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MicroRNAs: The Silent Regulators of Gene Expression, Disease Pathways, and Next-Generation Therapeutics

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ABSTRACT

MicroRNAs (miRNAs) are small, non-coding RNA molecules that represent the foundation of gene expression modulation, thereby controlling numerous biological processes. In this review, we discuss the diverse roles of miRNAs in relation to human health by focusing on their regulation of cellular processes like proliferation, differentiation, and apoptosis. The dysregulation of miRNA expression has been associated with a variety of diseases, such as cancer, cardiovascular disease, and neurodegenerative disease, highlighting their importance as biomarkers and as possible therapeutic targets. This review discusses the mechanism through which miRNAs influence gene networks, their role in post-transcriptional regulation, and how they target messenger RNAs (mRNAs). Moreover, the therapeutic potential of miRNAs is elaborated, with considerations of miRNA replacement and inhibition approaches from a clinical perspective. Advances in miRNA therapies, including the development of nanocarriers for site-specific delivery, contribute to the progress of future treatment modalities.

Lastly, this review highlights the need to understand miRNA biology for the determination of disease mechanisms as well as the design of new diagnostic and therapeutic strategies. With their diverse functions, a deeper understanding of miRNAs not only enhances our knowledge of molecular biology but also has the potential for breakthroughs in precision medicine.

Keywords: MicroRNAs (miRNAs) Biomarkers, Therapeutic Targets, Gene Regulation, Disease Diagnostics

2- Introduction

MicroRNAs are small non-coding RNA molecules, usually 18-25 nucleotides in length, that have central roles in the regulation of gene expression. These molecules control their action at the post-transcriptional level mainly by binding to the 3' untranslated regions (3' UTRs) of specific messenger RNAs (mRNAs), influencing protein synthesis [1]. MicroRNAs have been the focus of significant academic research since their discovery in the early 1990s because they are involved in essential biological processes such as development, cellular differentiation, proliferation, and apoptosis [2]. The biogenesis of miRNAs, characterized by a sequential processing pathway mediated by the Drosha and Dicer complexes, produces mature miRNAs that can regulate various disease processes, including cancer [3,4] This insight enables the development of putative therapeutic strategies [5].

The role of miRNAs is more than just gene regulation; they play a critical role in numerous cellular processes during development and homeostasis. During embryogenesis, certain miRNAs regulate the timing of gene expression such that developmental signals are co-ordinately expressed. For example, family members of let-7 play a crucial role in determining stem cell fate decisions, regulating transitions between pluripotency and differentiation [6]. Similarly, the miR-17-92 cluster has been linked to the regulation of hematopoiesis, promoting the differentiation of various blood cell lineages [7]. In addition to their developmental roles, miRNAs have a critical function in maintaining cellular homeostasis in adult organisms. They participate in the regulation of metabolic pathways, thus affecting processes like glucose homeostasis and lipid metabolism [8].

Dysregulation of miRNAs is involved in the development of cancer, cardiovascular diseases, neurodegenerative diseases, and autoimmune diseases. In the cardiovascular system, some miRNAs have been involved in regulating cardiac hypertrophy and remodeling in response to stress, indicating their roles in the maintenance of heart function [9]. Furthermore, miRNAs are also involved in immune responses, particularly in immune cell development and function, thereby affecting adaptive and innate immunity [10].

In neurodegenerative diseases such as Alzheimer's disease, dysregulated miRNA expression has also been implicated in amyloid-beta metabolism and tau phosphorylation, leading to the

connection of miRNAs with neuronal degeneration. While their roles are important in regulating normal physiology, dysregulation of miRNAs has been linked to a variety of diseases, most notably cancer. Oncogenic miRNAs, commonly referred to as oncomiRs, can promote tumorigenesis through the silencing of tumor suppressor genes, while tumor-suppressive miRNAs generally inhibit pathways toward cancer formation [11].

The miR-21 oncomiR has been found to be overexpressed in diverse cancers, such as breast, lung, and colorectal cancer where it represses numerous tumor suppressors [12].

Conversely, members of the let-7 family that function as tumor suppressors are frequently downregulated in the majority of tumor types. Since they have been associated with a variety of diseases, miRNAs are being targeted as new biomarkers of diagnosis, prognosis, and treatment. Extracellular miRNAs in body fluids, including blood and saliva, are stable and mirror physiological and pathological conditions of individuals, rendering them promising candidates for non-invasive diagnostic methods [13].

Several studies have demonstrated particular miRNA signatures in particular cancers, thereby enhancing the prospects of miRNAs as diagnostic markers [14].

Moreover, bioinformatics tools can help predict possible miRNA-mRNA interactions and enable researchers to discover regulatory networks implicated in disease development. Aside from their potential as biomarkers, the therapeutic use of miRNAs is being intensively studied. Some strategies involve miRNA replacement therapy, in which tumor-suppressive miRNAs are introduced to reconstitute their expression, and miRNA inhibitors, which block the activity of oncogenic miRNAs. The formulation of nanocarrier systems for targeted delivery further increases the therapeutic efficacy of these methods, allowing for the specific delivery of miRNA-based therapeutics to the target tissues [15].

Clinical trials are ongoing to establish the efficacy and safety of miRNA-based therapeutics in a variety of disease contexts, such as cancer and cardiovascular disease. Furthermore, miRNA expression control offers therapeutic potential for new methods of treating autoimmune diseases. Through the specific modification of a single miRNA, scientists can potentially restore equilibrium to the immune system and dampen unnecessary inflammation, offering a novel method of treating diseases such as rheumatoid arthritis and lupus [16].

3- The Biogenesis and Mechanisms of miRNAs

3.1. Initiation of miRNA Biogenesis

The initial step of miRNA biogenesis involves the transcription of the miRNA genes into longer primary transcripts termed pri-miRNAs as described in figure 1.

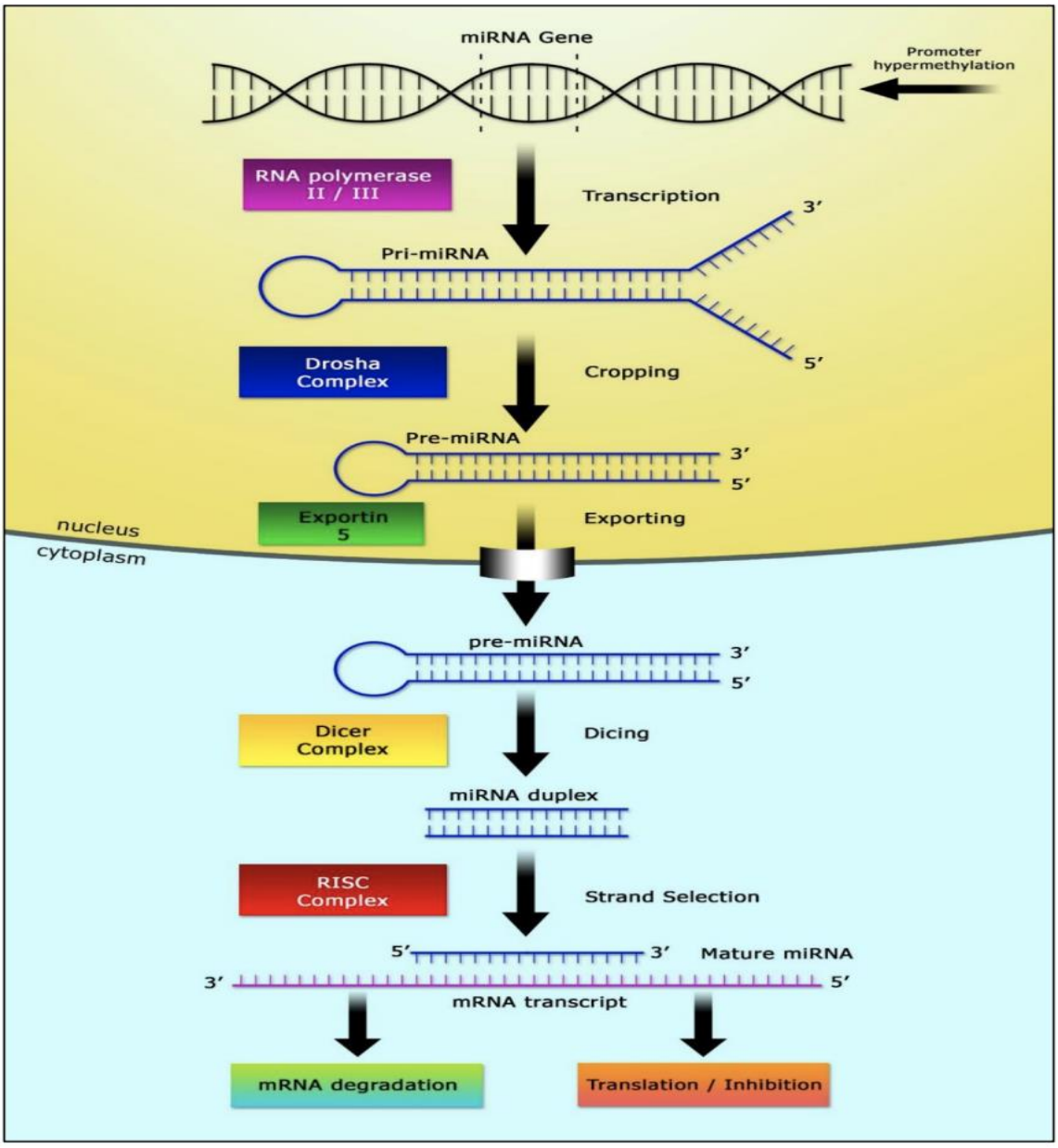

Figure 1. Biogenesis of miRNAs and assembly into RISC complex. RNA polgenerates capped and polyadenylated pri-miRNAs which are processed by Drosha in the nucleus to generate pre-miRNAs. After translocation into the cytoplasm by exportin 5, pre-miRNAs are processed by Dicer to form the RISC complex. Only one strand of the duplex is stably associated with the RISC complex. The mature miRNA directs repression of mRNA containing partially complementary miRNA binding sites. within the 3'UTR.

This typically takes place in the nucleus, done by RNA polymerase II. Although pri-miRNAs are diverse in length, they are mainly a stem-loop in structure, which is very important to know for proper processing . The production of pri-miRNAs is usually controlled by transcription factors and a number of upstream signaling pathways, suggesting a complexity in their formation that cannot be separated from the cellular environment [17].

3.2. Nuclear Processing

The pri-miRNAs, when synthesized, are converted to pre-miRNAs by the Drosha-DGCR8 (DiGeorge Syndrome Critical Region 8) complex, a very critical process that dictates the accuracy of miRNA maturation. The RNase III enzyme Drosha cleaves the pri-miRNA around 11 base pairs from the stem-loop base, resulting in a pre-miRNA of around 70 nucleotides in length [18].

Nuclear processing is also important in ensuring the pre-miRNAs are of the correct length and structure necessary for the downstream events in the miRNA biogenesis pathway. After cleavage by Drosha, the resulting pre-miRNAs are transported from the nucleus to the cytoplasm through the Exportin-5 pathway. The process of transport is mediated by the interaction of pre-miRNAs with Exportin-5, which binds the 5' cap and the two-nucleotide 3' overhang typical of pre-miRNAs [19]. This process of transport is essential for the further steps in miRNA maturation and function.

3.3. Cytoplasmic Processing

When they reach the cytoplasmic environment, pre-miRNAs are further processed by the enzyme Dicer, an RNase III endonuclease class. Dicer catalyzes the cleavage of pre-miRNA to form mature miRNA duplexes, typically comprising about 22 nucleotides in length. This processing is critical in yielding the mature strands of miRNA that are used in gene silencing. In this process, one strand of the duplex is selectively incorporated into the RNA-induced silencing complex (RISC), and the other strand, commonly known as the "passenger strand," is typically degraded [20].

3.4. Mechanisms of Gene Regulation

The incorporation of mature miRNA into the RNA-induced silencing complex (RISC) is essential for it to play its role in the regulation of gene expression. RISC, a protein complex made up of several proteins, facilitates the interaction of miRNA with its respective target mRNAs. The mode

of action mainly relies on the sequence complementarity between the miRNA and target mRNA. In most cases, this binding occurs in the 3' untranslated region (3' UTR) of target mRNAs [21].

The engagement of miRNAs with target mRNAs leads to one of two main consequences: translational repression or mRNA degradation. Translational repression refers to the inhibition of protein synthesis from the target mRNA without changing its stability, while mRNA degradation refers to the endonucleolytic cleavage of the target mRNA, typically triggered by the endonuclease activity of Argonaute proteins (the core constituents of RISC) This functional versatility of miRNAs allows them to regulate the gene expression levels according to the developmental stage and cellular context. Apart from that, recent studies have found other roles for miRNAs, including stimulation of translation under specific conditions, and therefore their regulatory potential is not always restricted to repression [22].

3.5. Regulatory Networks and Feedback Loops

MiRNAs are not only regulated by their biogenetic machinery but also participate in complex regulatory networks, often targeting multiple mRNAs, including those encoding transcription factors. This dynamic interaction forms feedback loops that can have a deep impact on cellular responses and outcomes. For instance, the expression of certain transcription factors can induce the synthesis of certain miRNAs, which can further have the potential to regulate the expression of the transcription factor itself, resulting in a complex mechanism of feedback [23]. These regulatory systems highlight the importance of deciphering miRNA biogenesis and function within larger processes since their ability to refine gene expression has a strong influence on cellular processes and far-reaching implications in development, disease, and therapeutic intervention.

4. Dysregulation of microRNAs

Dysregulation of miRNAs has been widely recognized as an important factor in the initiation and progression of most diseases, especially in oncology, cardiology, and neurobiology. In cancer, miRNAs can function as oncogenes or tumor suppressor genes. For instance, the overexpression of miR-21, found in most cancers such as breast, lung, and colorectal cancers, leads to silencing of tumor suppressor genes like PTEN and TPM1. This results in increased cell proliferation and decreased apoptosis, thereby promoting tumor growth and metastasis. Conversely, miRNAs such as

the let-7 family, which are generally downregulated in cancers, facilitate the overexpression of oncogenic proteins such as RAS and MYC, thereby facilitating malignant transformation. This double function highlights the ability of miRNAs to intricately influence tumor biology, positioning them as vital contributors to cancer dynamics and promising candidates for future therapeutic interventions.In cardiovascular disease, miRNA dysregulation is a central player in several pathological mechanisms, such as cardiac hypertrophy, heart failure, and atherosclerosis. MiR-133a has been found to maintain cardiomyocytes in an ordinary growth condition under physiological conditions. Its downregulation in pathological stimulation is implicated in myocardial hypertrophy and fibrosis [24]. Circulating miRNA levels of some miRNAs have been reported to be explored as cardiovascular disease biomarkers, with early diagnosis and monitoring potential for disease development.

Neurodegenerative diseases also involve widespread miRNA dysregulation, implicated in synaptic plasticity, neuroinflammation, and survival of neurons. miR-29 has been found to be responsible for controlling mRNAs that encode for proteins involved in amyloid precursor protein processing and amyloid-beta plaque deposition, hallmarks of the disease, in Alzheimer's [14].

miR-146a also becomes induced in response to neuroinflammatory signals, pointing to their roles in the neurodegenerative inflammatory response. The changes in miRNA profiles in the brain and body fluids are also being explored as possible biomarkers for early diagnosis and therapeutic monitoring of Alzheimer's and other neurodegenerative disorders.The impact of miRNA dysregulation is also seen in metabolic diseases like diabetes and obesity. MiR-375, which controls insulin release from pancreatic beta cells, tends to be downregulated in type 2 diabetes mellitus, leading to defective insulin release and glucose homeostasis. The connection emphasizes the complex functions miRNAs have in metabolic regulation as well as their promise as therapeutic agents in controlling metabolic disease.

Therapeutic application of miRNAs is an innovative field. MiRNA mimics, antagomirs that inhibit specific miRNAs, and small molecules that modulate miRNA processing have been promising in preclinical and clinical trials. The capability to engineer targeted drugs that correct miRNA dysregulation can potentially be extended to novel therapeutic approaches for multifactorial diseases.

5. MicroRNAs as Biomarkers and Therapeutic Targets

5.1. MiRNAs as Biomarkers

MiRNAs have proven to be useful biomarkers in a range of conditions, especially in cancers, cardiovascular diseases, and metabolic disorders. Their levels of expression can indicate pathological alterations, allowing for early detection and treatment. For example, some miRNAs, including miR-21 and miR-155, are reported to be highly overexpressed in different cancers. Circulating plasma miRNAs have also been investigated as possible tools for the early diagnosis of conditions like acute myocardial infarction and heart failure [25]. The stability of miRNAs in biological fluids such as blood and saliva and their unique expression profiles in various diseases make them an excellent choice for both early diagnosis biomarkers and therapeutic targets.

5.2. Therapeutic Targets by MiRNAs

The potential of miRNAs regulating gene expression at various levels opens new therapeutic windows. Therapies that restore the function of downregulated miRNAs or inhibit the activity of overexpressed oncogenic miRNAs are being developed. For example, miR-34a mimetics have been encouraging in preclinical models of various cancers since they can suppress cell proliferation and induce apoptosis [26]. However, miR-21 antagomirs have been explored as a therapeutic treatment in disease states of its overexpression, including breast cancer [27].

5.3. Recent Progress and Future Directions

Recent innovations in drug delivery systems, such as lipid nanoparticles and exosomes, are enhancing the efficacy of miRNA-based treatments [10]. Clinical trials are evaluating the efficacy and safety of miRNA-based treatments, further indicating a heightened interest in taking this research to the clinical setting. Off-targeting effects and the need for specialized delivery mechanisms are still challenges, however.

As biomarkers, miRNAs offer a powerful way to identify and follow diseases early, and as therapeutic targets, they promise to develop new medicines. Studies will continue to uncover their full clinical potential and pave the way toward personalized medicine approaches based on individuals' unique miRNA signatures.

6. Conclusion

MiRNAs are essential regulators of gene expression, playing important roles in a wide range of biological processes and disease mechanisms. Their capacity to target several processes simultaneously allows them to modulate critical cellular processes, such as proliferation and apoptosis. Misregulation of miRNAs has been implicated in numerous diseases, including cancers, cardiovascular diseases, and neurodegenerative diseases, pointing to their importance in both the initiation and progression of disease.

As biomarkers, miRNAs provide opportunities for early disease diagnosis and follow-up of patients since they express distinct profiles and are stable within body fluids. Their non-invasive diagnostic function can improve patient outcomes by permitting timely intervention. Certain miRNAs have demonstrated predictive and prognostic marking, thus stimulating personalized medicine practices.

Aside from being used as biomarkers, the therapeutic uses of miRNAs are increasingly being investigated. Techniques such as miRNA mimics, antagomirs, and targeted delivery systems are also being explored to restore normal miRNA function or inhibit oncogenic miRNAs. The advancements in delivery systems, including lipid nanoparticles and exosomes, increase the potential for these miRNA-based treatments to be developed.

However, there are challenges that remain, such as the development of precise delivery strategies, minimizing off-target effects, and completely understanding the regulatory networks that involve miRNAs. More research is needed to overcome these challenges and maximize the clinical potential of miRNAs.

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