A3G and cellular *7SL* RNA was mapped to the same regions in the HIV-1 nucleocapsid (NC) domain [77].

9. NEAT1

NEAT1 serves as a structural scaffold for nuclear paraspeckles [80]. It has two isoforms: *NEAT1_1* (3.7 kb in human) and *NEAT1_2* (23 kb in human); the isoforms are also named *MENε* and *MENβ* [60]. Besides *NEAT1* RNA, paraspeckles contain more than 30 nuclear proteins including p54nrb, PSF, and PSPC1, which are all RNA-binding proteins [60]. Despite much progress, the function of paraspeckles is still not well defined, but they are suggested to be involved in regulation of gene expression through nuclear RNA retention [81].

NEAT1 expression was reported to be increased in the central nervous system of mice during their infection with *Japanese encephalitis virus (JEV)* or *Rabies virus* [82]. More interestingly, several cellular proteins that play roles in HIV-1 replication are found in paraspeckles (e.g., PSF, p54nrb, and Matrin 3) [83,84]. Recently, we identified *NEAT1* as one of several lncRNAs whose expression is changed by HIV-1 infection, and we reported that the knockdown of NEAT1 enhances virus production through increased nuclear to cytoplasmic export of Rev-dependent INS-containing HIV-1 mRNAs [68].

10. BIC

BIC was first identified as an ncRNA upregulated by avian leukosis virus infection [85]. The integrated provirus activates *bic* gene expression by promoter insertion, resulting in high

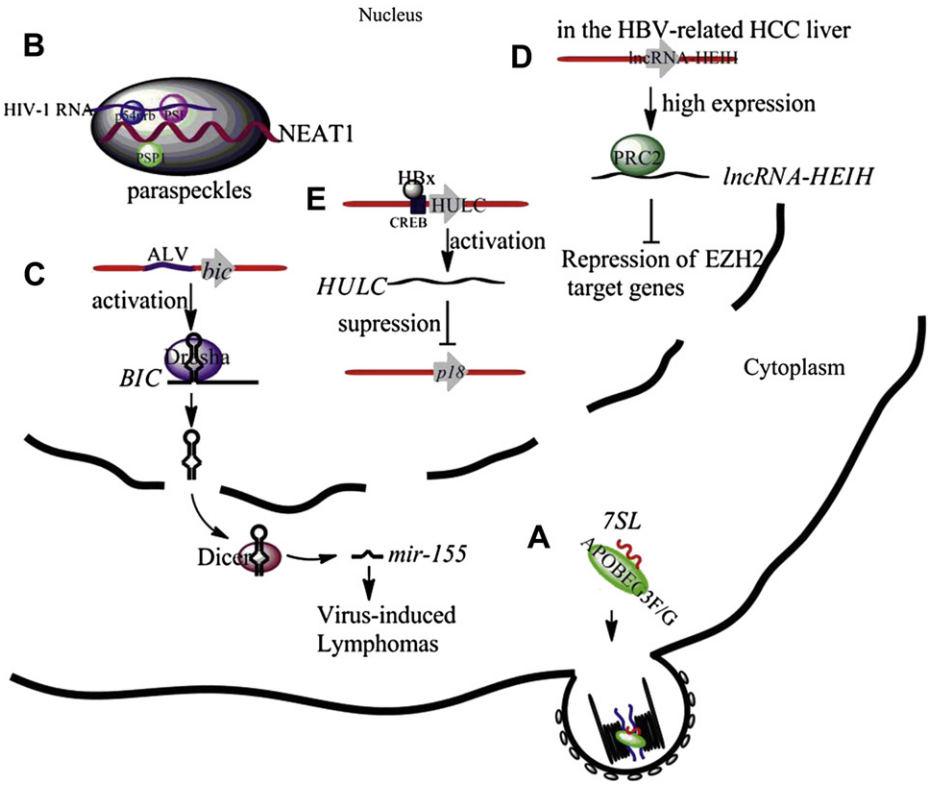

Fig. 1 – Illustrations of the functions of selected cellular lncRNAs in virus-infected cells. (A) The cytidinedeaminase APOBEC3G and APOBEC3F selectively interact with *7SL* RNAs and are incorporated into virions. (B) The lncRNA *NEAT1* serves as a structural scaffold for the nuclear substructure paraspeckles. Paraspeckle proteins PSF and p54nrb bind to HIV-1 RNA and retain the RNA in paraspeckles. (C) The integrated ALV activates *bic* gene expression by promoter insertion. *BIC* RNA, the precursor of *miR-155*, is suggested to be responsible for virus-induced lymphomas. (D) The *lncRNA-HEIH*, which is highly expressed in HBV-related HCC, recruits the PRC2 complex to repress EZH2 (an important subunit of the PRC2 complex) targeted genes. (E) *HULC* is upregulated by HBx protein through activation of the HULC promoter via CREB, leading to the suppression of the tumor suppressor gene *p18*. ALV = avian leukosis virus; CREB = cAMP responsive element binding protein; EZH2 = enhancer of zeste homolog 2; HBV = hepatitis B virus; HBx = hepatitis B virus X; HCC = hepatocellular carcinoma; lncRNAs = long noncoding RNAs; *lncRNA-HEIH* = lncRNA high expression in HCC; *HULC* = lncRNAs highly upregulated in liver cancer; PRC2 = polycomb repressive complex 2.

levels of expression of *BIC* RNA, which was suggested to be responsible for virus-induced lymphomas [85]. More recently, *BIC* was found to be the precursor of oncogenic *miR-155* [86], which is induced by several oncogenic viruses, e.g., Epstein–Barr virus, hepatitis C virus, and reticuloendotheliosis virus strain T [87–89]. Interestingly, Kaposi's sarcoma-associated herpesvirus, a gammaherpesvirus, and Marek's disease virus, an avian alphaherpesvirus, encode viral miRNAs, miR-K11, and miR-M4, as functional orthologs of *miR-155* [90,91]. Of interest, it has been shown that Epstein–Barr virus attenuates NF-κB signaling and stabilizes latent virus persistence by inducing *miR-155* [92]. In hepatitis C virus infection, upregulated *miR-155* has been demonstrated to promote hepatocarcinogenesis by activating Wnt signaling [88]. Reticuloendotheliosis virus strain T induces *miR-155* to target JARID2, a cell-cycle regulator that is a part of a histone methyltransferase complex, in order to promote cell survival [89]. Induction of *miR-155* by virus infection may not only be due to the induction of *BIC* RNA, but also arise from enhanced RNA processing [93].

11. Long ncRNA high expression in HCC and lncRNAs highly upregulated in liver cancer

Hepatitis B virus (HBV) infection is a major cause of hepatocellular carcinoma (HCC) [94]. Recent research has shown that some lncRNAs are aberrantly expressed in HBV-related HCCs. Two of these lncRNAs, *lncRNA-HEIH* (lncRNA high expression in HCC) and *HULC* (lncRNA highly upregulated in liver cancer), are reported to play key roles in HBV-related hepatocarcinogenesis [95,96]. Of these two lncRNAs, *lncRNA-HEIH* was reported to play a key role in G0/G1 arrest and be associated with enhancer of zeste homolog 2 (EZH2, an important subunit of the PRC2 complex), resulting in the repression of EZH2 target genes [95]. The other lncRNA *HULC*, a ~500 nt mRNA-like ncRNA, was reported to be upregulated by the hepatitis B virus X (HBx) protein through activation of the HULC promoter via cAMP responsive element binding protein. Upregulated HULC promotes proliferation of hepatoma cells through suppressing a tumor suppressor gene *p18* [96].

Table 1 – Virus-encoded lncRNAs.

Length	Name	Virus	Characteristics	References
<200 nt	*EBERs* (*EBER1*, *EBER2*)	Epstein–Barr virus	~170 nt, play roles in oncogenesis and modulate innate immune signaling	[102]
	HSURs (*HUSR1*, *HUSR2*)	Herpesvirus saimiri	*HSUR1* (143 nt), *HSUR2* (115 nt); *HSUR1* directs degradation of *miR-27* to manipulate host T-cell gene expression	[103,104]
	VA I and *II*	Human adenovirus	~160 nt, block PKR activity, avoiding phosphorylation of eIF-2α and inhibition of viral mRNA translation; can be processed by Dicer into small RNAs that are incorporated into RISC	[105–108]
>200 nt	*β2.7*	Human cytomegalovirus	2.7 kb, binds to the mitochondrial enzyme complex I, protecting virus-infected cells from apoptosis, resulting in continued ATP production	[100,109]
	sfRNA	Flaviviruses	0.3–0.5 kb, produced from the incomplete degradation of the viral genome by the host exonuclease XRN1 and required for virus-induced cytopathicity and pathogenicity	[110]

ATP = adenosine triphosphate; EBERs = Epstein–Barr virus-encoded RNAs; HSURs = Herpesvirus saimiri U-rich RNAs; lncRNAs = long non-coding RNAs; mRNA = messenger RNA; PKR = double-stranded RNA-activated protein kinase; RISC = RNA-induced silencing complex; VA I and II = virus-associated RNA I and II.

12. Theiler's murine encephalomyelitis virus persistence candidate gene 1

Previously, the *Tmevp3* locus, located on the telomeric region of chromosome 10, was shown to control the persistence of Theiler's virus in the central nervous system of mice [97]. More recently, an ncRNA *Tmevpg1* (Theiler's murine encephalomyelitis virus persistence candidate gene 1) was identified, at that locus through a positional cloning approach, as a candidate gene for controlling the persistence of Theiler's virus [98]. The promoter of *Tmevpg1* contains binding sites for E2A and the Ets family of transcription factors, indicating that it is regulated by transcription factors involved in the immune system [99]. Since *Tmevpg1* and its human ortholog, *TMEVPG1*, are located in a cluster of cytokine genes that includes the genes for gamma interferon and homologs of interleukin-10, *Tmevpg1* is suggested to be involved in the control of Interferon-gammagene (*Ifng*) expression [98]. However, its precise role requires further characterization.

13. Virus-encoded lncRNA

To date, over 200 miRNAs encoded by several virus families have been identified [18]. Similarly, several lncRNAs encoded by viruses have also been discovered [100,101] (Table 1) [102–110]. Although each is less than 200 nt in size, Epstein–Barr virus-encoded RNAs (*EBERs*) [102], herpesvirus saimiri U-rich RNAs (*HSURs*) [103,104], and virus-associated RNA I and II (*VA I* and *II*) encoded by adenovirus [105–108] are sometimes also referred to as viral lncRNAs, because they are significantly longer than viral miRNAs [111]. Here, we focus an illustrative discussion on two viral lncRNAs, *β2.7* and *sfRNA*, which are longer than 200 nt in size.

14. Viral lncRNA β2.7

β2.7 RNA, a highly conserved 2.7-kb transcript of human cytomegalovirus, accounts for more than 20% of total viral gene transcription during the early phase of infection [100]. Since the replication rate of a *β2.7* deletion mutant virus is similar to that of a wild-type virus, the *β2.7* gene was considered not to be essential for virus replication *in vitro* [112]. However, recently, by Northwestern screening of a human cDNA library with a *β2.7* probe, Reeves et al [109] found that *β2.7* binds directly to the mitochondrial enzyme complex I (reduced nicotinamide adenine dinucleotide–ubiquinone oxidoreductase). This binding protects virus-infected cells from apoptosis and results in continued adenosine triphosphate (ATP) production, which is critical for the successful completion of the viral life cycle. The *β2.7* RNA can also protect rat aortic endothelial cells from ischemia/reperfusion injury-induced apoptosis by reducing the formation of reactive oxygen species [113].

15. Subgenomic flavivirus RNA

The subgenomic flavivirus RNA (*sfRNA*), 0.3–0.5 kb, is derived from the 3′ untranslated region of the RNA genome of flaviviruses, a large group of single-stranded, positive-sense RNA viruses that includes several human pathogenic viruses, such as yellow fever virus, JEV, and West Nile virus (WNV) [101,114,115]. The *sfRNA* has been demonstrated to be produced from the incomplete degradation of the viral genome by the host 5′ to 3′ exonuclease XRN1. The rigid secondary structure stem-loop II located at the beginning of the 3′-UTR of the above viral genomes is resistant to nuclease XRN1 degradation and results in the production of *sfRNA* [116]. Production of *sfRNA* has been shown to increase the replication efficiency of WNVs and is important for virus-induced cytopathicity in

cell culture and also for viral pathogenicity in mice [110,117]. However, the exact mechanisms explaining how *sfRNA* leads to increased virus replication and cell death remain elusive. *sfRNA* is also found in JEV infection. In this setting, *sfRNA* becomes apparent at the time during which minus-strand RNA (antigenome) reaches a plateau, suggesting a role for *sfRNA* in the regulation of antigenome synthesis. The presence of *sfRNA* may inhibit antigenome synthesis and may exert a negative effect on JEV translation [118].

16. Perspective

In recent years, technological advances have made it possible to investigate the expression of whole transcriptomes in an unbiased manner. This new capability has driven the discovery of an increasing number of lncRNAs. Nonetheless, our knowledge regarding the functions of these lncRNA transcripts remains quite limited [119]. Because lncRNAs have diverse functions, they likely represent important bioentities that merit further investigation. Here, we have focused on a few examples of lncRNAs, including cellular and viral lncRNAs. Our brief survey shows that we are at the initial stages of uncovering their functions and their relationships with viruses. This review is meant to serve as a brief illustrative introduction to lncRNAs, which we hope may spur interest by readers for conducting further studies on these interesting and important biomolecules.

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