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Viral lncRNA: A regulatory molecule for controlling virus life cycle

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ABSTRACT

Long non-coding RNAs (lncRNAs) are found not only in mammals but also in other organisms, including viruses. Recent findings suggest that lncRNAs play various regulatory roles in multiple major biological and pathological processes. During viral life cycles, lncRNAs are involved in a series of steps, including enhancing viral gene expression, promoting viral replication and genome packaging, boosting virion release, maintaining viral latency and assisting viral transformation; additionally, lncRNAs antagonize host antiviral innate immune responses. In contrast to proteins that function in viral infection, lncRNAs are expected to be novel targets for the modulation of all types of biochemical processes due to their broad characteristics and profound influence. This review highlights our current understanding of the regulatory roles of lncRNAs during viral infection processes with an emphasis on the potential usefulness of lncRNAs as a target for viral intervention strategies, which could have therapeutic implications for the application of a clinical approach for the treatment of viral diseases.

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

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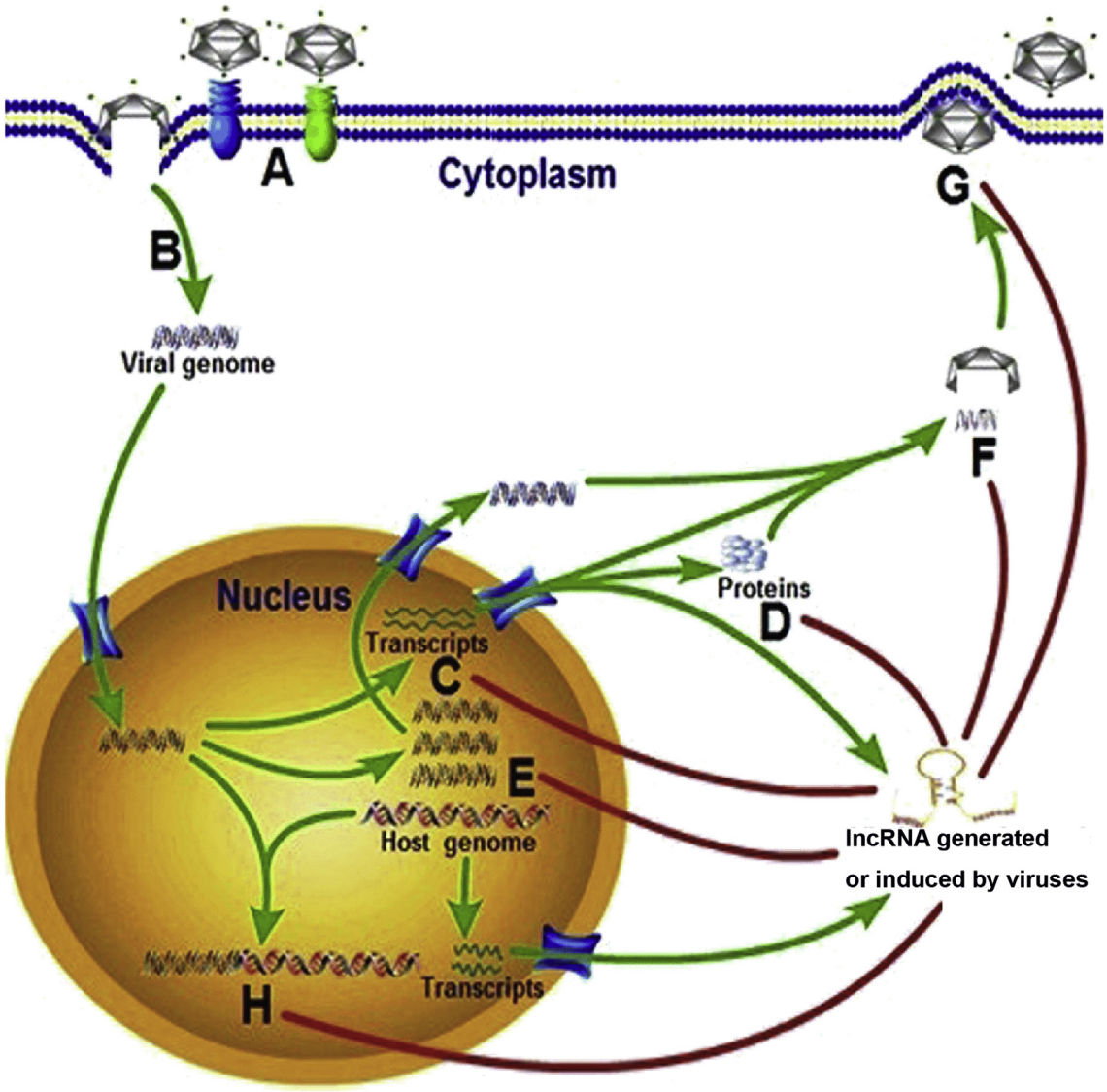

Fig. 1. A diagram highlighting the regulatory roles of lncRNAs in viral life cycles. Once virus enters the host cell by binding to receptors of the cell surface (A and B), lncRNAs generated or induced by viruses facilitate its life cycles through enhancing viral gene transcription (C) and translation (D), promoting viral replication (E) and genome packaging (F), boosting virion release (G) and maintaining viral latency (H).

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 eIF-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)