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REVIEW ARTICLE

A Review on Unveiling the Secrets of Epitranscriptomics: R.N.A. Modifications in Health and Diseases

*[1]Amruta Jadhav and [2]Aakash Pawar

*[1]Assistant Professor, Department of Microbiology, K.T.H.M. College, Nashik, Maharashtra, India.
[2]Research Scholar, Department of Environmental Science, K.T.H.M. College, Nashik, Maharashtra, India.

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ABSTRACT

Advancements in epi transcriptomics have reshaped our understanding of R.N.A.'s intricate roles in cellular processes and disease. This abstract provides insights into the emerging field of epi transcriptomics, highlighting its significant implications for health and disease. Epitranscriptomics has unveiled various chemical modifications decorating R.N.A. molecules, akin to D.N.A.'s epigenetic marks, intricately governing R.N.A. structure and function. Modern research has elucidated the intricate mechanisms underlying these R.N.A. modifications, emphasizing their crucial roles in various cellular processes. N6-methyladenosine (m6A), the most prevalent R.N.A. modification, influences gene expression, mRNA splicing, stability, and translation, impacting cellular responses to external stimuli and their implications for diseases such as cancer and neurodegenerative disorders.

Similarly, 5-methylcytosine (m5C), analogous to D.N.A. methylation, governs R.N.A. stability, translation, and immune responses, with implications for host-pathogen interactions and R.N.A. virus replication. Pseudouridine (Ψ), the most abundant R.N.A. modification, contributes to tRNA stability, function, and mRNA translation regulation, shedding light on its biological significance. Epitranscriptomics plays a pivotal role in various diseases, with dysregulated R.N.A. modifications increasingly associated with cancer and neurological disorders, offering promising avenues for tailored therapies and diagnostic tools in personalized medicine. This abstract underscores the transformative impact of modern epitranscriptomics research, emphasizing its potential to revolutionize our understanding of R.N.A. biology, disease mechanisms, and therapeutic interventions. As research delves deeper into R.N.A. modifications, the discoveries hold promise for novel treatments and precision medicine approaches. In the ever-evolving landscape of molecular analysis, the study of epi transcriptomics continues to illuminate the intricate workings of R.N.A. By uncovering the nuances of R.N.A. modifications, this research paves the way for groundbreaking advancements in personalized medicine and targeted therapeutic interventions.

Keywords: Epitranscriptomics, R.N.A. modifications, and R.N.A. Dynamics.

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INTRODUCTION

The R.N.A. Renaissance: Unveiling the Dynamic Molecule of Life

The biological journey through epi transcriptomics begins with an appreciation of the R.N.A. renaissance. This transformative era has redefined our understanding of R.N.A. Historically, R.N.A. was relegated to a messenger, ferrying genetic information from D.N.A. to protein. Yet, current years have borne witness to a profound shift in perspective.[1,2] R.N.A. is no longer perceived as a passive intermediary but is recognized as an intricate and dynamic molecule, playing multifaceted roles in cellular processes and gene regulation.[3,4]

The R.N.A. World Hypothesis

To understand the R.N.A. renaissance fully, we must first harken back to the concept of the "R.N.A. world hypothesis." Proposed in the late 20th century, this hypothesis posits that R.N.A. may have been the original biomolecule of life, preceding the emergence of D.N.A. and proteins.[5,6] R.N.A., with its unique dual capacity for information storage (like D.N.A.) and catalysis (like proteins), has always held a special

*Author for Correspondence: aakashpawar7373@gmail.com

place in the evolutionary story of life on Earth. Trending research has rekindled interest in this hypothesis, as it provides a tantalizing glimpse into the pivotal role of R.N.A. in the origins of life.[7,8]

Beyond the Central Dogma: R.N.A. as More Than a Messenger:

For decades, molecular biology adhered to the "central dogma," a concept introduced by Francis Crick in 1958, which outlined a unidirectional flow of genetic information from D.N.A. to R.N.A. to protein.[9] In this traditional framework, R.N.A. was viewed as a mere messenger, a passive conduit for genetic instructions. However, as scientific exploration delved deeper into R.N.A.'s intricacies, it became evident that R.N.A. was far more than a passive courier.[10] R.N.A. molecules exhibited dynamic properties that defied their simplistic portrayal. This shift in perspective was particularly profound with the discovery of ribozymes, R.N.A. molecules capable of catalyzing chemical reactions—a role previously ascribed solely to proteins. This revelation shattered the notion of R.N.A. as merely an intermediary, propelling it into the spotlight as an active participant in cellular processes.[11]

RNA's Multifaceted Roles:

In the R.N.A. renaissance, R.N.A.'s roles expanded exponentially. It was recognized as the linchpin of various cellular processes, including gene regulation, splicing, translation, and catalysis. Noncoding R.N.A.s, once dismissed as genomic "junk," emerged as potent regulators of gene expression, orchestrating intricate genetic symphonies. Small R.N.A.s like microRNAs and long noncoding R.N.A.s (lncRNAs) were found to modulate gene expression with remarkable precision, influencing diverse aspects of cellular physiology.[12]

Epitranscriptomics: R.N.A. Modifications Take Center Stage:

The R.N.A. renaissance reached its zenith with the emergence of epi transcriptomics—a field that explores chemical modifications of R.N.A. molecules. These modifications, akin to the epigenetic marks on D.N.A., serve as the accents in the R.N.A. composition, subtly altering its structure, stability, and function without changing the genetic code. This revolutionary perspective has catapulted R.N.A. into a realm of dynamic regulation previously unimagined.[13]

The R.N.A. Renaissance as a Prelude:

The R.N.A. renaissance represents not just a transformative period in our understanding of molecular biology but a prelude to the intricate world of epi transcriptomics. As we journey deeper into this realm, the dynamic nature of R.N.A. modifications will continue to unravel, offering profound insights into gene regulation, cellular processes, and the pathogenesis of diseases.[14] The R.N.A. molecule, once seen as a passive messenger, now stands as a testament to the ever-evolving nature of scientific discovery—a testament to the fact that the more we uncover, the more there is to explore in the intricate and dynamic world of life's essential molecule. In the ever-evolving landscape of molecular biology, a paradigm shift is underway—unveiling the complicated secrets of R.N.A. through the lens of epi transcriptomics.[15] Advanced research endeavors have ignited a transformative journey into R.N.A. modifications, reshaping our understanding of how this dynamic molecule contributes to cellular processes and disease pathogenesis. Epitranscriptomics, a burgeoning field, explores the chemical modifications that embellish R.N.A. molecules, akin to the epigenetic marks adorning D.N.A.[16] These R.N.A. modifications, long overlooked, are now recognized as central players in orchestrating gene expression, cellular responses to environmental cues, and the pathogenesis of various diseases. The journey begins with a deep dive into the R.N.A. renaissance. For decades, R.N.A. was relegated to a supporting role, primarily perceived as a passive messenger conveying genetic information from D.N.A. to protein. However, the narrative has evolved significantly. R.N.A. is no longer confined to the linear transmission of genetic instructions. Instead, it has emerged as a dynamic and multifaceted molecule, actively participating in regulating gene expression and cellular function.[17]

Epitranscriptomics Defined:

Epitranscriptomics, a term coined in the early 2010s, is the scientific exploration of R.N.A. modifications—chemical alterations to R.N.A. molecules that do not change the underlying genetic code but wield remarkable influence over R.N.A.'s structure, stability, and function.[18] These modifications can be likened to the accents in a musical score, subtly altering the composition without changing the notes. In the realm of R.N.A., these accents come in various forms, including N6-methyladenosine (m6A), 5-methylcytosine (m5C), and pseudouridine (Ψ).[19]

RNA Modifications: The Diverse Landscape:

N6-Methyladenosine (m6A):

The spotlight in the epitranscriptomic landscape often shines brightest on N6-methyladenosine (m6A). As the most prevalent R.N.A. modification, m6A has garnered significant attention for its pivotal role in regulating gene expression.[20] Studies have unveiled its far-reaching influence on mRNA stability, splicing, and translation. In essence, m6A acts as a traffic conductor on the mRNA highway, directing the fate of transcripts—whether they proceed to translation, storage, or degradation. The dysregulation of m6A marks has been implicated in many diseases, including cancer, neurodegeneration, and metabolic disorders, emphasizing the central role of m6A in health and disease.[21]

5-Methylcytosine (m5C):

5-Methylcytosine (m5C), akin to D.N.A. methylation, adds another layer of complexity to the epitranscriptomic symphony. Ongoing studies have revealed that m5C is not merely a passive decoration but plays an active role in regulating R.N.A. stability and translation.[22] This modification, predominantly found

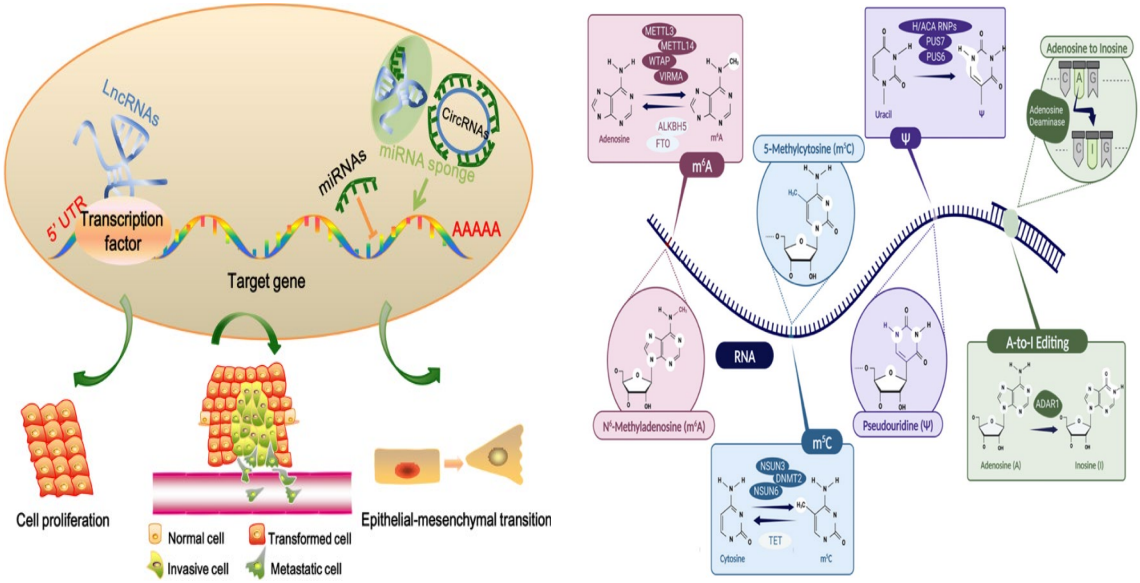

Figure 1: Outline a protocol for investigating the functional roles of epi transcriptomic regulators, including RNA-modifying enzymes and reader proteins, and Figure 2 Different therapeutic approaches targeting specific R.N.A. modifications.[84,85]

in transfer R.N.A. (tRNA) and ribosomal R.N.A. (rRNA), has been linked to essential cellular processes, including protein synthesis and immune responses. Additionally, m5C modification has gained recognition for its involvement in R.N.A. virus replication, opening new avenues for understanding host-pathogen interactions and antiviral strategies.[23,24]

Pseudouridine (Ψ)

While N6-methyladenosine (m6A) and 5-methylcytosine (m5C) often steal the spotlight, pseudouridine (Ψ) quietly assumes the role of the silent influencer. Pseudouridine is the most abundant R.N.A. modification, primarily in transfer R.N.A. (tRNA) and ribosomal R.N.A. (rRNA).[25] Historically, pseudouridine's significance remained elusive, obscured by the prominence of m6A and m5C. However, the Latest studies have started to unveil the enigma surrounding pseudouridine. It is now recognized as a critical player in maintaining tRNA stability and functionality, ensuring the accurate translation of genetic information into functional proteins.[26] Additionally, pseudouridine has emerged as an unexpected regulator of mRNA translation, revealing its intricate role in cellular processes far beyond tRNA and rRNA modification.[27]

Epitranscriptomics in Health and Disease

The revelation of R.N.A. modifications' pervasive presence and influence extends to human health and disease.[28] Epitranscriptomics is increasingly recognized as a central player in the pathogenesis of various disorders, reshaping our understanding of disease mechanisms and offering new avenues for therapeutic interventions.[29]

Cancer

One of the most striking revelations in current research is the dysregulation of R.N.A. modifications in cancer. The intricate interplay between R.N.A. modifications and cancer is a rapidly expanding field. Aberrant m6A modifications, for instance, can lead to the misregulation of oncogenes and tumor suppressor genes, driving tumorigenesis.[30] In leukemia, for example, mutations in the m6A machinery have been identified, highlighting the pivotal role of epi transcriptomic alterations in hematologic malignancies.[31] Beyond m6A, m5C modifications are also implicated in cancer, with studies linking altered m5C levels to oncogenic processes.[32] The discovery of these associations opens new vistas for precision medicine, as targeting epi transcriptomic writers and erasers holds promise as a novel therapeutic strategy in the fight against cancer.[33]

Neurological Disorders

The significance of R.N.A. modifications extends beyond cancer, reaching into the complex realm of neurological disorders. Research has unearthed the involvement of R.N.A. modifications in neurodevelopmental disorders, such as autism spectrum disorders (A.S.D.) and intellectual disabilities. [34.35] In these conditions, alterations in the epitranscriptomic landscape can disrupt neural development and function, offering valuable insights into the molecular basis of these disorders.[36] Moreover, epi transcriptomic changes have also been linked to neurodegenerative diseases like Alzheimer's and Parkinson's disease, adding a new layer of complexity to our understanding of neurodegeneration. As we journey deeper into the intricate world of R.N.A. modifications, the secrets unveiled therein hold the promise of illuminating the path toward novel treatments and precision medicine approaches. [37] In this research review, we embark on a comprehensive exploration of epi transcriptomics research, delving into the intricate mechanisms of R.N.A. modifications and their profound implications for human health and disease.[38] As

we navigate this epitranscriptomic odyssey, we anticipate the transformative impact of this burgeoning field and the countless opportunities it holds for advancing our understanding of cellular processes, unraveling disease mechanisms, and ultimately improving human health.[39]

APPROACHES FOR IDENTIFYING AND MEASURING RNA ALTERATIONS.

LC-MS/MS (Liquid Chromatography-Tandem Mass Spectrometry):

a. Sample Preparation: R.N.A. is isolated from the biological sample of interest and enzymatically hydrolyzed into nucleosides. b. Liquid Chromatography: The nucleosides are separated based on their physicochemical properties using liquid chromatography. c. Mass Spectrometry Analysis: The separated nucleosides are ionized and analyzed by mass spectrometry, allowing for the identification and quantification of specific R.N.A. modifications present in the Sample.[40,41]

MeRIP-seq (Methylated R.N.A. Immunoprecipitation Sequencing):

a. Immunoprecipitation: R.N.A. fragments containing the specific modification of interest are enriched using antibodies targeting the modification. b. Fragmentation and Library Preparation: The enriched R.N.A. fragments are fragmented and converted into a sequencing library. c. High-Throughput Sequencing: The library is subjected to high-throughput sequencing, generating reads that are subsequently mapped to the reference genome, enabling the identification and profiling of modified R.N.A. sites across the transcriptome.[42.43]

m6A-CLIP (m6A-Crosslinking Immunoprecipitation):

a. U.V. Crosslinking: Cells are treated with UV light to crosslink RNA-binding proteins to R.N.A. molecules containing the m6A modification. b. Immunoprecipitation: Crosslinked R.N.A. fragments are immunoprecipitated using antibodies specific to the m6A modification. c. R.N.A. Fragment Enrichment: The immunoprecipitated R.N.A. fragments are enriched and prepared for high-throughput sequencing to identify and map m6A sites across the transcriptome.[44,45 &46]

Nanopore Sequencing: a. R.N.A. Isolation:

Total R.N.A. is extracted from the Sample of interest and prepared for direct sequencing without reverse transcription. b. Nanopore Sequencing Setup: The R.N.A. is fed through nanopores embedded in a membrane, and changes in electrical current are recorded as individual R.N.A. molecules pass through the nanopores. c. Real-Time Analysis: The electrical signals are used to reconstruct the R.N.A. sequence, enabling the detection of various modifications at single-molecule resolution and providing insights into the temporal and spatial distribution of R.N.A. modifications within the transcriptome.[47,48]

DMS-seq (Dimethyl Sulfate Sequencing) and Shape-Seq (Selective 2'-Hydroxyl Acylation Analyzed by Primer Extension Sequencing):

a. Chemical Modification: R.N.A. samples are treated with chemical reagents such as D.M.S. or selective 2'-hydroxyl acylation to label specific R.N.A. modifications. b. Reverse Transcription: The chemically modified R.N.A. is reverse transcribed into cDNA, preserving the modified nucleotides. c. Library Preparation and Sequencing: The cDNA is converted into a sequencing library, and high-throughput sequencing is performed to identify and characterize specific R.N.A. structural changes and modifications at a nucleotide-specific level.[49,50]

Integration of the data obtained from these methodologies with sophisticated bioinformatics tools enables comprehensive analysis and interpretation of the dynamic landscape of R.N.A. modifications, contributing to a deeper understanding of their functional roles in gene expression regulation, cellular processes, and disease pathogenesis.

CONCLUSION

Epitranscriptomics, a realm of intricate R.N.A. modifications, unfolds an enthralling journey with profound implications for health and disease. Topical studies have expanded our understanding of R.N.A.'s multifaceted role, fuelling exploration of its therapeutic and diagnostic potential. Our review has navigated through the dynamic landscape of N6-methyladenosine (m6A), 5-methylcytosine (m5C), and pseudouridine (Ψ), revealing their orchestration of gene expression and cellular responses. This molecular renaissance signifies R.N.A.'s dynamic regulatory role, ushering us into a transformative era in molecular biology and medicine. The future of epi transcriptomics holds both promise and challenge. Advanced mapping tools like m6A-seq, m5C-seq, and Ψ-seq offer unprecedented precision, yet functional characterization remains a complex pursuit demanding interdisciplinary collaboration and innovative methodologies. Understanding the dynamic nature of R.N.A. modifications requires an in-depth exploration of the underlying regulatory mechanisms. In the context of health and disease, epi transcriptomics emerges as a pivotal player, influencing cancer research and treatment as well as unraveling complexities in neurological disorders. The potential for targeted therapies and diagnostic tools based on R.N.A. modifications is undeniable, underlining the need for responsible research practices and ethical considerations to ensure safety and efficacy in clinical applications. In conclusion, advancements in epi transcriptomics have propelled us into an era of unprecedented discovery, where R.N.A. modifications serve as keystones in non-identified gene regulation, disease mechanisms, and therapeutic interventions. As we venture into this transformative territory, our commitment to ethical and responsible research ensures that the potential of epi transcriptomics benefits humanity in profound and ethically sound ways. The revelations in epi transcriptomics serve as a guiding light, leading us toward a future where scientific innovation and ethical considerations march hand in hand.

FUTURE DIRECTIONS AND CHALLENGES

As epitranscriptomics continues to unveil the secrets of R.N.A. modifications, it is poised to shape the future of molecular biology and medicine. Modern research has illuminated the

transformative potential of this field, but it also reveals a landscape rife with challenges and untapped opportunities.

Technological Advancement

Current years have witnessed remarkable advancements in the technologies used to detect and analyze R.N.A. modifications. Techniques such as m6A-seq, m5C-seq, and Ψ-seq have enabled researchers to map R.N.A. modifications with unprecedented precision.[51] These breakthroughs have not only expanded our knowledge of the epi transcriptomic landscape but have also opened the door to exploring modifications beyond the well-studied m6A, m5C, and Ψ. In the future, we anticipate even more sophisticated methods that will provide higher resolution and sensitivity, allowing for a comprehensive mapping of R.N.A. modifications in diverse biological contexts.[52,53]

Functional Characterization

While we have made significant strides in mapping R.N.A. modifications, functional characterization remains a formidable challenge. Understanding how specific modifications influence R.N.A. structure, stability, and function is crucial.[54] Research has begun to unravel the functional consequences of R.N.A. modifications, particularly in the context of m6A and m5C. Future endeavors will likely focus on dissecting the precise mechanisms by which modifications modulate gene expression and cellular processes.[55] This will entail interdisciplinary collaborations between biologists, bioinformaticians, and structural biologists to bridge the gap between modification mapping and functional insights.[56]

RNA Modification Dynamics

Current Findings have also highlighted the dynamic nature of R.N.A. modifications. These marks are not static but undergo dynamic changes in response to cellular cues and environmental stimuli. Understanding the regulatory mechanisms governing modification dynamics is a frontier yet to be fully explored.[57] It raises intriguing questions about how cells maintain the delicate balance of R.N.A. modifications and how perturbations in this balance contribute to disease.[58] Future studies will delve into the dynamic interplay between writers, erasers, and readers of R.N.A. modifications, shedding light on the regulatory networks orchestrating this intricate symphony.[59]

Therapeutic Potential

The recognition of R.N.A. modifications as players in disease pathogenesis opens exciting therapeutic avenues. Contemporary research has hinted at the potential of targeting epi transcriptomic writers, erasers, and readers as a novel approach to disease treatment.[60] However, realizing this therapeutic potential is fraught with challenges. Identifying specific modification sites and developing precise therapies without off-target effects present formidable obstacles.[61] Furthermore, ethical considerations and safety concerns surrounding epi transcriptomic manipulation require careful deliberation. The future will likely witness a concerted effort to translate our knowledge of R.N.A. modifications into clinically viable interventions.[62,63]

Diagnostic Tools

Studies have illuminated the diagnostic potential of R.N.A. modifications as biomarkers for various diseases. Identifying disease-specific modification profiles could revolutionize disease diagnosis and monitoring.[64] However, the development of reliable diagnostic assays poses challenges related to sensitivity, specificity, and standardization. Overcoming these challenges will be essential for harnessing the diagnostic power of R.N.A. modifications.[65,66]

Epitranscriptomics in Drug Discover

Epitranscriptomics has the potential to revolutionize drug discovery by offering new targets for therapeutic intervention. [67,68] A new research has highlighted the druggability of R.N.A. modification enzymes, paving the way for the development of small molecule inhibitors and modulators. In the coming years, we anticipate an increased focus on screening for epi transcriptomic-targeted compounds and their evaluation in preclinical and clinical settings.[69]

Ethical and Regulatory Considerations

As epitranscriptomics advances, ethical and regulatory considerations come to the fore. Manipulating R.N.A. modifications for therapeutic purposes raises complex ethical questions, such as the potential for unintended consequences and long-term effects. Regulatory frameworks will need to adapt to accommodate the evolving landscape of epi-transcriptomic-based therapies, ensuring that innovations are ethically and safely translated to clinical practice.[70] In conclusion, studies in epi transcriptomics have unveiled a world of possibilities, from unraveling disease mechanisms to revolutionizing therapeutic strategies and diagnostics. However, these endeavors are not without their challenges. Overcoming these challenges and harnessing the full potential of epi transcriptomics will require multidisciplinary collaboration, cutting-edge technologies, and a commitment to ethical and regulatory standards. As we embark on this epitranscriptomic journey, we are poised to unlock a deeper understanding of cellular processes, uncover novel therapeutic targets, and ultimately improve human health in ways previously unimagined.[71] Ongoing studies in the burgeoning field of epi transcriptomics have ushered in a new era of understanding R.N.A.'s intricate role in cellular processes and disease pathogenesis. This transformative journey into the world of R.N.A. modifications has illuminated the landscape with unprecedented insights and has raised fundamental questions about the regulation of genetic information.[72] As we bring this exploration to a close, it is evident that epi transcriptomics is on the cusp of reshaping molecular biology and medicine in profound and unprecedented ways. The R.N.A. renaissance has redefined our perception of R.N.A. from a passive messenger to an active participant in gene expression and cellular function. The realization that R.N.A. is not only a transmitter of genetic information but also a regulator of cellular processes has opened the door to new realms of discovery.[73] This paradigm shift has culminated in the emergence of epi transcriptomics as

a dynamic and multifaceted field, where R.N.A. modifications serve as the keystones to understanding how cells respond to their ever-changing environments. Epitranscriptomics, as a term coined in the past decade, has encapsulated our growing fascination with R.N.A. modifications. It signifies the collective effort to decode the chemical language of R.N.A., revealing modifications such as m6A, m5C, and Ψ as central players in this intricate script.[74]New age research has unveiled the diverse landscape of R.N.A. modifications, each with its unique role in shaping R.N.A. structure, stability, and function. N6-methyladenosine (m6A), 5-methylcytosine (m5C), and pseudouridine (Ψ) have taken the forefront, offering new avenues for understanding their roles in cellular processes and disease pathogenesis.[75] In the realm of health and disease, epi transcriptomics has emerged as a central player. Present studies have illuminated the dysregulation of R.N.A. modifications in a spectrum of diseases, ranging from cancer to neurological disorders. These findings have offered exciting prospects for targeted therapies, diagnostic tools, and a deeper understanding of the molecular underpinnings of disease. As we look to the future, several key directions and challenges beckon us.[76] Technological advancements will continue to refine our ability to map R.N.A. modifications with precision, potentially unveiling novel modifications and their roles. Functional characterization of R.N.A. modifications remains a priority as we seek to understand how these chemical marks orchestrate cellular processes.[77] The dynamic nature of R.N.A. modifications presents an intriguing frontier, offering insights into how cells respond to stimuli and perturbations. Harnessing the therapeutic potential of R.N.A. modifications requires innovative strategies and ethical considerations, while diagnostic tools and drug discovery efforts are poised to revolutionize healthcare. [78] Ethical and regulatory considerations will be paramount as epi transcriptomics transitions from the laboratory bench to clinical practice. Ensuring the safety and efficacy of epi-transcriptomic-based interventions while maintaining ethical standards will require a collaborative effort from researchers, clinicians, and policymakers.[79] In conclusion, studies in epi transcriptomics have ushered in a new era of scientific discovery, where R.N.A. modifications take center stage in understanding cellular processes and diseases.[80] This field holds the promise of unlocking deeper insights into gene regulation, disease mechanisms, and therapeutic interventions. As we navigate this uncharted territory, we must remain steadfast in our commitment to ethical and responsible research, ensuring that the transformative potential of epi transcriptomics benefits humanity in ways that are both profound and ethically sound. [81,82] The future of molecular biology and medicine is undoubtedly intertwined with the secrets unveiled by epi transcriptomics, promising a brighter and more enlightened path ahead.[83]

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CONFLICT OF INTEREST

The authors declare no conflict of interest in the publication of this manuscript.

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