

MicroRNA in Human Diseases: Molecular Mechanisms, Diagnostic Applications, and Therapeutic Potential

Nameer AbdAlkhadher Haithuer 

Al-Iraqia Science University, Baghdad, Iraq

* Corresponding Author: Nameer1962@baghdadcollege.edu.iq

Abstract: The family of naturally occurring short non-coding RNA molecules that range in size from 18 to 25 nucleotides are known as microRNAs (miRNAs) and is involved in post-transcriptional gene regulation. Short messenger RNAs (miRNAs) have become crucial regulators of various biological processes since their discovery. These include metabolism, cell growth and maturation, immune system functioning, and programmed cell death. Abnormalities in miRNA expression have been associated with multiple human diseases such as cancer, cardiovascular disease, neurological disease, and chronic kidney disease. Recent developments in molecular biology and high-throughput sequencing have greatly aided our understanding of miRNA function and their role in disease pathogenesis. Furthermore, miRNAs in circulation show tremendous potential in the diagnosis, prognosis, and evaluation of therapeutic efficacy of diseases. Therapeutic strategies that target biological circuits associated with diseases have attracted a great deal of interest because of miRNA mimics and inhibitors. While recent progress has been made, safety, side effects, and efficiency issues are still major concerns that need to be resolved. This study provides a brief overview of the fundamental mechanisms for miRNA biogenesis and action. It also explores the role they play in numerous human diseases, diagnostic and therapeutic applications, and potential future applications in clinical translation.

Keywords: MicroRNA, Gene Regulation, Biomarkers, Cancer, Chronic Kidney Disease, Cardiovascular Disease, Neurological Disorders, Precision Medicine.

1. Introduction

A major discovery three decades ago was the identification of a new class of small, non-coding, regulatory RNAs called microRNAs (miRNAs). As small non-coding RNAs, they regulate the expression of genes by hybridizing with messenger RNAs (mRNAs) containing similar sequences, thereby either repressing translation or leading to the degradation of the mRNA [1]. It is believed that miRNAs control more than 60% of the human protein-coding genes, highlighting the critical role of miRNAs in maintaining cellular homeostasis. In 1993, the first microRNA (miRNA) was discovered, called Lin-4, in *Caenorhabditis elegans* [2]. Over the last decade, thousands of miRNAs have been discovered in a wide variety of species, including humans. MicroRNAs are produced by human cells and involved in the regulation of many processes such as metabolism, activity of the immune system, development of the embryo and repair of tissues [3]. Changes in the expression of miRNAs can promote the development of disease through

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a variety of ways, including affecting normal cellular functions. With the new technologies of transcriptomics, bioinformatics, and next-generation sequencing, it is possible to identify disease-specific miRNA signatures [4]. These signatures exhibit promise as diagnostic biomarkers and therapeutic targets. Investigating microRNAs (miRNAs) is one of the fastest growing areas in molecular medicine.

The goal of this review is to give a full overview of the miRNA biology, their role in human diseases, and their therapeutic and diagnostic potential.

2. Biogenesis of MicroRNA

MicroRNA biosynthesis is a complex process which is tightly controlled and involves both nuclear and cytoplasmic activities. The majority of miRNA genes are transcribed by RNA polymerase II to give rise to primordial miRNA transcripts (pri-miRNAs) that can possess miRNA sequences [5]. The Microprocessor complex, consisting of proteins Drosha and DGCR8, helps to produce pre-miRNAs from pri-miRNAs in the cell nucleus. Exportin-5 is involved in the export of structures that are hairpin shaped and around 70 nucleotides long from the nucleus to the cytoplasm [6]. In the cytoplasm, pre-miRNAs are further processed into mature miRNAs by the enzyme RNase III, Dicer [7]. Usually, the complementary strand is cut away, but in the RNA-induced silencing complex (RISC) one strand is incorporated. The mature miRNA directs RISC to specific mRNAs, leading to repression of translation or degradation of mRNAs. The effectiveness of miRNA synthesis is important for normal functioning of the cell [8]. The defects of miRNA processing machinery (including Drosha and Dicer) are associated with human diseases such as cancer and neurological diseases [9].

3. Mechanisms of Gene Regulation by MicroRNAs

The predominant control of microRNA transpires post-transcription. Upon incorporation into the RNA-induced silencing complex (RISC), mature miRNAs seek complementary sequences inside the 3' untranslated region (3'UTR) of target mRNAs for silencing purposes [10]. The degree of complementarity between miRNA and the target determines if the interaction causes repression of protein translation or degradation of the messenger RNA. The overall poor binding of miRNAs in mammals is found to have its main effect on translational inhibition. On the other hand, highly complementary interactions can result in direct degradation of the target mRNAs [11]. These strategies are part of the multiple ways microRNAs can control biological processes such as cell cycle, apoptosis, differentiation, immune system activation and metabolism. One miRNA can target multiple genes and a cluster of miRNAs can target one gene. This intricate regulatory network enables microRNAs to regulate gene expression and preserve cellular homeostasis. These regulatory processes could worsen pathological diseases such as cardiovascular disease, chronic inflammatory disorders and cancer [12]. Recent transcriptome analyses have uncovered that the pathways connected with miRNAs involve PI3K/Akt, Wnt/ β -catenin, TGF- β , NF- κ B and MAPK. These processes regulate immunological control, cell migration, cell proliferation and survival. Thus, the

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expression of miRNAs can have a major impact on symptom development and progression.

4. Role of MicroRNAs in Cancer

Cancer has been a main focus of miRNA research. Numerous studies have identified a correlation between dysregulated miRNA expression and tumor initiation, progression, metastasis, and therapy resistance. The biological role of miRNAs dictates their classification as either oncogenic miRNAs (oncomiRs) or tumor suppressor miRNAs. OncomiRs inhibit tumor suppressor genes, hence facilitating tumor proliferation. MiR-21 is a thoroughly investigated oncomiR that is overexpressed in various cancer types, including glioblastoma, lung, colorectal, and breast malignancies. Increased expression of miR-21 inhibits apoptosis and promotes cell proliferation by suppressing numerous tumor suppressor genes, including PDCD4 and PTEN. Tumor suppressor miRNAs inhibit cancer proliferation by targeting oncogenes. The miR-34 family is one of the most recognized microRNAs (miRNAs) that inhibit tumor growth. Decreased expression of miR-34 has been linked to an increase in tumorigenesis and metastatic potential in many malignancies [13].

Table 1. Major Cancer-Associated MicroRNAs

MicroRNA	Function	Associated Cancer
miR-21	Oncogenic	Breast, Lung, Colon
miR-155	Oncogenic	Lymphoma, Leukemia
miR-210	Hypoxia-associated	Renal Cell Carcinoma
miR-34a	Tumor Suppressor	Multiple Cancers
let-7 Family	Tumor Suppressor	Lung Cancer
miR-200 Family	EMT Regulation	Ovarian and Breast Cancer

MicroRNAs have a vital role in the regulation of cancer stem cells, epithelial-to-mesenchymal transition (EMT), immunological evasion, and angiogenesis. They exert several influences on tumor aggressiveness and therapeutic responsiveness. Recent study indicates that circulating miRNAs may serve as non-invasive biomarkers for the early diagnosis of cancer. An instance is the identification of elevated levels of miR-21, miR-155, and miR-210 in the bloodstream of cancer patients prior to the manifestation of any external signs [14]. This discovery highlights the importance of miRNAs for cancer screening and personalized therapies. Moreover, therapeutics utilizing microRNAs are exhibiting promising outcomes in the battle against cancer. Two strategies used to restore functions of tumor suppressor miRNAs or inhibit oncogenic miRNAs are the use of synthetic mimics and antisense oligonucleotides. Numerous pharmaceuticals targeting microRNAs are undergoing clinical trials and initial results are encouraging [15].

5. Role of MicroRNAs in Cardiovascular Diseases

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Cardiovascular diseases (CVDs) remain the predominant cause of mortality worldwide. Increasing evidence indicates that miRNAs are essential contributors to cardiovascular development, vascular homeostasis, and cardiac remodeling. A multitude of microRNAs regulates endothelial function, vascular inflammation, and smooth muscle cell proliferation. Disruption of these systems results in cardiovascular issues including hypertension, atherosclerosis, heart failure, and myocardial infarction. MiR-126 is highly expressed in endothelial cells and maintains the integrity of blood vessels. Studies have linked diminished miR-126 expression to atherosclerotic disease and endothelial dysfunction. Likewise, miR-1 and miR-1 govern heart growth and functionality.

Post-myocardial infarction, ventricular remodeling and cardiac fibrosis arise from the dysregulated expression of miR-21, miR-29, and miR-208. Untreated, these alterations may result in cardiac failure. Circulating miRNAs have been identified as possible biomarkers for cardiovascular disorders. The detection of elevated levels of particular miRNAs in patient plasma quickly after myocardial injury facilitates early diagnosis and risk assessment. Moreover, therapeutic modulation of miRNA expression has demonstrated encouraging outcomes in preclinical cardiovascular research.

6. Role of MicroRNAs in Neurological Disorders

The microRNAs play important regulatory roles in neuroinflammation, synaptic plasticity, neuronal differentiation and nervous system development. Many neurological and neurodegenerative disorders have been associated with aberrant expression of microRNAs. Alzheimer's disease is a disease associated with abnormal levels of expression of miRNAs that influence the processing of Amyloid precursor proteins and phosphorylation of tau proteins. Many miRNAs (micro RNA) such as miR-29, miR-107 and miR-132 have been associated with cognitive decline and cancer progression. There is a correlation between Parkinson's disease and alteration of miRNA expression. The dysregulation of miR-7 and miR-153 leads to a change in the level of alpha-synuclein that results in neuronal degeneration. In MS, miRNAs seem to be involved in immunological regulation and neuroinflammation. Some have proposed changes in miRNA blood markers as diagnostic markers.

7. Role of MicroRNAs in Kidney Diseases

New studies show that miRNA therapy could be a novel approach to treating neurological diseases by specifically targeting disease-related cellular pathways. Effective administration and the blood-brain barrier continue to be a significant obstacle.

The role of microRNAs in kidney diseases. The function of microRNAs in kidney diseases. MicroRNAs are well established to play a role in the regulation of kidney development, homeostasis, inflammation and fibrosis. The changes of miRNA expression play a significant role in renal fibrosis, acute kidney injury, diabetic nephropathy and chronic kidney disease (CKD). MiR-21 is the most-studied renal miRNA. High levels of miR-21 expression led to fibrosis by activation of TGF- β signaling pathways and repression of antifibrotic genes. High miR-21 expression is associated with impaired renal

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function and development of chronic kidney disease (CKD). MiR-192 is pivotal in diabetic nephropathy via modulating fibrotic pathways and the formation of the extracellular matrix. Renal fibrosis and excessive accumulation of collagen are caused by dysregulation of miR-29 family members. Several studies have been shown that miRNAs in urine and blood could be used as markers for early renal disease. Unlike common tests like serum creatinine, miRNAs are able to detect pathogenic changes before a significant loss of renal function. New studies have shown that miR-21, miR-29 and miR-192 in urine could be useful biomarkers of the severity and progression of disease. This has spurred many people to consider miRNA profiling as a promising tool for precision nephrology.

Table 2. Major Kidney Disease-Associated MicroRNAs

MicroRNA	Disease Association	Biological Function
miR-21	CKD, Renal Fibrosis	Promotes Fibrosis
miR-29	Renal Fibrosis	Regulates Collagen Production
miR-192	Diabetic Nephropathy	ECM Regulation
miR-146a	Inflammation	Immune Regulation
miR-200 Family	EMT Control	Antifibrotic Activity

8. Diagnostic Applications of MicroRNAs

The identification of circulating miRNA has opened up new possibilities for non-invasive monitoring and diagnosis of diseases. MicroRNAs (miRNAs) are unique biomarkers in their ability to be highly stable in a wide variety of body fluids, including blood, plasma, serum, urine, saliva, and cerebrospinal fluids. They are resistant to RNase degradation and are therefore ideal therapeutic agents. An advantage of miRNA diagnostics is the ability to detect diseases early in the course. An alteration in miRNA expression profile usually takes place before any evident symptoms show up. Therefore, microRNAs (miRNAs) could provide valuable information about the onset, progression and sensitivity to therapy of a disease. In oncology, certain circulating miRNAs have been suggested as biomarkers for the early detection of cancer. Lung, colorectal, breast and kidney cancer patients have been found to have higher levels of miR-21, miR-155 and miR-210. If the expression of miR-34a or other tumor suppressor miRNAs is decreased, it may be a sign of the onset of malignant transformation.

Circulating miRNAs, including miR-1, miR-133, and miR-208, have been used for diagnostics of heart failure and myocardial infarction. As an aid to the existing methods of diagnosis, these biomarkers can offer the potential to improve risk stratification. The use of urinary miRNAs as a promising diagnostic tool for renal diseases is a promising approach. Urine collection is non-invasive and urinary miRNA profiling can be used for routine screening and for monitoring the course of chronic kidney disease. Increased urinary miRNA levels were shown to be correlated with the extent of renal fibrosis.

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Although results have been promising, there are problems with test consistency, normalization procedures, and individual variability. In order to consider broad clinical use, extensive multi-centre trials are required.

9. Therapeutic Applications of MicroRNAs

MicroRNA-based therapies are a promising and growing field in precision medicine. Unlike genes, microRNAs have a huge therapeutic potential in the treatment of complex diseases since they regulate complete biological pathways. There are two main therapeutic approaches that have been developed:

9.1 MicroRNA Mimics

Researchers use synthetic molecules called microRNA mimics to reintroduce the ability of miRNAs that have been lost or reduced to function. This strategy is more useful as the disease progresses and the levels of tumor suppressor miRNAs decrease.

For example, re-expression of miR-34a in preclinical mice has shown promising antitumor effects. The increased miR-34a activity leads to apoptosis, decreased tumor growth and inhibits metastasis.

9.2 MicroRNA Inhibitors

Researchers create microRNA inhibitors called “antagomirs” to reduce over-expressed miRNAs associated with diseases. This technique is quite beneficial for oncogenic miRNAs, such as miR-21.

Experimental data suggests that inhibition of miR-21 levels leads to a reduction of fibrosis, inflammation and tumourgenesis. Similar methods have been shown to be of therapeutic benefit in renal and cardiovascular diseases.

9.3 Delivery Systems

To implement the therapeutic use of miRNA therapies, efficient delivery systems are needed. Research has focused on a vast range of techniques such as:

Lipid nanoparticles

Polymeric nanoparticles

The organisms that carry infectious diseases from one host to another.

Transport via exosomes

Antibody-targeting mechanisms

Nanotechnology-based delivery systems have significantly improved the selectivity of tissues and the steadiness of the treatments. However, additional improvement is needed before it is widely used in the clinical application.

10. Challenges and Limitations

Although considerable progress is being made with the clinical use of miRNA-based technology, there are still many obstacles to overcome.

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10.1 Off-Target Effects

A single miRNA can modulate several genes, and changes in the miRNA in the therapy may result in side effects on other pathways. The effects on targets not intended can cause potentially harmful biological consequences.

10.2 Delivery Efficiency

The effective and tissue-specific delivery of miRNA therapies continues to pose a significant problem. Synthetic miRNAs tend to be rapidly degraded in serum and do not reach tissues.

10.3 Immune Responses

Various administration techniques may elicit immunological or inflammatory responses. In clinical applications, long-term safety is thus a critical issue.

10.4 Standardization Issues

Prior to the utilization of diagnostics, it is imperative to create protocols for sample collection, processing, normalization, and result interpretation. At the present time, methodological differences within the studies are hampering reproducibility.

10.5 Cost and Regulatory Challenges

Nucleic Acid based medicines need comprehensive safety testing and regulatory assessment to be developed and approved. This results in a long development time and high costs.

11. Conclusion

MicroRNAs (miRNAs) play a significant role in the regulation of many disease pathways and biological processes. MicroRNA expression is dysregulated in cancer, cardiovascular disease, neurological disease, as well as renal disease. In recent years, tremendous progress has highlighted the important diagnostic and therapeutic roles of miRNAs. The utilization of miRNAs, both in circulation and in particular tissues, demonstrates potential as biomarkers for the early identification and forecasting of disease. Furthermore, miRNA mimics and inhibitors are new therapeutic approaches that have the ability to target complex cellular networks. Despite some challenges, such as off-target effects, regulatory concerns, and efficient delivery methods, this subject is moving forward with the help of scientific and technological developments. The amalgamation of miRNA research with forthcoming precision medicine strategies could fundamentally revolutionize illness management and enhance patient outcomes worldwide.

12. Future Work

MicroRNA research has great potential. The emergence of new systems biology, artificial intelligence, machine learning, and next-generation sequencing technologies is expected to hasten the identification of new miRNA markers and targets. Association of miRNA

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profiling with genomic, transcriptomic, proteomic and metabolomic data could provide a more comprehensive understanding of disease processes. In the future, multi-omics methods are likely to play a crucial role in the personalized approach to treatment. AI algorithms are increasingly being used for miRNA pattern identification associated with diseases and predicting treatment efficacy. These technologies have the potential to define individualized treatment plans optimally. Furthermore, current limitations in the therapeutic use of miRNAs could be overcome by improvements in gene-editing technology and the delivery of nanoparticles. Further clinical trials will determine the safety and effectiveness of these methods over time. In an era of precision medicine, microRNAs are expected to play a major role in the diagnosis, prognosis, and treatment of disease.

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