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REVIEW

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The role of long non-coding RNAs (lncRNAs) in gene regulation and biotechnology

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ABSTRACT

Long noncoding RNAs (lncRNAs) are a class of RNA molecules that play crucial regulatory roles in gene expression. Unlike protein-coding RNAs, lncRNAs influence gene expression at multiple levels, including chromatin modification, transcription, and post-transcriptional regulation. These regulatory functions are essential for various biological processes, such as development, disease, and cellular homeostasis. LncRNAs have diverse applications in biotechnology. For instance, targeting lncRNAs offers promising therapeutic strategies for treating diseases caused by aberrant gene expression. Additionally, lncRNAs can serve as valuable biomarkers for early disease detection and monitoring, improving patient outcomes. In agriculture, manipulating lncRNAs can enhance crop traits, such as disease resistance and stress tolerance, contributing to improved agricultural productivity and sustainability. Despite significant progress in lncRNA research, challenges remain in understanding their specific functions and developing effective applications. Continued research is essential to fully harness the potential of lncRNAs and advance our understanding of gene regulation and its implications for human health and agriculture. By addressing these challenges and exploring new avenues of research, we can unlock the full potential of lncRNAs to benefit society.

KEYWORDS

Gene expression regulation; Therapeutic strategies; Biomarkers; Agricultural biotechnology

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Introduction

Industrial biotechnology is revolutionizing multiple sectors, Long non-coding RNAs (lncRNAs) are a class of RNA molecules that do not encode proteins and were first identified during large-scale genome sequencing in the early 2000s. While initially considered non-functional genomic regions, it is now recognized that lncRNAs play vital roles in regulating gene expression [1]. Typically longer than 200 nucleotides, they are distinct from shorter non-coding RNAs like microRNAs. Although they do not produce proteins, lncRNAs participate in crucial cellular processes, including chromatin remodeling, transcription, RNA splicing, and post-transcriptional regulation. By interacting with DNA, RNA, and proteins, lncRNAs can influence gene expression by either promoting or repressing it [2]. For example, they can guide chromatin- modifying complexes to specific genomic regions, altering gene expression in a spatially and temporally controlled manner. This regulatory role has made lncRNAs a major focus of research in areas such as developmental biology, cancer, and genetic disorders [3]. In biotechnology, lncRNAs are gaining attention for their potential applications in diagnostics, therapeutics, and genome editing. Their tissue-specific expression makes them useful as biomarkers for diseases, and their dysregulation in cancer has linked them to tumor progression, making them promising therapeutic targets. Furthermore, advances in RNA-based technologies, including CRISPR/Cas9, are increasingly utilizing lncRNAs for precise gene editing and regulatory functions [4,5]. This review aims to explore the roles of lncRNAs in gene regulation and their potential biotechnological applications, highlighting the need for a deeper understanding of their regulatory mechanisms and contributions to innovative RNA-based technologies.

Overview of Gene Regulation

Gene regulation is the process by which cells control the expression of their genetic material to ensure proper development, function, and adaptation to environmental signals [4]. This regulation involves multiple layers of control, including transcriptional, post-transcriptional, translational, and epigenetic mechanisms, all essential for maintaining cellular homeostasis [5]. The complexity of gene regulation arises from the precise coordination of these processes in a spatial and temporal manner. Long non-coding RNAs (lncRNAs) have emerged as critical regulators within this network, adding a new dimension to gene control. Unlike protein-coding genes, lncRNAs influence gene expression at multiple levels, from chromatin remodeling to transcriptional and post-transcriptional regulation. Their ability to interact with DNA, RNA, and proteins allows them to modulate gene expression with specificity [6]. By acting as molecular scaffolds, decoys, or guides for chromatin-modifying complexes, lncRNAs broaden our understanding of gene regulation, revealing new insights into how genes are finely tuned in various biological contexts.

Mechanisms of lncRNA Function

Chromatin modification and remodeling

LncRNAs play a crucial role in chromatin modification and remodeling, a process essential for regulating gene expression

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at the epigenetic level. Chromatin, composed of DNA and histone proteins, must be dynamically altered to either allow or restrict access to the genetic material [7]. LncRNAs facilitate this process by recruiting chromatin-modifying complexes to specific genomic loci, thereby influencing the epigenetic state of genes. A well-characterized example of this is the recruitment of Polycomb repressive complex 2 (PRC2), a histone methyltransferase responsible for trimethylating histone H3 at lysine 27 (H3K27me3), a marker associated with gene silencing [8]. Through sequence complementarity or structural motifs, lncRNAs direct PRC2 to target genes, leading to chromatin condensation and transcriptional repression. For instance, the lncRNA Xist binds to the X chromosome in female mammals, recruiting chromatin modifiers to inactivate one X chromosome, ensuring dosage compensation.

Additionally, lncRNAs interact with chromatin remodeling complexes such as SWI/SNF, which opens chromatin and facilitates gene activation. In this role, lncRNAs act as molecular guides that enable these complexes to locate specific chromatin regions, allowing transcriptional machinery to access the genes. This dual capacity to either repress or activate genes underscores the diverse roles of lncRNAs in regulating chromatin dynamics, adding an essential layer of epigenetic control to gene regulation.

Transcriptional regulation

LncRNAs also regulate gene expression at the transcriptional level by interacting with transcription factors, RNA polymerase II, and other components of the transcriptional machinery [9]. They can either enhance or repress transcription depending on the context and their molecular interactions. In some cases, lncRNAs promote transcription by forming ribonucleoprotein complexes that stabilize transcription factor binding at gene promoters. For instance, the lncRNA HOTTIP (HOXA transcript at the distal tip) interacts with the WDR5 protein to facilitate chromatin looping, bringing distal enhancers into proximity with gene promoters within the HOXA locus [10]. This spatial arrangement enables transcriptional activation of target genes. Conversely, lncRNAs can repress transcription by interacting with repressor proteins or by physically obstructing RNA polymerase II from binding to gene promoters. An example of this is the lncRNA NRON, which binds to and sequesters components of the NFAT transcription factor complex, preventing it from activating immune-related genes [11]. These examples illustrate the versatility of lncRNAs in modulating transcription, either by facilitating transcription factor binding or inhibiting the recruitment of the transcriptional machinery.

Post-Transcriptional regulation

LncRNAs also play critical roles in post-transcriptional regulation, affecting processes such as mRNA splicing, stability, transport, and translation. These post-transcriptional mechanisms ensure that gene products are accurately processed and regulated within the cell [12]. LncRNAs regulate alternative splicing by interacting with splicing factors or influencing the splicing machinery. For example, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) interacts with SR proteins, modulating their phosphorylation state and thus affecting the splicing of pre-mRNAs. This allows lncRNAs to fine-tune the splicing of transcripts, generating different protein isoforms [13]. LncRNAs also affect mRNA stability by forming double-stranded RNA structures with complementary mRNA sequences, either stabilizing or marking them for degradation. Tissue differentiation-inducing non-coding RNA (TINCR), for example, binds specific mRNAs and protects them from degradation, thereby ensuring stable levels of important transcripts. Additionally, lncRNAs can influence mRNA localization and translation [14]. The lncRNA Linc-ROR, for instance, sequesters microRNAs, preventing them from binding to and repressing their target mRNAs. By acting as a buffer for microRNAs, lncRNAs enhance the translation of specific mRNAs, thereby controlling protein synthesis at the post-transcriptional level.

Scaffolding and decoy functions

LncRNAs function as molecular scaffolds and decoys, organizing protein complexes or sequestering regulatory molecules to influence gene expression. As scaffolds, lncRNAs facilitate the assembly of ribonucleoprotein complexes that are essential for cellular function and gene regulation. A prominent example is the lncRNA HOTAIR, which acts as a scaffold for two distinct protein complexes: PRC2 and the LSD1/CoREST/REST complex [15]. HOTAIR physically bridges these complexes, enabling coordinated chromatin modification and transcriptional repression at the HOXD locus. This scaffolding role is critical for the establishment of epigenetic marks and the regulation of specific gene loci [16].

In their decoy function, lncRNAs bind and sequester proteins or RNA molecules, preventing them from interacting with their intended targets. For instance, growth arrest-specific 5 (GAS5) binds to the glucocorticoid receptor (GR), preventing its activation of glucocorticoid-responsive genes [2]. Similarly, decoy lncRNAs can bind microRNAs, inhibiting their ability to downregulate target mRNAs. By functioning as decoys, lncRNAs play a key role in regulating the availability and activity of other molecules involved in gene expression, demonstrating their versatility in cellular processes.

Therapeutic Potential

RNA therapeutics

Long noncoding RNAs (lncRNAs) have emerged as promising candidates for RNA-based therapies, offering unique opportunities to modulate gene expression without altering the underlying DNA sequence. One key application of lncRNAs in therapeutics is their ability to act as gene silencers. LncRNAs can recruit chromatin-modifying complexes or RNA-induced silencing complexes (RISC) to specific genomic loci, leading to targeted gene repression. This ability to silence genes holds potential for treating diseases caused by aberrant gene expression, such as certain cancers and genetic disorders [17]. For example, therapeutic approaches could leverage synthetic lncRNAs or lncRNA mimics to target and suppress oncogenes or pathogenic genes in a highly specific manner.

In addition to gene silencing, lncRNAs can be used to modulate gene expression. By acting as molecular decoys or scaffolds, lncRNAs can influence transcriptional regulators or splicing factors, thereby controlling gene expression at multiple levels. These mechanisms offer therapeutic potential for a wide range of diseases where gene expression needs to be finely

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regulated. Advances in RNA delivery methods are enhancing the clinical viability of lncRNA therapies [18].

Cancer treatment

Targeting lncRNAs in cancer treatment has become a focus of recent research due to their involvement in key cancer-related pathways, including cell proliferation, apoptosis, and metastasis [19]. Abnormal expression of lncRNAs is frequently observed in various cancers, where they act as oncogenes or tumor suppressors. Therapeutic strategies aim to either inhibit oncogenic lncRNAs or restore the function of tumor-suppressive lncRNAs. For instance, antisense oligonucleotides (ASOs) can be designed to bind to and degrade specific oncogenic lncRNAs, thereby interfering with cancer cell survival and proliferation. Another approach involves using small molecules or RNA interference (RNAi) to target lncRNAs that regulate cancer stem cells or are involved in drug resistance [20]. LncRNAs such as HOTAIR, MALAT1, and PVT1 have been identified as key players in various cancer types, and their manipulation offers new avenues for cancer treatment. As research progresses, targeting lncRNAs could provide a new class of precision therapies in oncology.

Diagnostic Biomarkers

lncRNAs as biomarkers

The potential of lncRNAs as diagnostic biomarkers is gaining significant attention due to their tissue-specific expression patterns and stability in bodily fluids. Specific lncRNAs are differentially expressed in various diseases, particularly cancers, making them ideal candidates for non-invasive diagnostic tests [21]. For example, circulating lncRNAs, such as PCA3 in prostate cancer or HULC in hepatocellular carcinoma, are detectable in blood, urine, or saliva, providing early indications of disease presence or progression. These lncRNAs can serve as reliable biomarkers for early disease detection, improving the chances of successful treatment and management.

The stability of lncRNAs in biological samples further enhances their suitability as biomarkers [22]. Unlike protein-based biomarkers, lncRNAs are less prone to degradation, making them easier to detect in a clinical setting. As research advances, large-scale screening of lncRNA expression profiles across various diseases is becoming more common, contributing to the development of lncRNA-based diagnostic panels that could revolutionize early detection, prognosis, and disease monitoring.

Bio sensing platforms

To harness the diagnostic potential of lncRNAs, biosensing platforms are being developed to detect their presence in biological samples with high sensitivity and specificity. Advanced technologies, such as electrochemical sensors, microfluidic devices, and nanoparticle-based detection systems, are being tailored to identify lncRNAs in body fluids. These platforms are designed to capture lncRNAs from small sample volumes and provide rapid, real-time diagnostics. For example, graphene-based biosensors have shown promise in detecting cancer-related lncRNAs due to their high surface area and conductivity. As biosensing technologies continue to evolve, they hold the potential to become essential tools in clinical diagnostics, offering rapid, cost-effective solutions for detecting lncRNAs and diagnosing diseases at an early stage [23].

Agricultural Biotechnology

Crop improvement

LncRNAs are also making an impact in agricultural biotechnology, where they are being explored for their potential to improve crop traits, such as disease resistance, stress tolerance, and yield. In plants, lncRNAs have been shown to regulate key pathways involved in responses to biotic and abiotic stresses. For instance, certain lncRNAs are involved in modulating plant immune responses by interacting with transcription factors and signaling molecules. By targeting these lncRNAs, researchers can enhance a plant's ability to resist pathogens or withstand environmental stresses like drought, salinity, or extreme temperatures [24]. This approach could significantly improve crop productivity, especially in regions prone to harsh environmental conditions.

Moreover, lncRNAs can influence plant growth and development by regulating gene expression involved in flowering time, root architecture, and nutrient uptake. By modulating these lncRNAs, crop plants can be engineered for improved growth under diverse agricultural conditions. These advancements hold great promise for creating resilient, high-yield crops that can meet the growing demands of global food security [25].

Gene editing

LncRNAs are also playing a role in emerging gene-editing technologies aimed at improving agricultural biotechnology. With the advent of CRISPR/Cas9 and related genome-editing tools, lncRNAs are being utilized to target specific genomic loci to modulate gene expression without altering the DNA sequence itself. For example, lncRNAs can be engineered to guide CRISPR-associated complexes to regulatory regions of the genome, enhancing or repressing gene expression in a highly precise manner. This approach allows for the fine-tuning of genes involved in important agricultural traits, such as disease resistance and stress tolerance, without introducing permanent changes to the genome [26]. By incorporating lncRNAs into gene-editing strategies, researchers can develop crops with desirable traits while minimizing potential off-target effects. This technology is particularly appealing in the context of sustainable agriculture, where precision gene regulation is critical for creating crops that are both productive and environmentally resilient.

Challenges in lncRNA Research

Functional annotation

Despite the growing recognition of their importance, assigning specific functions to most long noncoding RNAs (lncRNAs) remains a significant challenge. This difficulty arises from several factors:

Diverse and Context-Dependent Roles: LncRNAs often exhibit multiple functions depending on the cellular context, developmental stage, or environmental conditions, making it difficult to establish a definitive link between a specific lncRNA and a particular biological process. Lack of Conserved Sequence Features: Unlike protein-coding genes, lncRNAs

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generally lack conserved sequence motifs that can be used to predict their functions, making it challenging to identify functional domains or motifs within lncRNA sequences. Complexity of Regulatory Interactions: LncRNAs can interact with a variety of cellular components, including proteins, other RNAs, and chromatin, to exert their functions. This complex regulatory network makes it difficult to dissect the specific mechanisms through which lncRNAs exert their effects.

Experimental limitations

Studying lncRNAs presents several technical challenges that can hinder progress in this field:

Low Expression Levels: Many lncRNAs are expressed at low levels, making it difficult to detect and quantify them in biological samples, which can limit the ability to study their functions and interactions. Transcriptional Noise: Distinguishing functional lncRNAs from transcriptional noise can be challenging. Many lncRNA transcripts may be non-functional byproducts of transcription, making it difficult to identify those that have specific biological roles. Technical Difficulties in Studying RNA-RNA Interactions: Understanding the interactions between lncRNAs and other RNAs, such as mRNAs or other lncRNAs, is crucial for elucidating their functions. However, studying RNA-RNA interactions can be technically challenging due to their transient and dynamic nature.

Future Perspectives

Despite these challenges, the field of lncRNA research is rapidly evolving, and several promising avenues are being explored:

High-Throughput Sequencing Technologies: Advances in sequencing technologies are enabling the identification and characterization of lncRNAs on a large scale, providing valuable insights into the diversity and complexity of the lncRNA transcriptome. Computational Approaches: Computational methods are being developed to predict the functions of lncRNAs based on their sequence, structural features, and interactions with other cellular components, which can help prioritize lncRNAs for further study. Functional Genomics: Functional genomics studies, including CRISPR-based gene editing and RNA interference, are being used to investigate the roles of specific lncRNAs in biological processes, providing direct evidence for the functions of lncRNAs [27].

Therapeutic Applications: LncRNAs have the potential to be developed as therapeutic targets or agents. Understanding the functions of lncRNAs in diseases can lead to the development of novel treatments.

Conclusion

Long noncoding RNAs (lncRNAs) have emerged as crucial regulators of gene expression, impacting a wide range of biological processes. This review has highlighted their diverse applications in therapeutics, diagnostics, and agricultural biotechnology. LncRNAs offer promising therapeutic potential by modulating gene expression without altering the DNA sequence, providing opportunities for treating diseases such as cancers and genetic disorders. Additionally, lncRNAs can serve as valuable diagnostic biomarkers, enabling early detection and monitoring of diseases. Their stability in biological samples and tissue-specific expression patterns make them ideal candidates for non-invasive diagnostic tests. In the realm of agricultural biotechnology, lncRNAs are being explored to improve crop traits, such as disease resistance, stress tolerance, and yield. By manipulating lncRNAs, researchers can enhance plant growth, development, and resilience to environmental challenges. Furthermore, lncRNAs play a crucial role in gene-editing technologies, enabling precise modulation of gene expression without altering the DNA sequence. Despite the significant progress made in lncRNA research, several challenges remain, including assigning specific functions to lncRNAs and overcoming experimental limitations. Continued research is essential to fully harness the potential of lncRNAs and translate their discoveries into practical applications, unlocking new avenues for therapeutic interventions, diagnostic tools, and agricultural innovations.

Disclosure statement

No potential conflict of interest was reported by the authors.

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