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Commentary

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Commentary on "transcription regulation by long non-coding RNAs: mechanisms and disease relevance"

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Abstract

The review article "Transcription regulation by long non-coding RNAs: mechanisms and disease relevance" by Jorge Ferrer and Nadya Dimitrova, published in *Nature Reviews Molecular Cell Biology*, explores the complex roles of long non-coding RNAs (lncRNAs) in gene transcription regulation. The authors discuss various mechanisms by which lncRNAs influence transcription, including their functions as cis-regulatory elements, transcription stabilizers, and scaffolds for regulatory complexes. The review also highlights the potential of lncRNAs in disease contexts and their therapeutic applications. However, it is essential to consider the potential limitations in current lncRNA research.

Keywords: lncRNA, transcription regulation, cis regulation, trans regulation, disease

Mechanistic insights of lncRNA functions

The review article by Ferrer and Dimitrova[1], published in *Nature Reviews Molecular Cell Biology*, provides a comprehensive overview of the emerging roles of lncRNAs in transcription regulation. It covers a wide range of lncRNA functions, from local cis-acting roles to broader trans-regulatory effects, providing a

detailed understanding of their regulatory potential. By addressing various mechanisms and providing specific examples, the review successfully illustrates the complexity and versatility of lncRNAs in gene regulation such as transcription activation, stabilization, and allele-specific repression. For example, the authors describe how lncRNAs like *XIST* control X-chromosome inactivation, providing a clear example of how lncRNAs can regulate gene expression on a chromosomal scale, while others, like imprinted lncRNAs, direct allele-specific repression[2,3]. The authors also describe how lncRNAs like *lincRNA-p21* and *Maenli* contribute to local activation of gene transcription through distinct mechanisms[4,5].

The discussion on specific mechanisms such as scaffold functions and transcriptional condensates elucidates the formation of RNA-protein complexes and the role of lncRNAs in chromatin organization. For instance, they discuss how lncRNA *HOTTIP* serves as scaffolds for regulatory complexes (MLL1 and WDR5), bringing chromatin-modifying enzymes into proximity with their target gene (*HOXA*)[6]. These details help elucidate how lncRNAs exert their regulatory effects, making complex concepts accessible to readers. By citing experimental studies that elucidate the roles of lncRNAs, such as defects in the transcription-stabilizing lncRNA CHASERR leading to developmental defects[7], readers can delve deeper into specific studies to explore the topic further.

LncRNAs in human diseases

The section on the involvement of lncRNAs in human diseases and their therapeutic potential is highly relevant and timely, considering the crucial regulatory roles of lncRNAs in various biological processes and in human diseases. The growing interest in lncRNAs in biomedical research is fueled by advancements in detection methods, which have led to the identification of a significantly higher number of lncRNAs - now exceeding the total number of protein-coding genes[8]. These improvements in sensitivity and specificity have expanded our understanding of lncRNA functions and their distribution across different cellular compartments, including the nucleus, nucleolus, cytoplasm, and mitochondria[9]. LncRNAs are primarily transcribed by RNA polymerase II, similar to protein-coding genes, and often undergo post-transcriptional modifications that further modulate their functions[10]. The localization of lncRNAs in various cellular compartments suggests that they may play diverse roles in gene regulation, chromatin organization, and cellular signaling, impacting a wide range of physiological and pathological processes[10].

A growing body of evidence suggests a mechanistic link between lncRNA dysregulation and the onset and progression of numerous human diseases, including cancer, cardiovascular disorders, and neurological conditions. For instance, in cancer, lncRNAs like *PVT1* have been implicated in tumorigenesis by stabilizing oncogenic mRNAs such as *MYC*, thereby promoting tumor growth and progression[11]. Elevated levels of *ANRIL, HOTAIR, LINC00641, LINC00565, MALAT1,* and *SAMMSON*, along with decreased *GAS5*, have been identified as blood biomarkers that could enhance early detection and improve outcomes in glioblastoma multiforme, an aggressive and fatal brain tumor[12]. Similarly, the lncRNA *Hdnr* has been associated with cardiac malformations through its influence on *Hand2* expression[13]. These examples underscore the translational potential of lncRNA research, particularly in identifying novel therapeutic targets and developing new diagnostic biomarkers. The dysregulation of lncRNAs in various diseases positions them as promising candidates for therapeutic intervention. Targeting specific lncRNAs could offer a novel approach to treating diseases where traditional therapies have been ineffective. Additionally, the ability of lncRNAs to serve as biomarkers may enhance the early detection and diagnosis of diseases, ultimately improving patient outcomes.

Limitations in current lncRNA research

Although advanced methodologies, such as single-cell RNA sequencing, have revealed the complexity and heterogeneity of lncRNA expression[14], low expression levels of lncRNAs make them difficult to detect and

quantify accurately. Current RNA sequencing technologies might miss these low-abundance transcripts. While single-cell RNA sequencing offers high resolution, it often suffers from dropouts where some transcripts are not detected in every cell, leading to incomplete representation of lncRNA expression profiles.

Advanced CRISPR methods, including CRISPR interference (CRISPRi) and CRISPR activation (CRISPRa), have facilitated the identification of numerous lncRNAs with critical regulatory functions[15]. However, the limitations of CRISPR in identifying critical regulatory functions of lncRNAs include off-target effects, incomplete knockouts, targeting difficulties in repetitive regions, complexity of lncRNA functions, compensatory cellular mechanisms, and the inability to capture interactions with proteins, other RNAs, or chromatin modifications.

In addition, a significant proportion of identified lncRNAs lack functional annotation. Many lncRNAs are classified based on expression data alone without experimental validation, leading to uncertainty about their biological roles. Furthermore, functional redundancy among lncRNAs supports the robustness of gene regulatory networks, maintaining stable gene expression even when certain lncRNAs are deleted or mutated[16]. Moreover, investigating the evolutionary origins and conservation of lncRNAs across species provides valuable insights into their functional significance.

However, the review article by Ferrer and Dimitrova[1] does not address these current limitations in lncRNA research, highlighting the importance of considering these challenges as the field continues to advance.

Conclusion

The review by Ferrer and Dimitrova provides an excellent foundation for understanding the diverse roles of lncRNAs in transcription regulation. The article effectively highlights the significance of lncRNAs; however, the readers should be aware of potential limitations in current lncRNA research. Future research should continue to explore the multifaceted roles of lncRNAs, leveraging advanced technologies and considering evolutionary and functional redundancy aspects to fully elucidate their contributions to gene regulation and disease.

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Authors' contributions

The author contributed solely to the article.

Availability of data and materials

Not applicable.

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Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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