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The Regulatory Role of Long Non-Coding RNAs in Modulating Immune Responses During Chronic Infections: Mechanisms and Therapeutic Potential

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ABSTRACT
Long non-coding RNAs (lncRNAs) are emerging as critical regulators of immune responses, particularly in the context of chronic infections. These non-coding transcripts influence key immunological pathways by modulating gene expression, cytokine signaling, and immune cell differentiation. This review explores the mechanisms by which lncRNAs regulate immune homeostasis during chronic viral and bacterial infections, highlighting their dual role in host defense and immune evasion. We also discuss the potential of lncRNA-based therapeutic interventions, including targeted RNA therapeutics and CRISPR-based gene regulation, for managing persistent infections such as HIV, tuberculosis, and hepatitis B.

1. INTRODUCTION

Chronic infections pose a significant challenge to immune regulation, often leading to persistent inflammation and immune exhaustion. While protein-coding genes have been extensively studied in immune regulation, the role of long non-coding RNAs (lncRNAs) in this process remains underexplored. lncRNAs, defined as transcripts longer than 200 nucleotides without protein-coding potential, have been implicated in various biological processes, including immune modulation. Their ability to interact with DNA, RNA, and proteins enables them to fine-tune immune responses. Understanding how lncRNAs contribute to immune regulation during chronic infections can provide insights into novel therapeutic strategies.

2. Mechanisms of lncRNA-Mediated Immune Regulation in Chronic Infections

2.1 Epigenetic and Transcriptional Regulation

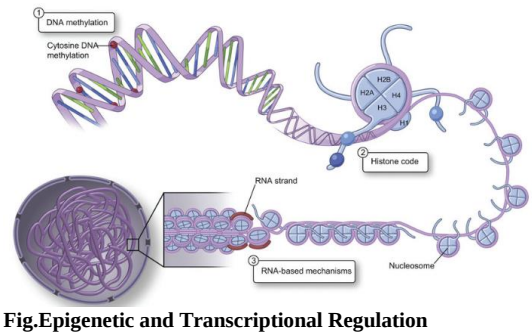

Fig.Epigenetic and Transcriptional Regulation

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lncRNAs modulate immune responses by altering chromatin structure and transcription factor recruitment. Notable examples include:

- **LncRNA NEAT1**, which facilitates nuclear body formation and enhances the transcription of antiviral genes.
- **LncRNA MALAT1**, which suppresses inflammatory responses by interacting with polycomb repressive complexes.
- **LncRNA Tmevpg1**, which promotes Th1 cell differentiation by enhancing IFN-γ expression.
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LncRNA	Function in Immune Response	Associated Chronic Infection
NEAT1	Enhances antiviral gene expression	HIV, HBV
MALAT1	Suppresses inflammation	Tuberculosis, Chronic Viral Infections
Tmevpg1	Promotes Th1 differentiation	Hepatitis C, TB

2.2 Post-Transcriptional Regulation and Cytokine Modulation

lncRNAs influence immune homeostasis by regulating mRNA stability and microRNA (miRNA) interactions. Mechanisms include:

- **Sponging miRNAs:** lncRNAs such as lncRNA-Cox2 act as competing endogenous RNAs (ceRNAs), preventing miRNAs from degrading key immune transcripts.
- **Modulating Cytokine Expression:** LncRNA IFNG-AS1 enhances IFN-γ production, whereas lncRNA PACER regulates NF-κB-mediated inflammation.

3. The Impact of lncRNAs on Chronic Infections

3.1 Viral Infections: HIV, HBV, and HCV

Chronic viral infections exploit lncRNAs to evade immune surveillance:

- **HIV:** LncRNA NRON suppresses HIV transcription by sequestering nuclear factor of activated T cells (NFAT), limiting viral replication.
- **HBV:** LncRNA HULC enhances HBV persistence by modulating host metabolism and immune evasion pathways.
- **HCV:** LncRNA IL7-AS1 regulates T cell exhaustion by influencing PD-1 expression.

3.2 Bacterial Infections: Tuberculosis and Helicobacter pylori

- **M. tuberculosis** exploits lncRNAs such as MSTRG.51018.2 to suppress macrophage activation.
- **H. pylori** infection alters lncRNA MEG3 expression, leading to immune evasion and chronic gastritis.

4. Therapeutic Potential of lncRNA-Targeted Interventions

4.1 RNA-Based Therapeutics

- **Antisense Oligonucleotides (ASOs):** Targeting pathogenic lncRNAs for degradation.
- **RNA Interference (RNAi):** Modulating lncRNA expression to restore immune function.

4.2 CRISPR/Cas9-Mediated Gene Regulation

- **CRISPR-based transcriptional activation or repression of key lncRNAs** offers precise therapeutic interventions for chronic infections.

4.3 Challenges and Future Directions

- **Delivery Mechanisms:** Efficient delivery of lncRNA-targeting molecules remains a hurdle.
- **Off-Target Effects:** Ensuring specificity to avoid unintended immune alterations.
- **Clinical Translation:** Bridging experimental findings to clinical applications requires extensive validation.

5. CONCLUSION

Long non-coding RNAs (lncRNAs) have emerged as key regulators of immune responses, influencing transcription, cytokine signaling, and immune cell differentiation. Their role in modulating innate and adaptive immunity underscores their significance in chronic infections, where immune dysregulation often leads to persistent pathogen survival and disease progression. By acting as molecular scaffolds, decoys, or enhancers, lncRNAs fine-tune gene expression, shaping immune homeostasis and inflammatory responses. Understanding the precise mechanisms through which lncRNAs regulate immune function could pave the way for novel therapeutic strategies. Targeting specific lncRNAs may offer new avenues for modulating immune responses in infections such as tuberculosis, HIV, and hepatitis. Future research should focus on integrating multi-omics approaches to map lncRNA interactions, identifying key regulatory circuits, and developing RNA-based therapies to harness their potential for immune modulation and disease intervention.

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