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THE ROLE OF MICRORNA IN GENE REGULATION: INSIGHTS AND IMPLICATIONS

Medicine

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ABSTRACT

MicroRNAs (miRNAs) have emerged as key regulators of gene expression, influencing a wide range of biological processes. These small, non-coding RNAs function primarily by binding to complementary sequences in messenger RNAs (mRNAs), leading to mRNA degradation or translational repression. In recent years, advances in molecular biology have uncovered the critical roles miRNAs play in development, differentiation, cell cycle control, and disease pathogenesis, particularly in cancer, cardiovascular, and neurodegenerative disorders. This review explores the mechanisms by which miRNAs regulate gene expression, highlights the latest insights into miRNA biogenesis and function, and discusses the implications of miRNA dysregulation in human disease. We also examine the potential of miRNAs as biomarkers for disease diagnosis and as therapeutic targets. The growing understanding of miRNA-mediated gene regulation provides a foundation for future research and therapeutic innovations.

KEYWORDS

miRNAs, miRNA biogenesis, miRNAs as biomarkers,miRNAs as therapeutic targets, miRNA-mediated gene regulation

INTRODUCTION:

The MicroRNAs (miRNAs) are in news in October 2024 since the announcement by The Nobel Assembly at the Karolinska Institute to confer "The 2024 Nobel Prize in Physiology or Medicine" jointly to Victor Ambros and Gary Ruvkun for the identification of microRNA and its function in post-transcriptional gene regulation. Their pioneering finding unveiled a novel theory of gene regulation that proved crucial for multicellular creatures, including humans. The human genome is currently understood to encode more than one thousand microRNAs. Their unexpected finding unveiled a completely novel aspect of gene control.[1]

MiRNAs accurately regulate gene expression without encoding proteins, unlike mRNAs. These 21-25 nucleotide RNA molecules regulate target mRNA stability and translational efficiency post-transcriptionally. Since their discovery in 1993 from Caenorhabditis elegans, miRNAs have been found in animals, plants, and viruses, demonstrating their evolutionary value. MiRNAs regulate gene expression by binding to complementary sequences in mRNAs' 3' untranslated regions (UTRs) to degrade or impede translation. [2] MiRNAs affect several biological processes. They help animals and plants develop, maintain tissue homeostasis, and respond to environmental stimuli. MiRNAs control cell cycle, differentiation, death, metabolism, and immunity. It is believed that miRNAs influence over 60% of human protein-coding genes, demonstrating their regulatory capacity. Beyond basic physiological functions, miRNAs are of interest in human illnesses. Medical conditions include cancer, cardiovascular illness, neurological disease, autoimmune disease, and metabolic imbalance have been linked to miRNA expression changes. miRNAs can be oncogenes or tumor suppressors, and their dysregulation often causes and progresses malignancies. This makes miRNAs promising diagnostic and therapeutic biomarkers. Cancer research uses miRNA signatures to classify tumors, predict disease outcomes, and determine treatment options.

MiRNAs are therapeutic outside oncology. In cardiovascular diseases, miRNAs regulate cardiac hypertrophy, fibrosis, and arrhythmogenesis. In neurodegenerative diseases, they control synaptic plasticity and neuron survival. In metabolic illnesses, miRNAs regulate glucose and lipid metabolism. As researchers understand the roles of certain miRNAs in numerous conditions, miRNA-based therapies—using miRNA mimics, antagomirs, or tiny chemicals to modulate miRNA activity—have become a viable biomedical research area. [3]

This review aims to provide a comprehensive understanding of miRNAs' biogenesis, molecular processes, gene expression pathways, physiological functions in health and development, and disease etiology. The article will conclude by discussing miRNAs' therapeutic promise and the barriers to practical deployment. Understanding miRNA biology can help in understanding how they affect gene expression patterns and how modulating these tiny regulators may lead to new treatments for human illnesses.

Biogenesis of MicroRNAs:

The biogenesis of microRNAs (miRNAs) is a highly regulated, multi-step process that transforms the genetic information encoded in miRNA genes into functional miRNAs, which then participate in post-transcriptional gene regulation. This process can be broken down into the following stages and is depicted in Figure 1 :

1. Transcription of Pri-miRNAs

The majority of miRNAs are transcribed from miRNA genes by RNA polymerase II, which produces a primary miRNA transcript known as pri-miRNA. Pri-miRNAs are typically several kilobases long and contain a characteristic stem-loop structure. These transcripts may also be polyadenylated and capped, like other RNA polymerase II products. Some miRNAs are located within the introns of protein-coding genes and are transcribed as part of the host gene's mRNA. These are known as "intronic miRNAs" and are processed co-transcriptionally.

2. Processing by Drosha-DGCR8 Complex

In the nucleus, the pri-miRNA is recognized and cleaved by the Microprocessor complex, which consists of the RNase III enzyme Drosha and its essential cofactor DGCR8 (DiGeorge syndrome critical region 8). This cleavage generates a precursor miRNA (pre-miRNA) that is approximately 70 nucleotides long and retains a stem-loop structure.

3. Export to the Cytoplasm

Once the pre-miRNA is formed, it is transported from the nucleus to the cytoplasm by exportin-5, a nuclear export receptor. Exportin-5 recognizes the double-stranded stem of the pre-miRNA and facilitates its passage through the nuclear pore complex into the cytoplasm.

4. Processing by Dicer

In the cytoplasm, the pre-miRNA is further processed by another RNase III enzyme called Dicer. Dicer cleaves the pre-miRNA at the loop region, producing a miRNA duplex of about 21-25 nucleotides. This duplex consists of two strands: the guide strand (which becomes the mature miRNA) and the passenger strand (often referred to as miRNA*), which is usually degraded.

5. Incorporation into RISC

The guide strand of the miRNA is then loaded into the RNA-induced silencing complex (RISC), a multi-protein complex that includes members of the Argonaute (Ago) family. The Argonaute protein, particularly Ago2, plays a critical role in guiding the miRNA to its target mRNA. The passenger strand of the miRNA duplex is discarded and degraded.

6. Regulation of Target mRNAs

Once the miRNA is incorporated into the RISC, it binds to its target mRNA based on sequence complementarity. This typically occurs in

the 3' untranslated region (3' UTR) of the mRNA. The miRNA-RISC complex then represses the expression of the target mRNA by either degrading the mRNA or inhibiting its translation. In some cases, miRNAs can also bind to the 5' UTR or coding region of target mRNAs, adding further complexity to their regulatory potential.[3]

Molecular Mechanisms of miRNA Action:
miRNAs regulate gene expression primarily through two mechanisms: mRNA degradation and translational repression. These mechanisms are determined largely by the degree of complementarity between the miRNA and its target mRNA.

1. mRNA Degradation
When miRNA attaches to its target mRNA with perfect or near-perfect complementarity, typically seen in plants and certain viral systems, the RISC complex cleaves the mRNA. The process is directed by the slicer activity of the Ago2 protein. The cleavage event is succeeded by exonucleolytic degradation, resulting in the total elimination of the mRNA transcript from the cytoplasm. This process efficiently diminishes the amounts of the target mRNA, leading to a decrease in the synthesis of the matching protein.

2. Translational Repression
In mammals, miRNAs typically associate with target mRNAs through partial complementarity, especially within the seed region (a 6-8 nucleotide sequence at the 5' terminus of the miRNA). This suboptimal base-pairing results in translational repression instead of mRNA breakdown. In this context, the miRNA-RISC complex disrupts the translation process by obstructing ribosome assembly, hindering polypeptide chain elongation, or facilitating deadenylation of the mRNA's poly(A) tail. The outcome is decreased protein synthesis without the immediate destruction of mRNA.[3]

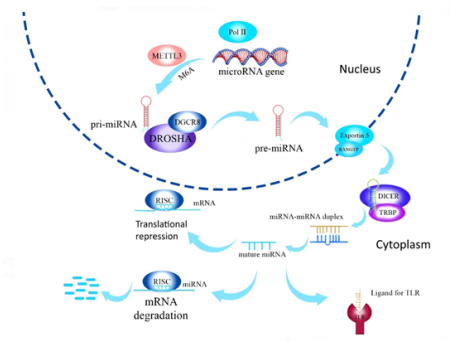

Figure 1- Showing the synthesis and mechanism of action of miRNA[4]

Pathways of miRNA Regulation:
miRNAs can regulate gene expression through various pathways, each influencing a wide range of biological processes:

1. Canonical miRNA Pathway
The canonical pathway of miRNA biogenesis, which involves Drosha, Dicer, and Argonaute proteins, is responsible for most miRNA-mediated gene regulation. In this pathway, miRNAs act within the cytoplasm to target mRNAs and modulate their expression.

2. Non-canonical Pathways
In addition to the canonical pathway, miRNAs can be processed through alternative routes that bypass Drosha or Dicer. For instance, miRNAs known as "mirtrons" are spliced directly from introns without the need for Drosha cleavage. Other non-canonical pathways involve the generation of miRNAs from small nucleolar RNAs (snoRNAs) or transfer RNAs (tRNAs), expanding the diversity of miRNA biogenesis and function.

3. Competitive Endogenous RNA (ceRNA) Network
The concept of competitive endogenous RNAs (ceRNAs) introduces an additional layer of complexity to miRNA regulation. ceRNAs, such as long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs), act as "sponges" by sequestering miRNAs and preventing them from binding to their target mRNAs. This competition for miRNA binding can influence the expression of numerous genes simultaneously, adding a regulatory feedback mechanism to gene expression.[5]

Physiological Roles of miRNAs :
miRNAs are essential regulators of numerous physiological processes. Their ability to fine-tune gene expression allows for precise control over cellular activities and organismal development.

1. Developmental Regulation
MicroRNAs are essential for growth and development, serving pivotal functions in embryogenesis, tissue morphogenesis, and organogenesis. The miR-17-92 cluster governs the development of the heart and lungs, whereas miR-34a participates in neural differentiation. MicroRNAs are crucial for preserving the equilibrium between stem cell self-renewal and differentiation. The miR-302 family enhances pluripotency in stem cells, whereas the miR-200 family facilitates differentiation into particular cell lineages.

2. Cell Proliferation and Apoptosis
MicroRNAs significantly regulate cell cycle development and apoptosis. The miR-15/16 family targets genes associated with cell cycle regulation, including Cyclin D1, and pro-apoptotic proteins such as BCL2. Dysregulation of these miRNAs can lead to unregulated cell growth or defective apoptosis, resulting in illnesses like cancer.

3. Immune Function
MicroRNAs regulate the growth and function of diverse immune cells throughout the immune system. miR-155, a pivotal microRNA in immunoregulation, influences the development of T cells and B cells while enhancing the inflammatory response in macrophages. The anomalous expression of miR-155 has been associated with autoimmune disorders, persistent inflammation, and malignancies.[6]

Contributions to Disease Pathogenesis:
Dysregulated miRNA expression has been implicated in a wide range of human diseases:

1. Cancer
In cancer, miRNAs serve as both oncogenes and tumor suppressors. OncomiRs such as miR-21 and miR-155 facilitate tumor proliferation by suppressing tumor suppressor genes, whereas tumor-suppressive miRNAs like let-7 and miR-34 limit oncogene expression. miRNA expression patterns, also known as "miRNA signatures," are utilized for cancer classification, prognosis prediction, and therapeutic target identification.

2. Cardiovascular Diseases
MicroRNAs (miRNAs) are crucial in modulating heart development, cardiac hypertrophy, and vascular function in cardiovascular disorders. Dysregulation of cardiac-specific microRNAs, including miR-1, miR-133, and miR-208, has been associated with heart failure and myocardial infarction.

3. Neurodegenerative Diseases
miRNAs are essential regulators of neuronal function and viability. In conditions such as Alzheimer's and Parkinson's, abnormal miRNA expression leads to neuronal degeneration and compromised synaptic plasticity. For instance, miR-124 and miR-132 are crucial for preserving neuronal identity and synaptic functionality, with their dysregulation noted in neurodegenerative disorders.

4. Metabolic Disorders
miRNAs play a role in metabolic control, and their dysregulation is associated with metabolic diseases, including obesity and diabetes. miR-122 is a liver-specific microRNA that affects cholesterol and fatty acid metabolism, whereas miR-375 modulates insulin production and glucose balance in the pancreas.

5. Mutations in one of the proteins required for microRNA production result in the **DICER1 syndrome,** a rare but severe syndrome linked to cancer in various organs and tissues.[7]

Therapeutic Applications and Challenges:
Given their critical roles in gene regulation and disease, miRNAs are promising therapeutic targets. Several approaches have been developed to modulate miRNA activity, including:

1. miRNA Mimics
miRNA mimics are synthetic entities engineered to reinstate the activity of downregulated tumor-suppressive miRNAs. For instance, miR-34a mimics have demonstrated potential in preclinical cancer models by suppressing tumor proliferation.

2. Antagomirs

Antagomirs are chemically altered oligonucleotides that suppress the function of overexpressed oncogenic microRNAs. Antagomir-122 is a notable example that has been developed as a treatment for hepatitis C infection.

3. Small Molecule Modulators

Small compounds that influence miRNA biogenesis or function are being investigated as potential treatments. These compounds can either suppress or promote the processing of certain miRNAs, providing a more precise method for miRNA control. Anti-miR 21 treatment reduces cardiac remodeling.[8]

However, **significant challenges** remain in developing miRNA-based therapies. These include:

- **Delivery**: Efficient delivery of miRNA mimics or inhibitors to target tissues, while avoiding off-target effects, remains a major hurdle. Nanoparticle-based delivery systems and viral vectors are being explored to address this issue.
- **Specificity:** miRNAs often have multiple mRNA targets, making it difficult to predict and control their effects. Off-target effects may lead to unintended consequences, particularly in complex diseases like cancer.
- **Immune Response**: Some miRNA therapies, such as the miR-34a mimic MRX34, have encountered challenges due to immune-related adverse events in clinical trials, highlighting the need for improved safety profiles.
- **Toxicity:** A single miRNA can target several mRNAs , this warrants extra attention due to unforeseen side effects. Even if a miRNA is targeted, on-target effects may occur. [9]

CONCLUSION:

MicroRNAs are potent regulators of gene expression that affect various biological processes, including development, cell proliferation, immunological function, and metabolism. Their dysregulation has a role in the etiology of various diseases, including cancer, cardiovascular diseases, neurodegenerative disorders, and metabolic problems. Despite the significant therapeutic promise of miRNAs, problems related to delivery, specificity, and safety must be addressed to fully utilize their capabilities in clinical settings. Current research in this domain offers significant potential for the advancement of miRNA-based diagnostics and therapies, perhaps revolutionizing the realm of personalized medicine.

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