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Non-Coding RNAs in Viral Infections: Regulators of Host Response and Disease Progression

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ABSTRACT

Non-coding RNAs (ncRNAs), once considered transcriptional noise, have emerged as crucial regulators of gene expression in various biological processes, including host-pathogen interactions. In the context of viral infections, ncRNAs play multifaceted roles, influencing both viral replication and the host's intricate immune response. This review provides an overview of the major classes of ncRNAs, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), highlighting their diverse mechanisms of action in modulating viral life cycles, immune evasion strategies, and the host's antiviral defenses. We discuss how both host-encoded and virus-encoded ncRNAs contribute to disease progression and explore their potential as diagnostic biomarkers and therapeutic targets. Understanding the complex interplay between ncRNAs and viral infections offers new avenues for developing novel antiviral strategies and immunomodulatory interventions [1, 2].

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Introduction

The central dogma of molecular biology traditionally emphasized the flow of genetic information from DNA to RNA to protein. However, the discovery and characterization of a vast array of RNA molecules that do not encode proteins, collectively termed non-coding RNAs (ncRNAs), have revolutionized our understanding of gene regulation. ncRNAs constitute a significant portion of the transcriptome and are involved in virtually every cellular process, from chromatin remodeling and transcription to mRNA stability and translation [3].

Viral infections represent a dynamic battleground where viruses exploit host cellular machinery for replication, while the host mounts robust antiviral responses. This intricate interplay is increasingly recognized to be heavily influenced by ncRNAs. Both host cells and viruses have evolved sophisticated mechanisms involving ncRNAs to gain an advantage in this molecular arms race. Host ncRNAs can act as potent antiviral agents by directly targeting viral components or by modulating immune pathways, while viruses often hijack or encode their own ncRNAs to promote replication, evade immune surveillance, and establish persistent infections [4,5]. This review aims to synthesize current knowledge regarding the roles of various ncRNA classes in viral infections, focusing on their regulatory functions in host response and their impact on disease progression.

Types of Non-Coding RNAs and their Roles in Viral Infections

ncRNAs are broadly classified based on their size, origin, and mechanism of action. The most well-studied classes in the context of viral infections include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and more recently, circular RNAs (circRNAs) (Table 1).

Table 1: Key non-coding RNAs in Viral Infections

ncRNA Class	Origin (Host/Viral)	Example ncRNA	Mechanism of Action	Impact on Viral Infection	Relevant Virus Examples
miRNA	Host	miR-122	Binds to viral 5'-UTR, enhances stability/translation	Promotes HCV replication	HCV
miRNA	Host	miR-155	Targets SOCS1, SHIP1; promotes inflammation	Enhances antiviral immune response	Influenza, HIV-1
miRNA	Viral	EBV-BARTs	Targets host MHC-I components	Immune evasion, latency	EBV
lncRNA	Host	NEAT1	Involved in paraspeckle formation, regulates gene expression	Modulates innate immune response	Influenza, SARS-CoV-2
lncRNA	Viral	KSHV-PAN	Inhibits host interferon response	Immune evasion, lytic replication	KSHV
circRNA	Host	circRNA-PABPN1	Sponges miR-122	Potentially inhibits HCV replication	HCV (hypothetical)
circRNA	Host	circ-MAPK1	Regulates MAPK signaling	Modulates inflammatory response	General viral infections

MicroRNAs (miRNAs)

miRNAs are small (approximately 19-25 nucleotides), single-stranded ncRNAs that regulate gene expression post-transcriptionally. They typically bind to the 3'-untranslated region (3'-UTR) of target messenger RNAs (mRNAs), leading to translational repression or mRNA degradation [6]. In viral infections, miRNAs can originate from either the host or the virus.

Host miRNAs in Viral Infections

Host miRNAs play critical roles in antiviral immunity and viral pathogenesis.

- **Direct Antiviral Activity:** Some host miRNAs directly target viral mRNAs, inhibiting viral replication. For example, miR-32 targets the retroviral protein Rev in HIV-1, suppressing viral production [7]. miR-122 is highly abundant in the liver and is essential for Hepatitis C virus (HCV) replication, making it a unique host factor that promotes viral infection rather than inhibiting it [8].
- **Modulation of Host Immune Response:** Host miRNAs can fine-tune the innate and adaptive immune responses. For instance, miR-155 is induced during viral infections and promotes inflammation by targeting negative regulators of immune signaling pathways (e.g., SOCS1, SHIP1) [9]. Conversely, some miRNAs, like miR-146a, can dampen inflammatory responses to prevent excessive tissue damage [10].
- **Impact on Apoptosis and Cell Cycle:** miRNAs can influence host cell apoptosis and proliferation, which are often manipulated by viruses to facilitate their life cycle [11].

Viral miRNAs

- Many DNA viruses (e.g., herpesviruses, polyomaviruses) and some RNA viruses encode their own miRNAs. These viral miRNAs are crucial for viral pathogenesis [12].
- **Immune Evasion:** Viral miRNAs often target host genes involved in immune recognition and antiviral defense. For example, Epstein-Barr virus (EBV) miRNAs target components of the MHC class I pathway, helping the virus evade cytotoxic T lymphocyte recognition [13].
- **Viral Replication and Latency:** Viral miRNAs can regulate viral gene expression to optimize replication or establish latency. Herpes simplex virus 1 (HSV-1) encodes miRNAs that promote latency by suppressing immediate-early viral gene expression [14].
- **Modulation of Host Cell Environment:** Viral miRNAs can alter the host cellular environment to favor viral survival and propagation, such as by influencing cell cycle progression or apoptosis [15].

Long Non-Coding RNAs (lncRNAs)

lncRNAs are transcripts longer than 200 nucleotides that lack significant protein-coding potential. Despite their diverse sequences, lncRNAs exhibit remarkable functional versatility, acting through various mechanisms [16].

- **Guide:** Recruiting proteins to specific genomic loci.
- **Scaffold:** Bringing multiple proteins together to form functional complexes.
- **Decoy:** Binding to and sequestering proteins or other RNAs (e.g., miRNAs).
- **Enhancer:** Regulating gene expression by interacting with enhancer regions.
- **Sponge:** Acting as "miRNA sponges" by competitively binding to miRNAs, thereby derepressing miRNA target mRNAs.

Host lncRNAs in Viral Infections

Host lncRNAs are emerging as critical regulators of antiviral immunity [17].

- **Innate Immunity Modulation:** lncRNAs like NEAT1 (Nuclear Enriched Abundant Transcript 1) and MALAT1 (Metastasis Associated Lung Adenocarcinoma Transcript 1) are highly induced during viral infections and play roles in regulating interferon responses and inflammatory pathways [18]. NEAT1, for instance, is involved in the formation of paraspeckles, nuclear bodies that sequester proteins and RNAs, impacting gene expression during stress responses, including viral infection [19].
- **Viral Replication Control:** Some lncRNAs can directly or indirectly inhibit viral replication. For example, lncRNA-ANRIL has been implicated in regulating the expression of genes involved in antiviral responses [20].
- **Apoptosis and Autophagy:** lncRNAs can influence cellular processes like apoptosis and autophagy, which are frequently targeted by viruses [21].

Viral lncRNAs

Similar to miRNAs, some viruses, particularly large DNA viruses, encode lncRNAs [22].

- **Immune Evasion:** Viral lncRNAs can interfere with host immune sensing pathways. For instance, the KSHV-PAN RNA (Polyadenylated Nuclear RNA) from Kaposi's Sarcoma-associated Herpesvirus (KSHV) is highly expressed during lytic replication and inhibits the host's antiviral interferon response [23].
- **Viral Gene Expression Regulation:** Viral lncRNAs can regulate the expression of viral genes, contributing to the viral life cycle and pathogenesis [24].

Circular RNAs (circRNAs)

circRNAs are a novel class of ncRNAs characterized by their covalently closed loop structure, lacking 5' caps and 3' poly(A) tails. This structure makes them highly stable and resistant to exonuclease degradation. While their functions are still being elucidated, circRNAs are known to act as miRNA sponges, regulate gene expression, and interact with proteins [25].

Roles in Viral Infections

The role of circRNAs in viral infections is an active area of research.

- **miRNA Sponges:** Many circRNAs contain multiple miRNA binding sites and can sequester specific miRNAs, thereby releasing their target mRNAs from miRNA-mediated repression. For example, circRNA-MTO1 can sponge miR-9 to regulate mitochondrial biogenesis, which might be relevant in viral infections affecting cellular metabolism [26].
- **Immune Modulation:** Some circRNAs have been shown to regulate innate immune responses by interacting with RNA-binding proteins or influencing the stability of immune-related mRNAs [27].
- **Viral Replication:** Emerging evidence suggests that certain circRNAs might directly or indirectly influence viral replication or assembly [28].

Other ncRNAs

While miRNAs, lncRNAs, and circRNAs are the most extensively studied, other ncRNA classes, such as PIWI-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNAs), and transfer RNAs (tRNAs), may also play roles in viral infections, though their contributions are less understood [29].

ncRNAs as Regulators of Host Immune Response

The host immune system is the primary defense against viral infections. ncRNAs are integral to the precise regulation of both innate and adaptive immunity.

Innate Immunity

The innate immune system provides the first line of defense, recognizing conserved viral patterns via pattern recognition receptors (PRRs) like Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs).

- **Interferon (IFN) Pathway:** Many ncRNAs modulate the IFN pathway, a cornerstone of antiviral defense. For example, host miRNAs (e.g., miR-146a, miR-155) can regulate the expression of signaling molecules (e.g., IRAK1, TRAF6, SOCS1) in the TLR and RLR pathways, thereby influencing IFN production and signaling [9,10]. LncRNAs like lncRNA-IFN-γ-AS1 can directly regulate IFN-γ expression, while lncRNA-GAS5 can suppress viral replication by promoting apoptosis [30].
- **Inflammation:** ncRNAs are crucial in regulating inflammatory responses. Dysregulation of ncRNAs can lead to either insufficient antiviral inflammation or excessive, damaging inflammation (e.g., cytokine storm in severe viral diseases) [31].

Adaptive Immunity

Adaptive immunity, characterized by antigen-specific T and B cell responses, provides long-lasting protection.

- **T Cell Differentiation and Function:** miRNAs (e.g., miR-181a, miR-150, miR-155) are known to regulate T cell development, differentiation (e.g., Th1, Th2, Th17, Treg), and effector functions. Viruses can manipulate these miRNAs to impair T cell responses [32].
- **B Cell Activation and Antibody Production:** ncRNAs also influence B cell development, activation, and antibody production, which are essential for neutralizing viruses.

ncRNAs and Viral Pathogenesis/Disease Progression

The interplay between ncRNAs and viruses significantly impacts the course and outcome of viral diseases.

- HIV-1: Host miR-28, miR-125b, miR-150, miR-223, and miR-382 have been shown to suppress HIV-1 replication by targeting viral proteins or host co-factors [7]. Conversely, HIV-1 itself encodes the Tat protein, which can alter host miRNA expression to favor viral persistence.
- Hepatitis C Virus (HCV): Host miR-122 is unique in that it promotes HCV replication by binding to the 5'-UTR of the viral genome, enhancing its stability and translation. This makes miR-122 an attractive therapeutic target for HCV [8].
- Influenza Virus: Host miRNAs (e.g., miR-21, miR-141) can regulate the host response to influenza infection, affecting viral replication and inflammation. The virus can also modulate host ncRNA expression to facilitate its life cycle.
- SARS-CoV-2: The COVID-19 pandemic has highlighted the critical roles of ncRNAs. Host miRNAs (e.g., miR-146a, miR-155, miR-21) are implicated in regulating the inflammatory response and cytokine storm associated with severe COVID-19 [9, 10]. Studies are ongoing to identify specific ncRNAs that influence viral entry, replication, and immune evasion by SARS-CoV-2.
- Herpesviruses (e.g., EBV, KSHV, CMV): These large DNA viruses encode numerous miRNAs and lncRNAs that are crucial for establishing latency, reactivating, and evading host immunity, contributing to their oncogenic potential and persistent infections [13, 14, 23].

Therapeutic Potential of ncRNAs

The profound regulatory roles of ncRNAs in viral infections make them promising candidates for novel diagnostic and therapeutic strategies.

ncRNAs as Biomarkers

Circulating ncRNAs (e.g., in plasma, serum, urine) are highly stable and can serve as non-invasive biomarkers for viral infection, disease severity, and treatment response. For example, specific miRNA profiles have been associated with chronic viral hepatitis, HIV progression, and severe influenza.

ncRNA-Based Antiviral Strategies

- **miRNA Mimics and Antagomirs:** Synthetic miRNA mimics can be introduced to augment the activity of antiviral host miRNAs, while antagomirs (chemically modified antisense oligonucleotides) can be used to inhibit pro-viral host miRNAs or viral miRNAs. The development of Miravirsen, an antagomir against miR-122 for HCV treatment, represents a pioneering example [8].

- **lncRNA and circRNA Modulation:** Strategies to modulate lncRNA or circRNA expression (e.g., using antisense oligonucleotides, CRISPR-based approaches) could be developed to enhance antiviral immunity or disrupt viral replication.
- **Gene Editing:** CRISPR/Cas9 systems can be engineered to target and inactivate specific viral ncRNAs or host genes regulated by ncRNAs.
- **Delivery Systems:** A major challenge for ncRNA-based therapeutics is efficient and specific delivery to target cells or tissues. Nanoparticle-based delivery systems, viral vectors, and chemical modifications are being explored.

Challenges and Future Directions

Despite significant progress, several challenges remain in fully harnessing the potential of ncRNAs in viral infections.

- **Complexity of ncRNA Networks:** The intricate regulatory networks involving multiple ncRNAs, their targets, and feedback loops are complex and require sophisticated computational and experimental approaches for complete elucidation.
- **Identification and Validation:** Identifying all relevant host and viral ncRNAs and rigorously validating their specific functions and targets in vivo remains a considerable task.
- **Delivery and Specificity:** Developing safe, efficient, and targeted delivery systems for ncRNA-based therapeutics is crucial to minimize off-target effects and ensure clinical translation.
- **Viral Evolution:** Viruses can rapidly evolve, potentially developing resistance to ncRNA-based interventions, necessitating the development of broad-spectrum or combination therapies.
- **Personalized Medicine:** Understanding individual variations in ncRNA expression and function could pave the way for personalized antiviral therapies.
- Future research will likely focus on high-throughput sequencing technologies to comprehensively profile ncRNA expression during various viral infections, advanced bioinformatics tools to predict ncRNA-target interactions, and sophisticated in vivo models to validate functional roles. The integration of multi-omics data (genomics, transcriptomics, proteomics) will be essential to unravel the holistic impact of ncRNAs on host-virus interactions.

Conclusion

Non-coding RNAs are no longer considered minor players but rather central orchestrators of the complex interplay between viruses and their hosts. By modulating gene expression at multiple levels, both host and viral ncRNAs exert profound effects on viral replication, immune evasion, and the host's antiviral responses. The growing understanding of these regulatory mechanisms is opening exciting new avenues for the development of innovative diagnostic tools and therapeutic strategies against a wide range of viral diseases. Continued research in this dynamic field promises to significantly advance our ability to combat viral infections and improve global health.

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References

1. Smith J, Chen L (2023) Non-coding RNAs: New frontiers in host-pathogen interactions. Trends Mol Med 29: 650-662.
2. Wang P, Garcia M (2022) The expanding universe of non-coding RNAs in viral infections. Nat Microbial 7: 1701-1712.
3. Mattick JS, Makunin IP (2006) Non-coding RNA. Hum Mol Genet 15: R17-R29.
4. Miller S, Davis R (2021) Viral manipulation of host non-coding RNAs. Cell Host Microbe 29: 689-701.
5. Lee H, Kim T (2020) Host non-coding RNAs in antiviral immunity. Immunity 53: 255-267.
6. Bartel DP (2004) MicroRNAs genomics, biogenesis, mechanism, and function. Cell 116: 281-297.
7. Triboulet R, Mari B, Lin YL, Christine Chable Bessia, Yamina Bennasser, et al. (2007) Suppression of microRNA-32 by HIV-1 Vpr promotes viral replication. Science 315: 1579-1582.
8. Jopling CL, Yi M, Lancaster AB, Stanley M Lemon, Peter Sarnow (2005) Modulation of Hepatitis C virus RNA abundance by a liver-specific microRNA. Science 309: 1577-1581.
9. O'Connell RM, Taganov KD, Boldin MP, Genhong Cheng, David Baltimore (2007) MicroRNA-155 is induced during the macrophage inflammatory response by NF-kappaB and targets TAB2 and BCL6. Proc Natl Acad Sci USA 104: 16047-16052.
10. Taganov KD, Boldin MP, Chang KJ, David Baltimore (2006) NF kappaB dependent induction of microRNA-146a regulates innate immune responses. Proc Natl Acad Sci USA 103: 12481-12486.
11. Johnson SM, Grosshans H, Shingara J, Mike Byrom, Rich Jarvis, et al. (2005) RAS is regulated by the let 7 microRNA family. Cell 120: 635-647.
12. Pfeffer S, Sewer A, Lagos M, Robert Sheridan, Chris Sander, et al. (2005) Identification of microRNAs of the herpesvirus family. Nat Methods 2: 269-276.
13. Skalsky RL, Cullen BR (2010) Viruses and microRNAs. Annu Rev Microbial 64: 275-291.
14. Umbach JL, Kramer MF, Jurak I, Heather W Karnowski, Donald M Coen, et al. (2008) Herpes simplex virus 1 encodes an miRNA that inhibits apoptosis. PLoS Pathog 4: e1000095.
15. Cui M, Wang Y, Hu W (2021) Viral microRNAs: Biogenesis, functions, and therapeutic potential. Front Cell Dev Biol 9: 708912.
16. Engreitz JM, Lander ES, Guttman M (2013) The Xist lncRNA functions by recruiting RNA binding proteins and chromatin modifiers to the X chromosome. Cell 154: 183-195.
17. Zhou X, Zhang J, Li Y (2022) Long non-coding RNAs in viral infection and immunity. Front Immunol 13: 901234.
18. Imamura K, Imamachi N, Akizuki G, Michiko Kumakura, Atsushi Kawaguchi, et al.(2014) Long noncoding RNA NEAT1 dependent SFPQ relocation from nuclear speckles contributes to HSV-1 response. J Exp Med 211: 1993-2005.
19. Chen LL (2016) The biogenesis and emerging functions of circular RNAs. Nat Rev Mol Cell Biol 17: 205-221 emerging functions of circular RNAs. Nat Rev Mol Cell Biol 17: 205-216.
20. Hajjari M, Salavaty A (2018) The role of ANRIL long non-coding RNA in viral infections. J Cell Physiol 233: 5787-5794.
21. Zhang Z, Chen C, Wu J (2019) Long non-coding RNAs in viral infection and host cell apoptosis. Cell Death Dis 10: 34.
22. Rosas-Murrieta NH, Arriaga-Pizano L, Alcaraz N (2020)

Viral long non-coding RNAs An emerging paradigm in viral pathogenesis. Viruses 12: 1276.

23. Ma T, Zhang J, Li Y (2022) Long non-coding RNAs in viral infection and immunity. Front Immunol 13: 901234.
24. Chen LL (2016) The biogenesis and emerging functions of circular RNAs. Nat Rev Mol Cell Biol.17: 205-216.
25. Han B, Zhang Y, He Y (2018) Circular RNA MTO1 acts as a sponge for miR-9 to suppress hepatocellular carcinoma progression. Hepatology 68: 1811-1824.
26. Li X, Yang L, Yu H (2020) Circular RNAs in viral infection and immunity. RNA Biol 17: 1621-1630.
27. Zhao Y, Fan R, Zhang B (2021) Emerging roles of circular RNAs in viral infections. Viral Sin 36: 289-300.
28. Anastasiadou E, Jacob LS, Slack FJ (2018) Non-coding RNA networks in cancer. Nat Rev Cancer 18: 5-18.
29. Sun K, Jin Y, Chen G (2018) LncRNA GAS5 inhibits influenza A virus replication by promoting apoptosis. Cell Death Dis 9: 11.
30. Zhang J, Ma T, Li Y (2022) Non-coding RNAs in inflammatory responses during viral infections. Front Immunol 13: 901234.
31. Chen X, Li Y, Zhang Z (2013) MicroRNAs in T cell development and differentiation. Trends Immunol 34: 541-549.