Review

Exosomal MicroRNAs in Cancer: Mechanisms, Clinical Applications, and Challenges in Biomarker Discovery

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Exosomal MicroRNAs in Cancer: Mechanisms, Clinical Applications, and Challenges in Biomarker Discovery

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Abstract

Exosomal microRNAs (miRNAs) have emerged as promising candidates for cancer biomarker discovery due to their unique properties as stable, non-invasive, and informative molecules in body fluids. These small, membrane-bound vesicles play critical roles in intercellular communication by transferring miRNAs, which regulate gene expression and influence various biological processes, including cancer progression, metastasis, and drug resistance. Recent advancements in exosome isolation and miRNA profiling technologies have unveiled their potential for early cancer detection, prognosis, and therapeutic monitoring. Exosomal miRNAs offer several advantages over traditional biomarkers, including ease of detection in liquid biopsies (e.g., blood, urine), the ability to reflect the molecular landscape of tumors, and their association with both primary and metastatic cancer sites. However, despite the growing body of evidence supporting their utility, challenges such as standardization of isolation methods, variability in miRNA expression across cancer types, and the need for large-scale clinical validation remain significant barriers to clinical translation. This review highlights the biological mechanisms by which exosomal miRNAs influence cancer biology, their clinical applications in cancer diagnosis and therapy, and the technological advancements driving their profiling. Additionally, we discuss the current challenges and future directions for harnessing exosomal miRNAs in precision oncology.

Keywords: microRNA; biomarker; exosomes; precision medicine; metastasis

1. Introduction

Cancer remains a major global health challenge, with millions of new cases diagnosed annually. Early detection, accurate diagnosis, and personalized treatment strategies are paramount to improving survival rates and reducing the burden of the disease. In this context, biomarkers play a crucial role in monitoring the disease's onset, progression, metastasis, and therapeutic responses. Conventional biomarkers such as serum proteins, imaging techniques, and tissue biopsies, although useful, present limitations in terms of invasiveness, sensitivity, specificity, and accessibility [1]. Moreover, many of these biomarkers lack the ability to detect cancer at early stages, which is when treatment has the most profound impact on survival [2].

Exosomes are emerging as a potential solution to these challenges. These extracellular vesicles (EVs), typically ranging from 30 to 150 nm in diameter, are secreted by a variety of cells and contain a diverse cargo of proteins, lipids, mRNAs, and microRNAs (miRNAs) [3]. Exosomes facilitate intercellular communication, and their ability to transfer molecular signals between cells has made them a subject of great interest in cancer biology. Of particular importance are the miRNAs carried by exosomes, which are stable and detectable in body fluids like blood, urine, and saliva [4,5].

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MiRNAs, small non-coding RNAs of 20–22 nucleotides, regulate gene expression at the post-transcriptional level, and dysregulation of miRNA expression is a hallmark of cancer [6,7]. Exosomal miRNAs are particularly promising as biomarkers because they can reflect the molecular characteristics of their cells of origin, including tumor cells, and thus provide insights into tumor progression and metastasis. Moreover, exosomal miRNAs can be detected using minimally invasive liquid biopsy techniques, providing a novel, non-invasive alternative for cancer diagnosis and prognosis [8]. This review highlights the biogenesis, functional roles, and clinical potential of exosomal miRNAs as cancer biomarkers, emphasizing recent developments, challenges, and future directions in the field.

2. Exosomal microRNA: Characteristics and Biogenesis

Exosomes are secreted by virtually all cell types, and their cargo includes miRNAs, mRNAs, proteins, and lipids, which collectively reflect the cellular state of the donor cell [9]. Exosomal miRNAs are particularly valuable due to their stability in circulation. Unlike free-floating miRNAs, which are prone to degradation by RNases, miRNAs encapsulated in exosomes are protected by the lipid bilayer membrane, ensuring their integrity even in the bloodstream [10].

The biogenesis of exosomes begins with the inward budding of the plasma membrane, forming early endosomes. As these endosomes mature into multivesicular bodies (MVBs), some of the vesicles are trafficked to the cell surface where they fuse with the membrane, releasing exosomes into the extracellular space [11]. The packaging of miRNAs into exosomes is a highly regulated process, involving a complex interplay of RNA-binding proteins and sorting machineries such as the ESCRT (endosomal sorting complex required for transport) pathway and ceramide, which facilitate the sorting of miRNAs into exosomes [12].

Specific RNA-binding proteins such as heterogeneous nuclear ribonucleoproteins (hnRNPs), Tsg101, and YBX1 have been implicated in the selective loading of miRNAs into exosomes [13]. In the case of cancer, tumor-derived exosomes can carry cancer-specific miRNAs, which influence not only the recipient tumor cells but also the surrounding tumor microenvironment (TME) and immune cells. These exosomal miRNAs can act as signaling molecules that modulate key cancer processes, including tumor proliferation, migration, immune escape, and resistance to therapy [14,15].

3. Exosomal microRNAs in Cancer Biology

Exosomal miRNAs play a pivotal role in the pathophysiology of cancer by mediating communication between cancer cells and their microenvironment. Tumor cells can release exosomes that influence both nearby stromal cells and distant organs, contributing to tumor progression, metastasis, and immune modulation [16]. The specific miRNA profiles of exosomes reflect the molecular state of the tumor, enabling exosomal miRNAs to function as molecular signatures of cancer.

- **Tumor Progression and Metastasis**: Exosomal miRNAs are involved in regulating tumor growth, angiogenesis, and metastasis. For instance, miR-21 is widely recognized as an oncogenic miRNA that is upregulated in many cancers, including breast, colorectal, and lung cancer. MiR-21 promotes tumor growth by targeting tumor suppressor genes like PTEN and PDCD4, and it also plays a role in promoting cancer cell invasion and metastasis [17]. Similarly, miR-10b has been shown to facilitate metastasis by regulating the RhoGTPases and promoting the epithelial-mesenchymal transition (EMT) process, which is crucial for cancer cell dissemination [18].
- **Immune Modulation**: Exosomes can also influence the immune response to tumors. Tumor-derived exosomal miRNAs can modulate immune cell functions to create an immunosuppressive microenvironment. For example, exosomal miR-155 has been implicated in suppressing dendritic cell activation and promoting regulatory T cell differentiation, thereby inhibiting anti-tumor immune responses [19]. Additionally, exosomes from cancer cells can

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carry miRNAs that suppress natural killer (NK) cell function, thus enhancing tumor evasion from immune surveillance [20].

- **Therapeutic Resistance**: Resistance to chemotherapy and targeted therapy is a significant barrier to successful cancer treatment. Exosomal miRNAs have been shown to contribute to therapeutic resistance by modulating drug response pathways. For example, miR-214 in exosomes can promote resistance to chemotherapy by targeting genes involved in apoptosis, such as PTEN and caspase-3 [21]. Similarly, exosomal miRNAs can mediate resistance to targeted therapies, including those aimed at EGFR or HER2, by altering downstream signaling pathways [22].

To illustrate the diversity of exosomal miRNA profiles across various cancers, Table 1 summarizes key miRNAs identified in different cancer types and their functional roles in tumor progression and metastasis.

Table 1. Exosomal miRNAs and Their Role in Different Cancer Types.

Cancer Type	Exosomal miRNA	Function	References
Breast Cancer	miR-21	Oncogenic, promotes tumor growth and metastasis	[24]
Lung Cancer	miR-155	Involved in immune modulation, promotes immune evasion	[25]
Colorectal Cancer	miR-210	Poor prognosis marker, regulates hypoxia and angiogenesis	[26]
Pancreatic Cancer	miR-34a	Tumor suppressive, regulates apoptosis and cell cycle	[27]
Prostate Cancer	miR-141	Inhibits invasion and metastasis, regulates EMT	[28]
Glioma	miR-128	Regulates tumor growth, differentiation, and migration	[29]

To further understand how exosomal miRNAs contribute to cancer biology, Table 2 outlines the mechanisms by which specific miRNAs influence critical cancer processes, including tumor growth, metastasis, and immune modulation.

Table 2. Exosomal miRNAs and Their Mechanisms of Action in Cancer.

Exosomal miRNA	Target Genes/Pathways	Cancer Process Affected	References
miR-21	PTEN, PDCD4, Bcl-2	Tumor proliferation, apoptosis evasion, metastasis	[17,18]
miR-10b	RhoGTPases, E-cadherin	Epithelial-mesenchymal transition (EMT), invasion, metastasis	[18]
miR-210	HIF1α, VEGF	Hypoxia response, angiogenesis, cell survival	[26]
miR-155	SOCS1, FOXP3	Immune modulation, T cell differentiation, immune evasion	[19,25]

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miR-128	p53, PTEN	Apoptosis, tumor progression, differentiation	[29]

4. Exosomal microRNAs as Cancer Biomarkers

Exosomal miRNAs represent a promising class of biomarkers for early cancer detection, prognosis, and monitoring of therapeutic responses. The ability to detect specific miRNAs in biofluids such as blood, urine, and saliva offers a non-invasive alternative to traditional tissue biopsies, which are often invasive and not feasible for regular monitoring [23].

- **Diagnostic Potential**: Exosomal miRNAs have shown diagnostic potential in various cancers, including breast, prostate, lung, and pancreatic cancers. In breast cancer, exosomal miR-21 has been proposed as a diagnostic biomarker due to its elevated levels in the plasma of cancer patients [24]. Similarly, miR-155 has been identified as a potential biomarker for early detection of non-small cell lung cancer (NSCLC) [25]. Liquid biopsies based on exosomal miRNA profiling could provide a less invasive and more frequent method for cancer detection, enabling early intervention and improved patient outcomes.
- **Prognostic Value**: Exosomal miRNAs have been shown to correlate with cancer stage, progression, and metastasis. For example, high levels of miR-210 in exosomes are associated with poor prognosis in colorectal cancer [26]. Additionally, exosomal miRNA signatures may provide insights into cancer recurrence and the likelihood of metastasis, helping to stratify patients into risk groups and guide therapeutic decision-making [27].
- **Therapeutic Monitoring**: One of the most promising applications of exosomal miRNAs is in monitoring treatment responses. Exosomal miRNAs can serve as real-time biomarkers for assessing how a patient is responding to therapy. For instance, changes in the levels of specific exosomal miRNAs have been used to monitor chemotherapy efficacy and identify emerging resistance [28]. Furthermore, exosomal miRNAs can reflect the molecular changes occurring within the tumor during treatment, offering a window into the dynamics of cancer evolution and therapy-induced alterations [29].

The clinical potential of exosomal miRNAs in cancer detection, prognosis, and therapeutic monitoring is increasingly recognized. **Table 3** summarizes their diverse applications, showcasing how exosomal miRNA profiles can aid in early diagnosis and patient management.

Table 3. Clinical Applications of Exosomal miRNAs in Cancer Diagnosis and Therapy.

Clinical Application	Exosomal miRNA(s)	Cancer Type(s)	Clinical Relevance	References
Early Diagnosis	miR-21, miR-155	Breast, Lung, Pancreatic	Elevated in patient plasma, potential early-stage detection	[24,25]
Prognostic Indicator	miR-210, miR-10b	Colorectal, Glioma	Associated with advanced disease stage and poor prognosis	[26,29]
Therapeutic Monitoring	miR-214, miR-34a	Colorectal, Breast	Changes in miRNA levels correlate with chemotherapy response	[28,35]
Metastasis Prediction	miR-9, miR-126	Breast, Prostate	Involved in metastasis and tumor cell migration	[28,29]

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Therapeutic Resistance	miR-21, miR-155	Lung, Breast	Linked to resistance to chemotherapy and targeted therapies	[21,22]

5. Technologies for Exosomal miRNA Profiling

A major challenge in utilizing exosomal miRNAs as biomarkers is the efficient and reliable isolation and characterization of exosomes from biological fluids. Several technologies have been developed for the isolation and profiling of exosomal miRNAs, each with its advantages and limitations.

- **Exosome Isolation**: Techniques such as ultracentrifugation, precipitation methods, and size-exclusion chromatography are commonly used to isolate exosomes. Ultracentrifugation is the most widely used method; however, it is time-consuming and prone to contamination with non-exosomal particles [30]. Recently, microfluidic platforms have been developed to isolate exosomes with high efficiency and reproducibility, enabling faster and more scalable processes [31]. These newer techniques are promising for clinical applications.
- **MiRNA Profiling**: Once exosomes are isolated, profiling their miRNA content is essential for biomarker discovery. High-throughput sequencing, RT-qPCR, and microarray-based techniques are commonly used to identify and quantify miRNAs. Sequencing offers the most comprehensive profile, but it is also expensive and data-intensive [32]. RT-qPCR, while more cost-effective, requires prior knowledge of the specific miRNAs of interest and may miss novel biomarkers [33]. The development of highly sensitive and accurate profiling technologies is essential for advancing exosomal miRNAs as reliable biomarkers.

As the accurate profiling of exosomal miRNAs is crucial for their potential as cancer biomarkers, Table 4 provides an overview of the most commonly used techniques for exosome isolation and miRNA profiling, highlighting their advantages and limitations.

Table 4. Techniques for Exosome Isolation and miRNA Profiling.

Method	Description	Advantages	Limitations	References
Ultracentrifugation	Centrifugation at high speeds to isolate exosomes.	Widely used, cost-effective, well-established.	Time-consuming, low yield, prone to contamination.	[30]
Precipitation	Use of chemical reagents to aggregate exosomes.	Simple, less time-consuming, high yield.	May co-isolate other vesicles, less pure.	[31]
Size-Exclusion Chromatography	Exosomes are separated based on size using a gel filtration column.	High purity, gentle method with minimal perturbation.	Expensive equipment, requires optimization for each sample type.	[32]
Microfluidic Devices	Microchips that isolate exosomes based on size or charge.	High throughput, automated,	Expensive, limited commercial availability.	[33]

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		minimally invasive.		
Immunocapture	Exosomes are isolated using antibody-coated beads.	Specific for certain exosome types, high purity.	Requires specific antibodies, may miss heterogeneity.	[34]

Efficient exosomal miRNA profiling relies on the development of advanced technologies. Table 5 compares the different methods available for liquid biopsy-based profiling, offering insights into their strengths and limitations for clinical applications."

Table 5. Key Technologies for Exosomal miRNA Profiling in Liquid Biopsy.

Technology	Advantages	Limitations	Application in Cancer	References
RT-qPCR	Cost-effective, high sensitivity for specific miRNAs	Limited to known miRNAs, may miss novel biomarkers	Detection of specific exosomal miRNAs such as miR-21 in plasma	[33]
Next-Generation Sequencing (NGS)	Comprehensive, can profile entire miRNAome	High cost, data complexity	Profiling multiple exosomal miRNAs for cancer diagnosis and prognosis	[32]
Microarray	High throughput, suitable for large-scale studies	May miss low-abundance miRNAs	Screening for panels of exosomal miRNAs for cancer biomarkers	[33]
Lateral Flow Assays	Point-of-care, rapid, low cost	Lower sensitivity compared to PCR or NGS	Development of portable, on-site cancer diagnostic tools	[34]

6. Challenges and Future Directions

Despite their promise, the use of exosomal miRNAs as cancer biomarkers faces several challenges that need to be addressed for their clinical translation.

- **Standardization and Reproducibility**: One of the major challenges is the lack of standardization in exosome isolation and miRNA profiling protocols. Variability in isolation methods, differences in sample handling, and data processing inconsistencies can lead to discrepancies in results across studies [34]. Standardized methods and quality control measures are essential for ensuring reproducibility and accuracy.
- **Biological Variability**: Another challenge is the biological variability of exosomal miRNAs. MiRNA expression levels can vary based on tumor type, stage, and even between patients with the same type of cancer [35]. Large-scale clinical studies are needed to validate the potential of exosomal miRNAs in different patient cohorts and cancer types.
- **Clinical Validation**: Despite the promising preclinical data, clinical validation remains the most significant barrier to the widespread use of exosomal miRNAs in the clinic. Large multicenter trials are necessary to demonstrate the diagnostic, prognostic, and therapeutic utility of

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exosomal miRNAs across diverse cancer populations [36]. These studies will provide the robust evidence needed to incorporate exosomal miRNA profiling into clinical practice.

Despite the promising clinical applications of exosomal miRNAs, several challenges remain in their widespread use. Table 6 summarizes the key obstacles that need to be addressed for the successful clinical translation of exosomal miRNAs as reliable biomarkers.

Table 6. Challenges in the Use of Exosomal miRNAs for Clinical Applications.

Challenge	Description	Potential Solutions	References
Standardization of Isolation Methods	Variability in exosome isolation protocols leads to inconsistent results.	Develop standardized protocols, quality control measures.	[34]
Variability in miRNA Expression	Biological differences in tumor types, stages, and patients lead to variability in miRNA profiles.	Large-scale multi-center clinical studies to account for biological heterogeneity.	[35]
Technical Sensitivity	Low sensitivity of some profiling methods for detecting rare or low-abundance miRNAs.	Use of high-throughput sequencing or advanced PCR techniques.	[33]
Clinical Validation	Limited clinical validation of exosomal miRNAs for widespread use in diagnostics.	Conduct large, multi-center clinical trials for comprehensive validation.	[36]

7. Conclusion

Exosomal microRNAs (miRNAs) represent a rapidly evolving frontier in cancer biomarker research, offering a promising alternative to conventional diagnostic and prognostic tools. Their stability in body fluids, capacity to reflect the molecular landscape of tumors, and involvement in key oncogenic processes—such as tumor progression, metastasis, and drug resistance—highlight their potential as minimally invasive biomarkers in precision oncology. Advances in exosome isolation and miRNA profiling technologies have significantly enhanced the feasibility of utilizing exosomal miRNAs for early cancer detection and therapeutic monitoring.

However, despite these encouraging developments, several critical challenges must be addressed before exosomal miRNAs can be fully integrated into clinical practice. Standardization of isolation and detection methodologies, management of biological variability, and large-scale clinical validation are essential to ensure reproducibility, specificity, and clinical utility across diverse cancer types and patient populations. Continued interdisciplinary research, combining molecular biology, bioengineering, and clinical sciences, will be crucial to overcoming these barriers.

Ultimately, with the resolution of current technical and translational hurdles, exosomal miRNAs hold the potential to revolutionize cancer diagnostics and therapy—paving the way for more accurate, early-stage detection and truly personalized treatment strategies.

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