*Review*

# Long Non-Coding RNAs in Viral Immunity: From Regulatory Mechanisms to Therapeutic Potential

Majd H. Aldweik [1] and Yasmin Hisham [2,*,†]

[1] Molecular Biology and Genetics, Istinye University, İstanbul 34396, Turkey
[2] Laboratory of Cytokine Immunology, Department of Biomedical Science and Technology, Konkuk University, Seoul 05029, Republic of Korea
* Correspondence: yasmin.aldweik@riken.jp
† Current address: RIKEN Center for Sustainable Resource Science (CSRS), Yokohama, Kanagawa 230-0045, Japan.
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**Abstract:** Long non-coding RNAs (lncRNAs) are a class of regulatory RNAs that do not encode proteins but play essential roles in controlling gene expression at multiple levels, including chromatin modification, transcription, and RNA stability. LncRNAs have emerged as important regulators of antiviral immunity. These molecules function in both cis and trans to modulate chromatin states, guide transcription factors, scaffold signaling complexes, or act as decoys for regulatory proteins and RNAs. During viral infection, host lncRNAs are dynamically expressed and can either enhance antiviral responses or be hijacked by viruses to suppress immunity, promote replication, or facilitate latency. Virus-encoded lncRNAs also manipulate host gene expression to their advantage. Recent research has uncovered specific lncRNAs involved in regulating interferon signaling, cytokine production, antigen presentation, and immune cell differentiation. Concurrently, advances in computational biology have enabled the discovery and characterization of lncRNAs through methods such as RNA-seq analysis, transcript assembly, coding potential prediction, co-expression network analysis, and interaction modeling with proteins and RNAs. Functional inference is further supported by enrichment analyses and studies of conservation and localization. This mini review summarizes the current understanding of host and viral lncRNAs in antiviral defense and pathogenesis. It also highlights the translational potential of lncRNAs as biomarkers and therapeutic targets, discussing emerging strategies including CRISPR-based modulation, synthetic RNA therapeutics, and innovative delivery methods. Together, these findings underscore the critical role of lncRNAs in viral immunity and their promise in guiding novel approaches for diagnosing and treating viral infections.

**Keywords:** long non-coding RNAs (lncRNAs); viral immunity; computational analysis; lncRNAs tools; lncRNAs databases

## 1. Introduction

Long non-coding RNAs (lncRNAs) are an integral and expanding class of functional RNAs that are transcribed from the genome but do not encode proteins. Unlike messenger RNAs, which mainly serve as templates for protein synthesis, lncRNAs exert their biological functions through diverse mechanisms and interact with DNA, RNA, and proteins to regulate gene expression. They modulate gene expression both in *cis*, at or near their site of transcription, and in *trans;* at distant genomic locations. Through these interactions, lncRNAs function by guiding chromatin modifiers, serving as decoys for transcription factors, scaffolding molecular complexes, and affecting chromatin remodeling. These mechanisms reveal a paradigm shift in molecular biology, illustrating that regulatory complexity extends well beyond classical protein-coding genes [1,2]

LncRNAs can be categorized based on their genomic location and orientation relative to nearby protein-coding genes, reflecting their diverse origins and signifying their distinct roles in regulatory gene expression. Genomically, the main types include sense lncRNAs that overlap with coding sequences on the same strand, antisense lncRNAs transcribed from the opposite strand, intronic lncRNAs that arise from within introns, intergenic lncRNAs (often referred to as lincRNAs) located between genes, and bidirectional lncRNAs that originate from promoter regions but are transcribed in the opposite direction of an adjacent coding gene. Furthermore, lncRNAs are classified by their molecular functions based on how they exert their regulatory effects, and these classes are: decoy lncRNAs that bind and sequester regulatory molecules, preventing them from

interacting with their usual targets; scaffold lncRNAs assemble distinct protein components into functional complexes; guide lncRNAs recruit chromatin-modifying enzymes to specific loci; and enhancer lncRNAs enhance the transcription of nearby genes in cis machinery. These structural and functional classifications reflect lncRNAs' versatility, which reinforces their emerging roles in gene regulation and immune responses. However, these two classification arrangements often intersect; for example, a lincRNA (intergenic) might function as a scaffold or a guide [1–4].

In recent years, increasing numbers of studies have highlighted the important roles of lncRNAs in fine-tuning genomic activity, controlling the expression of protein-coding genes [5–7]. They participate in key regulatory processes such as dosage compensation, genomic imprinting, mRNA splicing, and cellular differentiation, and they contribute to developmental programming across cell types and tissues [2,8–12]. Despite these insights, the precise molecular mechanisms governing many lncRNAs remain incompletely understood, warranting further investigation.

In the context of viral infections, some lncRNAs enhance innate immune defenses by promoting the expression of interferon-stimulated genes, while others may facilitate viral replication or immune evasion by interfering with host antiviral pathways. Accumulating evidence from diverse viral models, including influenza, HIV, hepatitis viruses, and SARS-CoV-2, has highlighted a growing list of lncRNAs with virus-specific or broadly conserved functions [13–16]. This review summarizes the current understanding of lncRNAs in antiviral immunity and provides an overview of infection-associated lncRNAs and their proposed immunological roles. While computational tools contribute to the discovery and annotation of these non-coding transcripts, this review emphasizes the functional relevance of lncRNAs in shaping immune responses to viral infection and their potential as future biomarkers or therapeutic targets.

## 2. lncRNAs Modulating Innate Immune Responses

The immune system presents a compelling context in which to study lncRNA function, especially during infection, where rapid and dynamic gene regulation is essential [17]. Investigations into host lncRNAs during viral infections have revealed their capacity to modulate innate and adaptive immune responses, including interferon signaling, cytokine production, and immune cell differentiation [13,15,18,19]. These studies show that lncRNAs fine-tune antiviral immune responses. For instance, the lncRNA NRAV is rapidly downregulated during viral infection; its overexpression suppresses multiple interferon-stimulated genes (ISGs), thereby enhancing influenza A virus replication. Conversely, some lncRNAs are upregulated to boost immune responses. NEAT1, induced by influenza and herpesviruses, promotes cytokine expression by sequestering the transcriptional repressor SFPQ into paraspeckles, increasing the levels of IL-8 and other antiviral cytokines. In adaptive immunity, NeST (IFNG-AS1) enhances IFN-γ expression in $CD8^+$ T cells through epigenetic regulation, influencing both viral persistence and T cell differentiation [20,21]. These findings underscore the regulatory versatility of lncRNAs in shaping immune responses and maintaining immune homeostasis.

## 3. lncRNAs in Viral Infections

Viral infection activates host pattern recognition receptors (PRRs), like Toll-like receptors (TLRs), RIG-I and MDA5, which initiate type I interferon (IFN-I) signaling and stimulate the expression of antiviral genes [22]. An expanding body of evidence demonstrates that both host-encoded and virus-derived long non-coding RNAs (lncRNAs) play pivotal roles in modulating this antiviral response [13–16,23]. These lncRNAs can either enhance or suppress IFN pathways, modulate immune cell functions, and influence key aspects of viral dynamics, including replication and latency. Dysregulation or malfunction of lncRNAs has been increasingly associated with various human diseases, including infections [17]. In viral pathogenesis, some lncRNAs are activated to strengthen host defense, while others are designated by viruses to support replication and evade immune detection [14,24]. As such, lncRNAs are emerging not only as key regulators of host–pathogen interactions but also as promising candidates for diagnostic and therapeutic development. Several well-characterized lncRNAs play opposing roles in antiviral immunity. NEAT1, a nuclear retained lncRNA, is upregulated in response to viruses such as influenza, HIV, and SARS-CoV-2 [23,25,26]. Its induction promotes paraspeckle formation and enhances antiviral gene expression (e.g., IL-8) by sequestering repressors away from immune gene promoters [27]. In contrast, MALAT1, another nuclear speckle-associated lncRNA, acts as a negative regulator of type I interferon responses [28]. A 2020 PNAS study showed that viral infection downregulates MALAT1, and its loss enhances IRF3 activation and IFN-β production, ultimately reducing viral load. Similarly, Negative Regulator of Antiviral Response (NRAV) suppresses key interferon-stimulated genes (e.g., IFITM3, MxA), promoting viral replication, its silencing increases resistance to influenza A virus *in vitro* and *in vivo* [29]. All together further highlight the expanding

landscape of lncRNA-mediated immune regulation. The frequent publication of these discoveries in high-impact journals reflects the growing recognition of lncRNAs as central players in host–virus interactions. Given their dual roles in host defense and viral pathogenesis, lncRNAs are increasingly recognized as pivotal regulators of host–virus interactions.

Table 1 provides an overview of representative lncRNAs implicated in the regulation of viral infections, detailing their targets, mechanisms of action, and therapeutic potential. This synthesis highlights the emerging importance of lncRNAs in fine-tuning host–virus interactions and shaping antiviral immunity.

**Table 1.** Common lncRNAs with their targets, function, therapeutic potential, and associated viral conditions.

| lncRNA | Target(s) | Function/Effect | Therapeutic Potential | Condition | Ref. |
|---|---|---|---|---|---|
| lnc-ISG15, lnc-BST2/BISPR | ISG15, BST2/Tetherin | Upregulated by IFN and enhances expression of ISG20 and BST2; inhibits IAV replication | Yes, enhances innate antiviral response | Influenza A virus (IAV), hepatic viral infections. | [30,31] |
| lncRNA ISR | RIG-I signaling pathway | Reduces IAV replication via RIG-I-dependent signaling | Yes, inhibits IAV replication | IAV, SARS-CoV-2 | [32,33] |
| lnc-PAAN | Influenza A viral polymerase PB1 | Stabilizes PB1, promoting viral RNA synthesis and replication | No, promotes the virus, so it's not suitable as a therapy, but it can be targeted to block its action | IAV | [33,34] |
| lnc-MxA | IFN-β promoter (triplex formation) | Binds to the IFN-β promoter to inhibit transcription | No, suppresses antiviral IFN response, but it can be targeted to block its action | IAV | [35] |
| NRAV | MxA, IFITM3, IFIT– antiviral and ISG promoters (e.g., H3K4me3/H3K27me3) | – Downregulates ISGs, promoting replication of IAV and RSV<br>– Represses expression of ISGs, dampens antiviral response<br>– Represses ISGs via histone modification; ↑ influenza, HSV, SeV, MDRV | contradictory effects and several targets | Several Viral infections include SARS-CoV-2, IAV, RSV, HSV, SeV and MDRV | [21,36,37] |
| VILMIR | IFN-β signaling | Interferon-stimulated; knockdown reduced host IFN-β response magnitude | Yes, modulates IFN response | IAV, RSV, SARS-CoV-2 | [38,39] |
| NEAT1 | inflammasomes: NLRP3, NLRC4, AIM2, and SFPQ, IL-8 | – Potent activator amplifies inflammatory response; promotes pyroptosis and tissue damage in severe COVID-19<br>– Enhances IL-8 transcription by relocating SFPQ; promotes antiviral cytokine | Yes, by targeting NEAT1, it could mitigate 3nflammasome-driven pathology | IAV, SARS-CoV-2 | [23,25–27,40] |
| MALAT1 | NLRP3 inflammasome; NF-κB pathway | Immunomodulatory/suppressive—supports M1-like activity in mild COVID; may feedback-regulate NF-κB; contributes to milder inflammation | Yes, modulating MALAT1 may help regulate immune balance in mild disease | SARS-CoV-2, HIV, HBV | [28,29,40,41] |
| lncBST2/BISPR | BST2 | Upregulates BST2 (tetherin), an ISG; antiviral enhancer | Yes | HCV, HBV | [30,42] |
| lncRNA-CD244 | EZH2, IFN-γ, TNF-α | Recruits EZH2 to IFNG/TNFA loci, represses their expression in exhausted CD8+ T | Biomarker candidate | HBV | [43,44] |

**Table 1.** *Cont.*

| lncRNA | Target(s) | Function/Effect | Therapeutic Potential | Condition | Ref. |
|---|---|---|---|---|---|
| EGOT | PKR pathway, Multiple ISGs | – Promote replication of HCV by inhibiting innate immune pathways<br>– Suppresses ISG expression | Yes, Negative regulator | HCV, IAV, SFV, SARS-CoV-2 | [36,45] |
| LncRNA-ACOD1 | Metabolic enzyme IRG1 | Regulates the TCA cycle intermediate itaconate, limits excessive inflammation | Yes | HSV-1, VSV | [46,47] |
| Lethe | RelA (NF-κB subunit) | NF-κB decoy; inhibits inflammatory gene transcription | Yes, Anti-inflammatory role | HCV, CCHF | [48,49] |
| lnc-ISG20 | ISG20 | Enhances ISG20-mediated degradation of viral RNA | Yes | IAV | [50] |
| IVRPIE | IFNβ & ISG loci | Enhances IFNβ, IRF1, IFITs, MxA, ISG15; ↓ IAV replication | Yes | IAV | [51] |
| LUARIS (lncRNA#32) | ISG promoters (via hnRNPU/ATF2) | Increases ISGs; ↓ EMCV, HBV, HCV replication | Yes | EMCV, HBV, HCV | [52] |
| OASL-IT1 | IFNβ, Mx1, IFITM1 | Upregulates antiviral genes; inhibits ZIKV | Yes | Zika virus | [53] |
| HEAL | HIV promoter (recruits p300) | Enhances HIV transcription/reactivation | Yes | HIV, SARS-CoV-2 | [33,54] |

## 4. Computational Analysis of lncRNAs in Viral Immunity

The study of lncRNAs requires integrative computational pipelines that combine transcriptomics, structural prediction, and functional association methods. In this section, we summarize the main computational analysis steps with their goals. Table 2 lists these main lncRNAs analysis steps for Viral Immunity Research, along with their respective goal, tools, and Databases.

**Table 2.** lncRNAs analysis steps for Viral Immunity Research, along with their respective goal, tools, and Databases.

| Step | Goal | Tools/Databases | Viral Immunity-Specific Notes |
|---|---|---|---|
| 1. RNA-seq QC & Trimming | Ensure high-quality viral infection transcriptome data | FastQC, Trim Galore, Cutadapt | Include both infected and mock-infected samples; ensure multiple time points post-infection |
| 2. Read Mapping | Align reads to host genome ± viral genome | STAR, HISAT2, Bowtie2 | Build hybrid reference: host genome + viral genome to capture virus-derived RNAs |
| 3. Transcript Assembly | Reconstruct transcripts | StringTie, Scallop, Cufflinks | Capture novel lincRNAs induced only under viral infection |
| 4. LincRNA Filtering | Identify long intergenic ncRNAs | BEDTools, gffcompare, custom scripts | Filter > 200 nt, intergenic; exclude overlaps with viral coding regions |
| 5. Coding Potential Analysis | Exclude protein-coding RNAs | CPC2, CPAT, PLEK, CNCI | Helps distinguish host lncRNAs from viral transcripts with coding capacity |
| 6. Expression Quantification | Quantify lincRNA abundance | Salmon, Kallisto, FeatureCounts | Test differential expression in infected vs control; focus on immune response stages |
| 7. Differential Expression (DE) | Identify virus-responsive lincRNAs | DESeq2, edgeR, limma-voom | Cluster DE lncRNAs with viral load, cytokine expression, or defense gene activation |
| 8. Functional Association (cis/trans) | Predict function by proximity and co-expression | WGCNA, correlation with immune genes | Look for links to IFN-stimulated genes, PRRs, R genes, antiviral effectors |
| 9. Interaction Prediction | Predict RNA–RNA, RNA–protein binding | lncTar, RNAplex, catRAPID, RPISeq | Identify lnRNA (especially lincRNAs) that may sponge miRNAs targeting antiviral genes or bind viral proteins |
| 10. Subcellular Localization | Predict nuclear/cytosolic role | lncLocator, LncATLAS (for human), experimental FISH | Nuclear lncRNAs: chromatin regulation of immune genes; Cytosolic: antiviral RNA decay or translation control |
| 11. Enrichment & Pathway Mapping | Functional annotation of correlated targets | ClusterProfiler, gProfiler, ReactomePA | Enrichment for "response to virus", "interferon signaling", "RNA silencing" |
| 12. Visualization | Genome and network inspection | IGV, UCSC Genome Browser, Cytoscape | Map lncRNAs near known antiviral gene clusters or visualize immune regulatory networks |
| 13. Conservation & Structure | Identify conserved viral immunity lncRNAs | phastCons, RNAz, RNAfold | Check for conservation across species or viral infection models |

### *4.1. Data Acquisition and Preprocessing*

High-throughput RNA-seq, often from virus-infected vs control tissues or cells, provides the foundation for lncRNA discovery. Hybrid alignment strategies that map reads to both host and viral genomes enable the detection of host-derived lincRNAs as well as potential virus-encoded lncRNAs. Quality control and trimming tools (e.g., FastQC, Trim Galore) ensure data reliability [55,56].

### *4.2. Identification and Coding Potential Assessment*

Transcript assembly (e.g., StringTie, Cufflinks) is followed by filtering for intergenic, >200 nt transcripts. Computational tools such as CPC2, CPAT, and PLEK are applied to distinguish lncRNAs from protein-coding transcripts [57,58].

### *4.3. Expression Profiling and Differential Analysis*

Quantification with Salmon or Kallisto, and differential expression analysis using DESeq2 or edgeR, which identifies virus-responsive lncRNAs. Time-course analyses are especially valuable for capturing lincRNAs involved in distinct infection stages [59].

### *4.4. Functional Prediction*

Functional roles of lncRNAs in immune responses are often inferred through multiple computational and experimental approaches. Cis-regulatory functions are suggested when lincRNAs are located near key immune genes, such as NLRs in plants or ISGs in animals. Trans-regulatory roles are explored through co-expression network analyses, like Weighted Gene Co-expression Network Analysis (WGCNA), which link lincRNAs to broader immune pathways. Additionally, interaction predictions using tools such as lncTar, catRAPID, and RPISeq facilitate the identification of RNA–RNA and RNA–protein interactions, uncovering potential regulatory links with microRNAs, viral transcripts, or host immune factors [60,61].

### *4.5. Pathway and Immune Signature Enrichment*

Correlated gene sets undergo Gene Ontology (GO) and KEGG pathway analysis (ClusterProfiler, gProfiler), highlighting enrichment in antiviral defense processes, interferon signaling, and RNA silencing [62,63]. On the other hand, localization and conservation prediction tools (lncLocator, LncATLAS) suggest whether lincRNAs act in the nucleus (e.g., regulating chromatin accessibility of immune genes) or cytoplasm (e.g., controlling mRNA stability during infection). Structural conservation analysis, like phastCons, helps prioritize functionally important lincRNAs across species [64–66].

Furthermore, VirhostlncR (http://ciods.in/VirhostlncR/, accessed on 11$^{th}$ August 2025) offers a unified and comprehensive platform for exploring host lncRNAs modulated during viral infections. The database curates 2803 lncRNAs perturbed by 32 viral strains across diverse mammalian cell types, integrating detailed metadata such as viral strain, multiplicity of infection, infection duration, host cell type, and fold-change expression. Notably, it highlights 150 lncRNAs, including NEAT1, MALAT1, MEG3, DANCR, and PVT1, that are commonly modulated by multiple viruses, underscoring their potential as cross-viral regulatory signatures. By incorporating viral–human protein–protein interaction networks, particularly those involving transcription factors and regulatory complexes, such a database provides mechanistic insights into how viruses dynamically reprogram host lncRNA expression. This resource represents a critical tool for prioritizing lncRNAs for functional studies, facilitating the discovery of novel biomarkers, and advancing therapeutic strategies against viral infections [67].

Computational pipelines have uncovered lncRNAs that fine-tune immune signaling, act as competing endogenous RNAs (ceRNAs), or directly interact with viral proteins to suppress replication. In plants, virus-induced lncRNAs, particularly lincRNAs, modulate RNA silencing pathways, while in animals, lincRNAs regulate interferon responses and adaptive immunity. These insights provide new opportunities for antiviral strategies, including biomarker discovery and therapeutic targeting.

## 5. LncRNAs as Novel Avenues for Antiviral Development

LncRNAs, including lincRNAs, have emerged as crucial regulators of host–virus interactions, making them attractive targets for antiviral strategy development. Their ability to fine-tune immune signaling and directly modulate viral replication positions them as both biomarkers and therapeutic tools.

Figure 1 illustrates several therapeutic strategies.

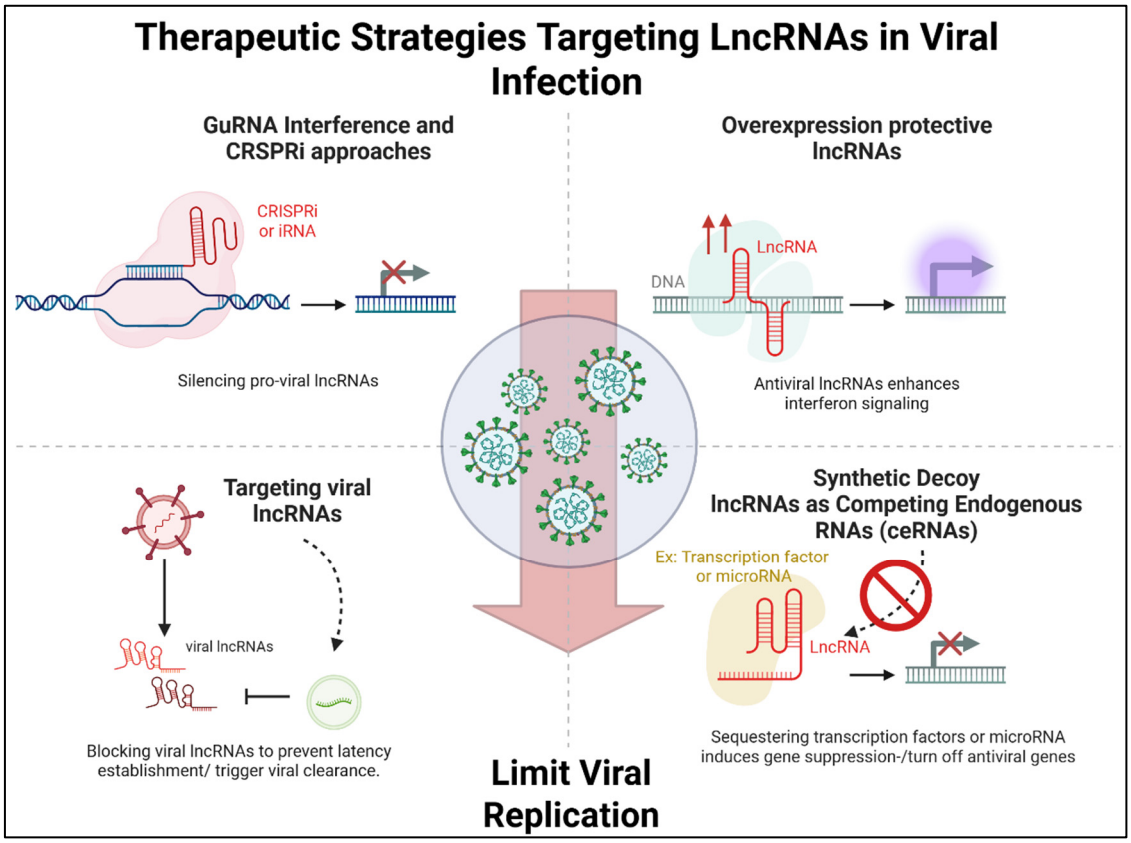


**Figure 1.** An illustration of some lncRNA therapeutic strategies to limit viral replication. Several approaches have been developed to modulate lncRNAs to limit viral replication. (i) GuRNA Interference and CRISPRi approaches can silence pro-viral lncRNAs, thereby reducing viral transcription and replication. (ii) Overexpression of protective lncRNAs enhances host antiviral responses, for example, by promoting interferon signaling, which helps restrict infection. (iii) Targeting viral lncRNAs directly blocks viral RNA functions, preventing the establishment of latency and promoting viral clearance. (iv) Synthetic decoy lncRNAs functioning as ceRNAs can sequester transcription factors or microRNAs, thus reprogramming gene expression toward antiviral states. Collectively, these strategies illustrate the dual roles of lncRNAs in infection: some act as pro-viral factors that support viral replication, while others function as antiviral regulators that strengthen host defenses. Therapeutic modulation of lncRNAs, therefore, represents a promising avenue for limiting viral replication and improving antiviral therapies.

LncRNAs are emerging as multifaceted agents in antiviral defense, with several exhibiting virus-responsive expression patterns that align with the stage and severity of infection. Some are induced early during interferon signaling, serving as potential indicators of the host's antiviral response strength [21,36–39,68]. Others display virus-specific expression signatures such as those selectively activated by influenza or SARS-CoV-2, allowing more precise discrimination of infection types [69]. Dysregulation of immune-related lncRNAs has also been linked to adverse clinical outcomes in viral diseases like hepatitis and HIV, underscoring their promise as prognostic biomarkers [26,41,54,70]. Therapeutically, targeting lncRNAs is gaining momentum through RNA interference and CRISPR-based approaches that silence pro-viral lncRNAs such as ACOD1 using siRNAs, antisense oligonucleotides (ASOs), or CRISPR interference (CRISPRi), thereby reducing viral replication [71,72]. Conversely, the overexpression or delivery of protective antiviral lncRNAs can bolster interferon signaling and suppress viral genome transcription, enhancing host defenses [73]. Small molecules that disrupt lncRNA–protein interactions represent another avenue to modulate immune pathways and improve antiviral responses [74,75]. As ceRNAs, lncRNAs can sponge microRNAs that would otherwise repress antiviral genes, and synthetic lncRNAs engineered as decoys may restore the expression of interferon-stimulated or effector genes [76,77]. Targeting virus-encoded lncRNAs such as EBV's sisRNAs or KSHV's PAN RNA offers promising strategies to disrupt latency and promote immune clearance [78,79]. Modulating host lncRNAs involved in viral persistence may also help reactivate latent viruses for elimination [79,80]. Genetic variations in lncRNA loci, including SNPs and epigenetic modifications, influence susceptibility to viral infections and disease progression, supporting the integration of lncRNA profiling into personalized antiviral medicine [81]. Baseline expression levels of specific lncRNAs could stratify patient responses to immune therapies. To enable these interventions, delivery technologies

such as lipid nanoparticles and plant-derived exosomes are being explored for efficient and biocompatible administration of synthetic lncRNAs, ASOs, or CRISPR modulators. Additionally, scalable platforms like *Nicotiana benthamiana* transient expression systems using pEAQ-HT vectors offer cost-effective solutions for RNA-based therapeutic production, broadening the accessibility of lncRNA-targeted antiviral strategies [9,72,82–85].

## 6. Conclusions

Long non-coding RNAs are increasingly recognized as critical regulators of antiviral immunity, orchestrating processes ranging from interferon signaling and cytokine production to viral replication and latency control. Advances in computational pipelines have enabled their systematic discovery, functional annotation, and integration into immune regulatory networks. Importantly, their dual roles in both enhancing host defense and being exploited by viruses underscore their therapeutic potential. By harnessing strategies such as silencing pro-viral lncRNAs, overexpressing protective transcripts, blocking lncRNA–protein interactions, or designing synthetic decoy lncRNAs, researchers can explore novel avenues for antiviral intervention. Together, these insights position lncRNAs as both biomarkers and therapeutic targets, offering promising opportunities for precision antiviral medicine.

In summary, lncRNAs represent a novel and versatile class of therapeutic targets and tools for antiviral intervention. Their dual capacity to either enhance host defense or be hijacked by viruses underscores the importance of systematic identification and functional validation. Integration of computational predictions with experimental validation will be essential for translating lncRNA biology into clinically viable antiviral strategies.

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