JHB

Journal of Health and Biology

https://journalhb.org/

SPBH

Review Article

The Regulatory Landscape of MicroRNAs in Human Pathogenesis: From Molecular Mechanisms to Clinical Applications

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DOI: https://doi.org/10.71428/JHB.2026.0113

Abstract:

MicroRNAs (miRNAs) have emerged as pivotal post-transcriptional regulators, controlling a wide range of biological processes, from cell differentiation to programmed cell death. Their dysregulation is closely linked to the mechanisms underlying many complex diseases, including tumors and autoimmune disorders. This article reviews current knowledge about microRNA synthesis, its mechanistic role in gene silencing, and its clinical utility as non-invasive biomarkers and therapeutic targets. It focuses particularly on its role in breast cancer and rheumatoid arthritis, highlighting the transition from basic molecular biology to clinical diagnostic applications.

Keywords: Biomarkers miRNAs, mRNA Targeting, Gene Regulation, Molecular Mechanism.

1. Interaction

The discovery of microRNAs (miRNAs) has fundamentally transformed the core concept of molecular biology, revealing a complex layer of post-transcriptional gene regulation that was previously unseen. MicroRNA molecules are classified as non-coding, single-stranded, endogenous RNA molecules, typically ranging from 18 to 25 nucleotides in length. Once the identification of the first miRNA molecule, lin-4, in the worm Caenorhabditis elegans, thousands of microRNA molecules have been characterized in humans, collectively regulating more than 60% of the protein-coding genome. [1, 2].

These small molecules act as regulators of gene expression. By binding, either partially or completely, to the 3′ untranslated regions (3′ UTRs) of target messenger RNA (mRNA), they coordinate either the inhibition of translation or the direct degradation of the mRNA. This regulatory capacity enables a single miRNA molecule to control hundreds of different genes, placing it at the heart of vital biological processes, including embryonic development, cell proliferation, apoptosis, and metabolic homeostasis. [3,4].

In the context of human pathology, the "microRNA fingerprint"—that is, the specific pattern of expressed microRNA—is often severely distorted. In oncology, microRNA molecules can act either as tumor-promoting molecules, which promote tumor growth by silencing oncogenes, or as onco-suppressive genes, which normally suppress the

Received: March 10, 2026. Accepted: May 5, 2026. Published: June 18, 2026

expression of oncogenes but are often lost in cancer cells [5]. In addition to their role in cancer, microRNAs play a crucial role in regulating the immune system. Their dysregulation is a hallmark of autoimmune diseases such as rheumatoid arthritis, where they mediate chronic inflammation and synovial hyperplasia. [6].

Due to their high stability in biological fluids (such as serum, plasma, and saliva), thanks to their encapsulation in extravesicles or their binding to Ago2 proteins (Argonaute2), the molecules of miRNA have emerged as strong candidates for a non-invasive diagnostic biomarker. This review aims to provide a comprehensive analysis of microRNA composition, its mechanistic roles in breast cancer and rheumatoid arthritis, and the current challenges in translating these findings into clinical treatments [7].

2. Biogenesis and Molecular Mechanism of Action

The synthesis of miRNA molecules is a fragmented process involving both the nucleus and cytoplasm. This process begins with the transcription of long primary transcripts (pri-miRNAs) by RNA polymerase II. These transcripts are subsequently processed in the nucleus by the Drosha-DGCR8 "microprocessor" complex, producing hairpin-shaped pre-miRNA molecules (pre-miRNAs) approximately 70 nucleotides long(Figure 1). [8].

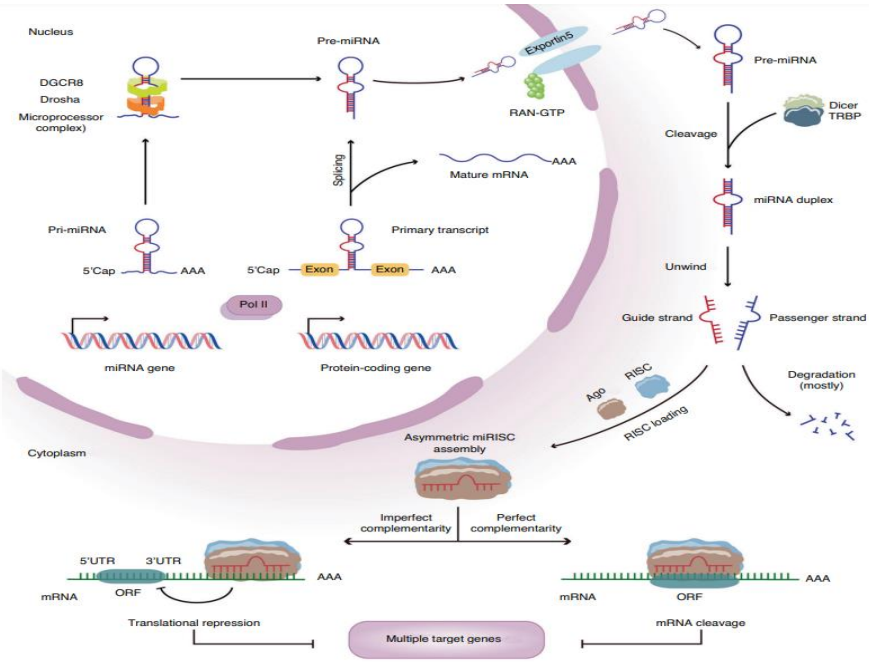

Figure 1: Overview of the biogenesis and mechanism of action of miRNAs [8].

The pre-miRNA is then exported to the cytoplasm via the Exportin-5/Ran-GTP pathway. Once it reaches the cytoplasm, the Dicer enzyme, an RNase III enzyme, cleaves the terminal loop, producing a mature double-stranded miRNA molecule. One of its strands, the guide strand, is loaded into the RISC-inducible RNA silencing complex and specifically binds to Argonaute (Ago) proteins. The RISC complex then scans mRNA molecules for complementary sequences, leading to gene silencing—a process essential for maintaining cellular protein homeostasis. [9, 10].

4. MicroRNAs in Breast Cancer: Oncogenic vs. Tumor Suppressive Networks

The role of microRNA molecules (miRNAs) in breast cancer, for example, is multifaceted; they act as either promoters or inhibitors of tumor formation, depending on their target genes. Research has increasingly shown that the disruption of specific patterns of microRNA molecules is not merely a byproduct of malignant transformation; it is a key factor in determining the disease phenotype. [11].

4.1. Oncogenic MicroRNAs (OncomiRs)

OncomiR molecules are characterized by increased expression in cancerous tissues. These cells target and inhibit tumor suppressor genes, thus promoting cell survival, proliferation, and spread.

- *miR-21*: One of the most frequently overexpressed miRNA molecules in breast cancer. This molecule works by targeting the programmed cell death gene 4 *(PDCD4).* Inhibition of *PDCD4* by *miR-21* prevents apoptosis (programmed cell death) and promotes cancer cell invasion and metastasis into surrounding tissues [12].
- miR-155: Often associated with advanced stages of breast cancer, miR-155 modifies the tumor microenvironment. It has been shown to target the *SOCS1* gene, leading to activation of the *STAT3* signaling pathway, which promotes tumor cell proliferation [13].
- *miR-10b*: Closely associated with metastatic behavior. It is activated by the transcription factor Twist and leads to the inhibition of *HOXD10*, which in turn leads to the upregulation of pro-metastatic genes such as *RHOC* [11].

4.2. Tumor Suppressor MicroRNAs

Conversely, tumor suppressor miRNAs are often downregulated or lost in breast cancer. This leads to the uncontrolled expression of the absence of oncogenes.

- The *let-7* family: One of the first miRNA families whose role in suppressing tumor growth was discovered. In breast cancer, *let-7* levels are often reduced, leading to the overexpression of its target genes, such as *RAS* and *HMGA2,* which are essential for maintaining the characteristics of cancer stem cells [14].
- miR-34a: Directly regulated by the tumor suppressor protein p53. It induces p53-dependent apoptosis and cell cycle arrest. Loss of *miR-34a* expression is a common feature of triple-negative breast cancer (TNBC), contributing to chemotherapy resistance [15].
- miR-200 family: These microRNAs are key regulators of the epithelial-mesenchymal transformation (*EMT)* process. By targeting the transcription factors *ZEB1* and *ZEB2*, the miR-200 family maintains the epithelial phenotype and inhibits early stages of cancer metastasis [11, 16].

4.3. miRNA and Hormonal Receptor Regulation

A unique feature of miRNAs in breast cancer is their interaction with hormone receptors. For example, miR-206 and miR-125a/b have been identified as regulators of estrogen receptor alpha (ERα) and HER2 expression, respectively. Disruption of these miRNAs can alter the hormonal status of the tumor,

significantly influencing the choice of hormonal or targeted therapies [11].

5. MicroRNAs in Rheumatoid Arthritis (RA): Mediators of Inflammation and Joint Destruction

Rheumatoid arthritis is a systemic autoimmune disorder. It is characterized by chronic inflammation of the synovial membrane and progressive joint destruction.5.1. Modulation of Synovial Inflammation. Recent evidence suggests that dysregulation of microRNA molecules (miRNAs) within the synovial tissue and systemic circulation plays a key role in the initiation and spread of the autoimmune response [17,18].

5.1. Modulation of Synovial Inflammation

In rheumatoid arthritis, synovial fibroblasts (RASFs) exhibit an aggressive, "tumor-like" phenotype. Several miRNA molecules have been identified as key drivers of this transformation.:

- *miR-155* and *miR-146a*: These are perhaps the most studied miRNA molecules in rheumatoid arthritis. While *miR-155* levels are significantly elevated in synovial fluid and phagocytic cells, promoting the production of pro-inflammatory cytokines such as *TNF-α* and *IL-6, miR-146a* is stimulated as a compensatory negative regulator, but often insufficient. *miR-146a* targets cellular signaling [19].
- • Molecules such as TRAF6 and IRAK1, which are essential in the NF-κB pathway [20].
- miR-124: In contrast, miR-124 levels are often reduced in the synovial tissue of patients with rheumatoid arthritis. Under normal conditions, miR-124 inhibits synovial fibroblast proliferation by targeting CDK6 and MCP-1. Its deficiency leads to synovial membrane hyperplasia and increased leukocyte recruitment [21].

5.2. Role in Osteoclastogenesis and Bone Erosion

The hallmark of RA severity is the irreversible erosion of bone and cartilage. MicroRNA molecules (miRNAs) play an important role in regulating osteoclast differentiation.

- miR-223: Elevated levels of miR-223 have been found in the early stages of rheumatoid arthritis. This molecule influences the differentiation of primary myeloid cells into osteoclasts. Studies have shown that its expression in serum can predict the rate of joint destruction in newly diagnosed patients [22].
- miR-17-92 subset: This subset regulates STAT3 signaling, a key transcription factor for Th17 cell formation. Th17 cells are the primary producers of IL-17, which stimulates osteoclasts and leads to bone resorption [17, 23].

5.3. miRNAs as Circulating Diagnostic Markers in RA

Using circulating miRNA molecules to monitor disease activity is one of the most promising clinical applications discussed in recent studies. Unlike traditional indicators such as C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), RNA molecules, such as miR-16 and miR-103, provide a more accurate picture of the underlying molecular disease mechanism, offering a potential tool for personalized rheumatology [24].

6. Integrating miRNA Knowledge: Tabular Summary and Therapeutic Frontiers

To better understand the organizational complexity of miRNAs, it is essential to classify them based on their specific targets and biological effects across various diseases.

6.1. Summary of Key miRNAs in Oncology and Autoimmunity

The following table summarizes the most significant miRNAs identified in this review, their gene targets, and their functional roles:

Table 1 summarizes the most significant miRNAs identified in this review, their gene targets, and their functional roles.

miRNA	Primary Target(s)	Biological Role	Clinical Context
miR-21	*PDCD4, PTEN*	Oncogenic (Inhibition of Apoptosis)	Breast Cancer Metastasis
miR-155	*SOCS1, SHIP1*	Pro-inflammatory Signaling	RA & Breast Cancer
miR-146a	*TRAF6, IRAK1*	Feedback Regulation (Inflammation)	Rheumatoid Arthritis
miR-34a	*CDK4, BCL2*	Tumor Suppressive (Cell Cycle Arrest)	*p53*-related Cancers
miR-200	*ZEB1, ZEB2*	Inhibition of EMT	Metastasis Prevention
let-7	*RAS, MYC*	Growth Inhibition	Cancer Stem Cell Control
miR-124	*CDK6, MCP-1*	Anti-proliferative	Synovial Hyperplasia in RA

6.2. miRNA-Based Therapeutics: The Next Frontier

The transition from the laboratory to the patient's bedside involves two key strategies: MicroRNA replacement therapy and microRNA inhibition.

1. MicroRNA Mimics: This approach aims to restore the function of tumor suppressor microRNAs, which lose their function in diseases such as breast cancer. For example, miR-34a mimics have reached clinical trials due to their ability to resensitize cells to chemotherapy [25].
2. Anti-microRNAs (anti-microRNAs): These are chemically modified oligonucleotide molecules designed to bind to and neutralize tumor- or inflammation- causing microRNAs (such as anti-*microRNA-21*). They have demonstrated significant efficacy in reducing tumor size and inflammatory responses in animal models [26].

6.3. Challenges in Clinical Translation

Despite the immense potential, several hurdles remain:

- Delivery systems: miRNA molecules are susceptible to damage by RNase enzymes in the

bloodstream. Therefore, developing stable delivery systems, such as lipid nanoparticles or exosomes, is crucial [27].

- Off-target effects: Since a single miRNA molecule can regulate multiple genes, unintentionally silencing off-target genes can lead to toxicity.
- Immune Response: Synthetic RNA molecules can stimulate innate immune sensors such as *TLR7*, leading to undesirable inflammatory side effects.

7. Discussion and Future Perspectives

The evidence compiled in this review underscores the dual nature of miRNAs: They are both clinical biomarkers and therapeutic targets. Dysregulated miRNA expression has been reported in many cancers, manifesting tumor suppressive or oncogenic roles [27]. In breast cancer, the shift toward molecular subclassification using miRNA fingerprinting enables more precise diagnosis than traditional histology. In rheumatoid arthritis, miRNAs provide a window into early disease activity, potentially eliminating the need for invasive synovial biopsies [28]. Not only the miRNAs in the tissue, but also those in the peripheral blood are involved in the tumorigenesis, and they may be taken as biomarkers for the diagnosis of patients [29].

Future research should focus on the miRNA-lncRNA-mRNA axis. The interaction between different types of non-coding RNA adds another dimension of complexity to gene regulation. Furthermore, large-scale longitudinal studies are essential to validate these markers across diverse ethnic groups to ensure their global clinical cancers [30].

8. Conclusion

MicroRNAs have revolutionized our understanding of the molecular structure of human diseases. As precise regulators of gene expression, these molecules coordinate complex signaling networks in oncology and autoimmune diseases. While challenges related to delivery and identification persist, the continued integration of microRNA analysis into clinical practice heralds a new era of precision medicine, characterized by non-invasive diagnostics and highly targeted therapies.

Conflict of interest: **NIL**

Funding: **NIL**

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