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REVIEW ARTICLE

# miRNAs: Potential as Biomarkers and Therapeutic Targets for Cancer

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**Abstract**

**Background** MicroRNAs (miRNAs) are pivotal regulators of gene expression, playing a significant role in various human and canine disorders. Dysregulation of miRNA expression is a hallmark of most malignancies.
**Objective** This review aims to analyze the importance of miRNAs in cancer research, focusing on their potential as diagnostic and prognostic biomarkers. Additionally, the study explores the therapeutic possibilities of miRNA-based therapies and the role of miRNAs in revealing mechanisms of resistance to conventional chemotherapy.
**Results** The study underscores the diverse roles of miRNAs in cancer research. miRNAs hold promise as diagnostic and prognostic indicators, offering significant clinical insights. Furthermore, miRNA-based therapies show potential in improving patient outcomes by providing tailored approaches to cancer treatment. Understanding miRNA production and regulation in cancer can elucidate mechanisms of chemotherapy resistance, paving the way for more effective cancer therapies.
**Conclusion** miRNAs hold immense promise for revolutionizing cancer management through liquid biopsies. Their ability to facilitate early detection, monitor disease progression, and guide personalized therapies offers a powerful tool in the fight against cancer. As research progresses, we can anticipate a future where liquid biopsies powered by miRNAs become a cornerstone of effective cancer care, leading to improved patient outcomes and a brighter future for cancer management.

**Keywords:** miRNA; Cancer; MIR-21; TS-miRNAs; Tumor

## 1 Introduction

microRNAs (miRNAs) are small, non-coding RNA molecules that play a crucial role in regulating gene expression at the post-transcriptional level. Since their discovery, miRNAs have been identified as key regulators of various biological processes, including cell differentiation, proliferation, and apoptosis. Their dysregulation is implicated in a wide range of diseases, particularly cancers, where they act as either oncogenes (oncomiRs) or tumor suppressors (TS-miRNAs) [1].

Cancer is a complex, multifactorial disease characterized by uncontrolled cell growth, invasion, and metastasis. Traditional diagnostic and therapeutic approaches, while effective to some degree, often face limitations, particularly in early detection and treatment resistance. This has led to a growing interest in understanding the molecular underpinnings of cancer, where miRNAs have emerged as promising candidates for research. Studies have shown that abnormal miRNA expression is a hallmark of many cancers, affecting tumor development, progression, and response to therapy [2].

In addition to their regulatory roles, miRNAs offer potential as both diagnostic and prognostic biomarkers due to their stability in biological fluids and their tumor-specific expression patterns. Moreover, miRNA-based therapies are being explored as innovative approaches to target cancer at the molecular level, offering a more personalized and precise treatment method. Understanding the role of miRNAs in cancer biology could not only improve early detection and treatment outcomes but also unveil the mechanisms behind chemotherapy resistance, a major challenge in current cancer therapies [3, 4].

This review aims to explore the significance of miRNAs in cancer research, focusing on their diagnostic and therapeutic potential. By analyzing their involvement in cancer progression and their emerging role in overcoming treatment resistance, this study provides a comprehensive overview of miRNAs as pivotal tools in the fight against cancer.

## 2 MicroRNAs and their Emerging Role in Cancer

MicroRNAs (miRNAs) are small, non-coding RNA molecules that exert a highly significant influence on cellular biology. These brief sequences, usually ranging from 18 to 22 nucleotides in length [1], have a significant impact on gene expression by controlling mRNA through post-transcriptional mechanisms [2]. MiRNAs can exert potent control over protein synthesis by selectively binding to particular target mRNAs, therefore inducing either their destruction or a temporary interruption of their translation [2]. The complex interplay between miRNAs and mRNAs governs extensive biological activities, and any disturbance in this equilibrium can lead to the development of illnesses (Figure 1).

MiRNA dysregulation is highly influential in the context of cancer progression. MiRNAs can act as either suppressors or oncogenes of tumors, depending on the specific target genes they control. MiRNAs can exert regulation on tumor formation and progression by specifically targeting genes associated with cell proliferation, differentiation, and apoptosis [3–5].

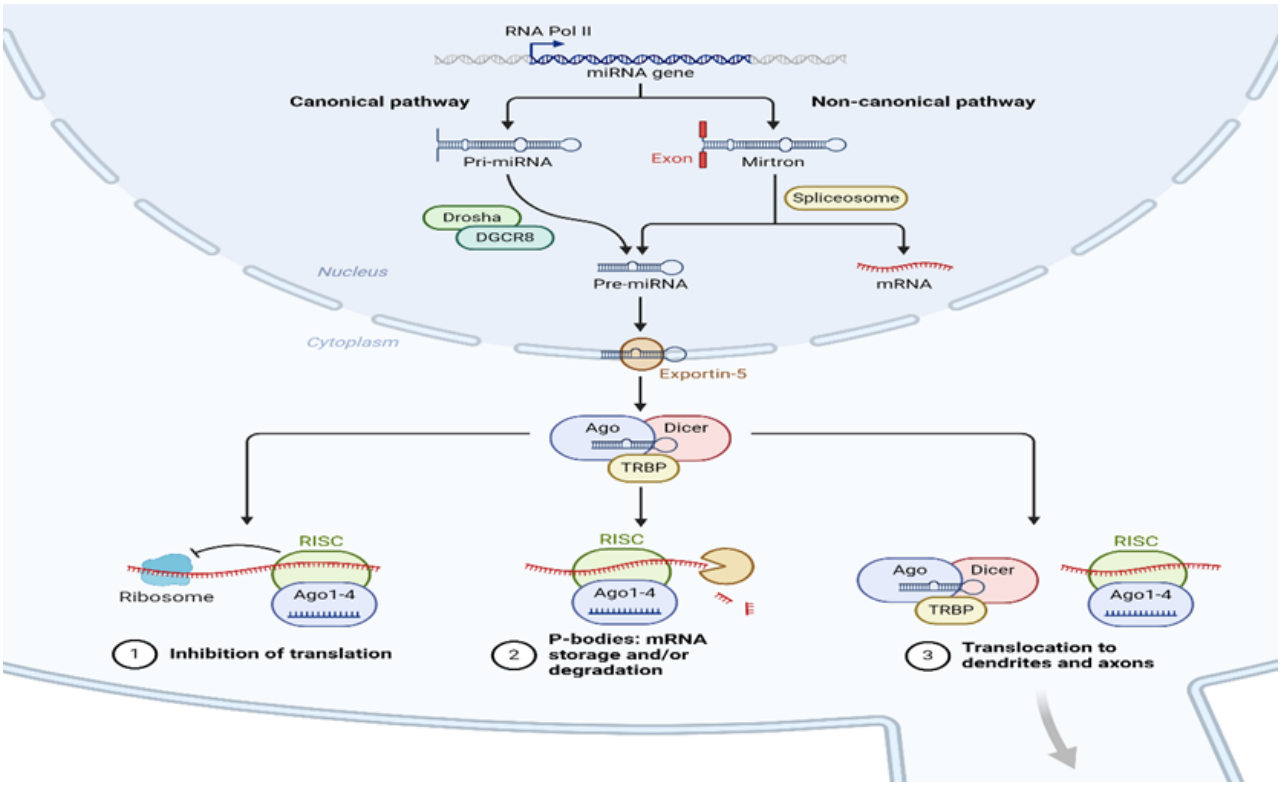


**Figure 1:** MicroRNAs (miRNAs) are tiny, non-coding RNA molecules with a mighty impact on cellular biology. These short sequences, typically 18-22 nucleotides long, exert a powerful influence on gene expression by regulating mRNA at the post-transcriptional level.

The identification of miRNAs has created new opportunities for cancer research, as they have great potential for application in diagnosis, prognosis, and even treatment [6].

This review explores the complex realm of miRNAs within the framework of cancer. We investigate the many roles of miRNAs, their capacity to serve as biological indicators of cancer, and the increasing potential of treatment approaches based on miRNAs.

# 3 Unveiling the Two Faces of miRNAs in Cancer: OncomiRs and Tumor Suppressors

MicroRNAs (miRNAs) play a complex and multifaceted role in cancer development. Depending on their target genes, miRNAs can either act as oncogenes, promoting tumor growth and metastasis, or as tumor suppressors, hindering cancer progression. Let us delve deeper into these two sides of the miRNA coin [7].

## 3.1 OncomiRs: Fueling the Fire of Cancer

OncomiRs are miRNAs whose expression is abnormally high in cancer cells. By targeting and downregulating tumor suppressor genes, they create a permissive environment for cancer to flourish. A prime example is the miR-17-92 cluster. This group of six miRNAs represses crucial genes like PTEN, which regulates cell growth, and TGF-$\beta$, a signaling pathway that inhibits proliferation [8–10].

Consequently, miR-17-92 overexpression is linked to various cancers, including lung, colon, and thyroid cancers [11].

Similarly, miR-21 is another oncomiR associated with a diverse range of cancers, such as breast, ovarian, and colon cancers. It silences genes like PTEN and PDCD4, which are involved in cell death processes. Elevated levels of miR-21 are not only found in tumor tissues but also the blood of cancer patients. Interestingly, studies have shown that decreasing miR-21 levels can reduce cancer cell proliferation and even reverse drug resistance [12,13]. Other prominent oncomiRs include miR-181, miR-146a, and the miR-221/222 cluster. They all exhibit similar patterns of upregulation in various cancers, promoting tumor growth metastasis and even influencing patient prognosis [14–16].

## 3.2 Tumor Suppressor miRNAs (TS-miRNAs): Guardians Against Cancer

Converse to oncomiRs, TS-miRNAs function as protectors against cancer. They inhibit the progression of cancer by specifically targeting oncogenes, which are genes responsible for unregulated cell proliferation and division. Tragically, tumor suppressor microRNAs (TS-miRNAs) are frequently suppressed in malignant cells. This decrease in expression can arise from mutations, malfunctioning biogenesis machinery, or genetic changes [17]. An extensively researched TS-miRNA is miR-16. Its absence is linked to the advancement of several malignancies, such as leukemia, gastric cancer, and pancreatic cancer. Furthermore, the Let-7 family of miRNAs are highly effective inhibitors of tumor growth that specifically attack cancer-related genes such as Rasa and Myc. Multiple studies have demonstrated that the restoration of Let-7 expression in lung cancer cells can trigger cell death, therefore emphasizing their potential as valuable therapeutic agents.

Important TS-miRNAs such as miR-29 and miR-34 are associated with aggressive malignancies like breast cancer, lung cancer, and colon cancer when they are downregulated. These microRNAs specifically target genes implicated in cell proliferation, invasion, and resistance to chemotherapeutic medications. Significantly, studies indicate that augmenting the expression of miR-29 and miR-34 may not only inhibit the proliferation of tumors but also improve the efficacy of chemotherapy [18–21].

MiR-362-3p and miR-193b provide further examples that highlight the many functions of TS-miRNAs. This study investigates the inhibitory effects of miR-362-3p on cell cycle progression and tumor growth in colorectal cancer. Furthermore, miR-193b inhibits the production of fatty acids, therefore increasing the vulnerability of cancer cells to certain agents. The results emphasize the considerable potential of TS-miRNAs as targets for therapy and biomarkers to enhance cancer detection and treatment [22].

Another developing field of study is the influence of genetic differences within miRNA genes, referred to as polymorphisms. Evidence indicates that certain genetic variations can elevate the susceptibility to acquiring particular types of cancer.

Ultimately, miRNAs are an intriguing category of regulators that exert a remarkable impact on the progression of cancer. Enhanced comprehension of the functions of oncomiRs and TS-miRNAs enables researchers to explore innovative diagnostic and treatment approaches for this intricate disease [23].

# 4 miRNAs: Orchestrators of the Devastating Dance of Metastasis

Metastasis, the ability of cancer cells to spread from their original location to distant organs, is the hallmark of aggressive cancers and the leading cause of cancer-related deaths. MicroRNAs (miRNAs) emerge as intriguing players in this deadly dance, influencing the metastatic cascade.

One way miRNAs contribute to metastasis is by promoting epithelial-to- mesenchymal transition (EMT) [24]. EMT is a crucial step where cancer cells lose their epithelial characteristics and gain mesenchymal properties, allowing them to detach from the primary tumor, migrate, and invade distant tissues. miRNA-10b, for instance, is found to be overexpressed in advanced-grade gliomas and promotes EMT by downregulating PDCD4, a protein involved in cell death. Interestingly, inhibiting miRNA-10b not only suppresses glioma cell growth and invasion but also spares normal brain cells, highlighting its potential as a therapeutic target with minimal side effects [25].

Another mechanism by which miRNAs influence metastasis involves regulating key oncogenes and metastasis-suppressor genes. miRNA-320a offers a fascinating example. While its overexpression in pancreatic cancer fuels aggressive behavior like proliferation, invasion, and drug resistance, it acts as a metastasis suppressor in breast cancer. This seemingly contradictory behavior can be explained by its target genes. In pancreatic cancer, miRNA-320a downregulates PDCD4, promoting metastasis. Conversely, in breast cancer, it targets the potent metadherin oncogene, thereby inhibiting metastasis [26, 27]. These findings underscore the context-dependent nature of miRNA function and the importance of understanding their specific targets in different cancer types.

Furthermore, miRNAs can modulate the tumor microenvironment, the ecosystem surrounding the tumor that can either hinder or promote metastasis. For instance, the downregulation of miR-335 in neuroblastoma cells leads to the upregulation of TGF-$\beta$ signaling pathway members. This pathway activation enhances the invasive and migratory potential of these cancer cells, potentially contributing to metastasis [28].

# 5 miRNAs: Unmasking the Hidden Footprints of Cancer

Achieving early detection is crucial in the battle against cancer. Historically, this has depended on intrusive techniques or tissue-excised samples. Nevertheless, miRNAs provide a groundbreaking method - functioning as impartial observers of the existence and kind of cancer by virtue of their distinct presence in body fluids [29].

Consider miRNAs as minuscule fragments of tissue debris left behind by a tumor during its growth. Remarkably persistent in circulation, these breadcrumbs provide crucial information for determining the source and aggressiveness of the malignancy. Through the analysis of miRNA profiles in blood or other fluids, scientists have the ability to innovate non-invasive screening methods for the early diagnosis of cancer [30].

A key advantage of miRNAs is their high degree of specificity. Multiple studies have demonstrated that unique miRNA profiles distinguish between normal tissues and those from tumors. This enables not only the identification of cancer but also the precise determination of the tissue from where it originates. This is of utmost importance in advanced-stage malignancies because identifying the original tumor can be highly difficult [31].

An investigation found a panel of only 200 miRNAs capable of accurately classifying poorly differentiated cancers, outperforming the conventional method that relies on thousands of messenger RNAs. Thus, the higher discriminating ability of miRNA profiles is emphasized [32].

Moreover, scientists have effectively employed miRNA profiling to differentiate between several forms of malignancies by thoroughly examining more than 400 samples from diverse tumors and their metastases. This enables not just the early identification but also the implementation of tailored treatment approaches depending on the particular form of cancer detected [33].

Translating this potential into reality, however, necessitates surmounting an obstacle. These minute miRNA "breadcrumbs" provide a hurdle in terms of precise detection. One potentially effective approach entails nanotechnology. The development of novel DNA nanomachines has enabled scientists to selectively visualize particular miRNAs, such as miR-21, even at exceedingly low concentrations. This facilitates the development of very sensitive diagnostic mechanisms capable of efficiently identifying cancer in its first phases [34].

# 6 miRNAs: Unlocking Personalized Cancer Therapies

Cancer is an astute adversary, frequently distinguished by a distinct pattern of deregulated genes. Here, microRNAs (miRNAs) stand out as potent friends in the battle against cancer, providing a tailored approach to therapy.

Every form of cancer displays a distinct miRNA profile. Certain microRNAs, referred to as oncomiRs, are excessively produced, suppressing important tumor suppressors and promoting the proliferation of cancer. The downregulation of tumor-suppressor miRNAs enables oncogenes to proliferate unrestrained. Through the examination of these miRNA profiles, scientists might acquire a beneficial understanding of the precise molecular mechanisms that propel a certain type of cancer [35]. This understanding enables a fundamental change in cancer treatment - personalized medicine specifically designed to target the distinct miRNA fingerprint of each patient's tumor. miRNA-based therapeutics show great potential, involving two primary approaches: inhibiting oncomiRs and reinstating tumor-suppressor miRNAs [36].

### 6.1 Silencing the Villains: Targeting OncomiRs

OncomiRs act as villains in the cancer drama, and silencing them is a key therapeutic strategy. One approach involves using anti-miRNA molecules. These molecules act like decoys, binding to the oncomiRs and preventing them from silencing tumor suppressor genes. This allows the tumor suppressors to regain their function and trigger cell death in cancer cells [37]. A prime example is miR-21, an oncomiR overexpressed in glioblastoma, a deadly brain tumor.

Scientists have developed antisense oligonucleotide inhibitors specific to miR-21. These inhibitors can potentially control glioblastoma growth by reactivating silenced tumor suppressor genes and inhibiting the activity of pathways crucial for cancer cell survival [38].

### 6.2 Restoring the Guardians: Boosting Tumor-Suppressor miRNAs

Another therapeutic avenue involves restoring the function of downregulated tumor-suppressor miRNAs. This can be achieved by introducing synthetic copies of these miRNAs directly into cancer cells. These synthetic miRNAs can act as replacements for the missing tumor suppressors, silencing oncogenes and promoting cell death [37]. Challenges remain in delivering these therapeutic miRNAs to their target sites within cancer cells. However, researchers are exploring innovative solutions. One promising strategy involves attaching miRNA mimics to specific peptides that can navigate the acidic tumor microenvironment and deliver the cargo directly to cancer cells [38].

## 7 Beyond Silencing and Restoration: Emerging Frontiers

The potential of miRNA-based therapies extends beyond silencing and restoration. Researchers are exploring the use of miRNA-modified viruses – oncolytic viruses. These viruses are engineered to be selectively replicated only in cancer cells lacking specific miRNAs. As the virus replicates, it destroys the cancer cells from within [39]. Furthermore, combining miRNA therapy with conventional therapies like chemotherapy shows promising results. Studies suggest that combining a miR-21 inhibitor with the chemotherapeutic drug Taxol can significantly enhance the effectiveness of treatment in glioblastoma [40].

## 8 Future Directions

A cancer diagnosis often resembles a race against time. Traditional methods may lead to delayed detection, hindering treatment efficacy. Here, miRNAs emerge as game-changers, offering a minimally invasive approach to cancer management through the power of liquid biopsies.

Unlike conventional tissue biopsies, liquid biopsies analyze readily obtainable bodily fluids like blood. This makes them not only patient-friendly but also allows for more frequent monitoring of the disease. miRNAs, with their remarkable stability in circulation, are ideal candidates for analysis in liquid biopsies.

One of the most exciting applications of miRNAs in this context lies in early cancer detection. Their unique profiles, often reflecting specific tumor types, can potentially serve as red flags for the presence of cancer, even at its early stages. This early detection window provides a crucial opportunity for timely intervention, potentially leading to better treatment outcomes and improved survival rates. Furthermore, miRNAs can offer valuable insights into tumor progression and metastatic spread. By analyzing miRNA profiles in liquid biopsies over time, healthcare professionals can monitor the aggressiveness of the cancer and detect the presence of metastases. This real-time information empowers them to tailor treatment strategies and adjust them as needed. The potential of miRNAs extends beyond diagnosis and monitoring. Their role as both oncomiRs and tumor-suppressor miRNAs offers a glimpse into the molecular machinery driving a particular cancer. This knowledge can pave the way for the development of personalized therapeutic approaches, targeting the specific miRNA signatures of each patient's tumor.

In conclusion, miRNAs hold immense promise for revolutionizing cancer management through liquid

biopsies. Their ability to facilitate early detection, monitor disease progression, and guide personalized therapies offers a powerful tool in the fight against cancer. As research progresses, we can anticipate a future where liquid biopsies powered by miRNAs become a cornerstone of effective cancer care, leading to improved patient outcomes and a brighter future for cancer management.

## 9 Conclusion

miRNAs have emerged as essential players in cancer biology, offering valuable insights into the mechanisms driving tumor progression and resistance to therapy. Their role as diagnostic and prognostic biomarkers is increasingly recognized, and miRNA-based therapies represent a promising avenue for personalized cancer treatment. By targeting specific miRNAs involved in tumor growth and metastasis, researchers are opening new pathways for therapeutic interventions that may enhance the efficacy of existing treatments. Moreover, understanding the complex interplay between miRNAs and chemotherapy resistance can help in developing strategies to overcome these obstacles, leading to more effective cancer management and improved patient outcomes. Continued research into the regulation and function of miRNAs in cancer is crucial for translating these findings into clinical practice, ultimately transforming the landscape of cancer treatment.

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