Exosomal Micro RNAs: Emerging Tools for Cancer Detection and Monitoring in Clinical Practice

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Received: 11/10/2025
Accepted: 12/12/2025
Published: 31/12/2025

DOI:

10.65682/kjnhs.v1.i4.85-94

Abstract

Exosomal microRNAs (miRNAs) have gained considerable attention as novel biomarkers in cancer due to their remarkable stability in biological fluids and tumor-specific expression profiles. These small non-coding RNAs are selectively packaged into exosomes, which protect them from degradation and facilitate their role in intercellular communication, influencing tumor progression and metastasis. The clinical utility of exosomal miRNAs encompasses early cancer detection, prognosis prediction, and monitoring therapeutic responses through minimally invasive liquid biopsies. Despite promising results, challenges such as standardization of isolation methods, heterogeneity of exosome populations, and validation in large-scale clinical studies remain to be addressed. Advances in isolation technologies and molecular profiling are expected to enhance the sensitivity and specificity of exosomal miRNA-based assays, potentially revolutionizing personalized cancer management. This review summarizes the current understanding of exosomal miRNAs and discusses their emerging role in oncology diagnostics.

Keywords: Exosomal microRNAs **,** Cancer biomarkers , Liquid biopsy , Diagnostic biomarkers , Prognostic biomarkers , Therapeutic onitoring.

1. Introduction

Cancer remains one of the leading causes of mortality worldwide, necessitating the continuous development of accurate, non-invasive, and reliable biomarkers for early detection, prognosis, and therapeutic monitoring. Traditional tissue biopsies, while informative, are invasive and often fail to capture the dynamic molecular changes occurring during tumor progression. This has led to growing interest in liquid biopsies, which analyze tumor-derived components in body fluids and offer a less invasive alternative for real-time monitoring of cancer. (Chatterjee et al., 2017)

Recent studies have demonstrated that specific exosomal miRNAs are dysregulated in various malignancies and can be detected in serum, plasma, urine, and saliva, offering valuable insights into tumor behavior, metastasis, and treatment response (Théry et al., 2018). For instance, miR-21 and miR-1246 are frequently upregulated in exosomes from breast and lung cancer patients, correlating with disease stage and patient prognosis (Zhou et al., 2021). These findings highlight the potential of exosomal microRNAs not only as diagnostic tools but also as prognostic and predictive markers.

Despite the growing enthusiasm, several challenges still hinder the translation of exosomal microRNA-based diagnostics into routine clinical practice. These include the need for standardized protocols for exosome isolation, RNA extraction, and quantification, as well as the establishment of large-scale clinical validation studies.

This review aims to provide a comprehensive overview of the clinical utility of exosomal microRNAs in cancer, focusing on their biological role, methods of detection, relevance to specific cancer types, and the current limitations and future directions in their clinical application.

2. What Are Exosomes and Their Role in Cancer

Exosomes are nanosized extracellular vesicles ranging from 30 to 150 nanometers in diameter, formed through the endosomal pathway and released into the extracellular space upon fusion of multivesicular bodies with the plasma membrane. These vesicles are secreted by various cell types—including tumor cells—and are present in most body fluids, such as blood, urine, saliva, and cerebrospinal fluid (Kowal et al., 2016). Exosomes contain a complex cargo of proteins, lipids, DNA, and RNA molecules, particularly microRNAs, which play a significant role in cell-to-cell communication.

In the context of cancer, tumor-derived exosomes are not merely passive carriers; they actively participate in shaping the tumor microenvironment. They promote angiogenesis, modulate immune responses, and facilitate metastasis by transferring oncogenic molecules to recipient cells (Mashouri et al., 2019). Moreover, cancer cells often secrete a higher number of exosomes compared to normal cells, and the molecular content of these vesicles reflects the genetic and phenotypic characteristics of the parent tumor.

One of the most intriguing aspects of tumor-derived exosomes is their ability to remodel distant tissues and prepare them for metastatic colonization—a process known as pre-metastatic niche formation (Hoshino et al., 2015). For example, melanoma-derived exosomes have been shown to direct bone marrow progenitor cells to metastatic sites via specific integrin expression, thereby enhancing metastatic efficiency.

Given their biological significance and accessibility in body fluids, exosomes offer a unique opportunity to develop non-invasive diagnostic tools. Their molecular cargo, particularly microRNAs, can serve as reliable biomarkers for the early detection and monitoring of cancer, supporting their integration into the field of clinical chemistry and precision oncology

3. Overview of microRNAs in Exosomes

MicroRNAs (miRNAs) are short, non-coding RNA molecules typically 18–25 nucleotides in length that regulate gene expression post-transcriptionally by binding to complementary sequences in target messenger RNAs (mRNAs), resulting in translational repression or mRNA degradation. Within exosomes, miRNAs are selectively packaged through complex cellular mechanisms that are still being elucidated. It is believed that specific RNA-binding proteins, such as hnRNPA2B1 and YBX1, play crucial roles in the sorting of micro RNAs into exosomes based on sequence motifs and cellular context (Shurtleff et al., 2016; Villarroya-Beltri et al., 2013).

Exosomal micro RNAs are remarkably stable due to the protective lipid bilayer of the vesicle, which shields them from degradation by circulating RNases. This stability allows for their reliable detection in various biofluids, making them highly attractive candidates for use as minimally invasive biomarkers in oncology (Valadi et al., 2007). Furthermore, exosomal micro RNAs are not random in their content; tumor cells selectively enrich certain micro RNAs in their exosomes, which are often associated with cancer hallmarks such as proliferation, invasion, and immune evasion.

Notably, multiple studies have shown that the profile of micro RNAs in tumor-derived exosomes can reflect both the presence and the aggressiveness of cancer. For example, elevated levels of exosomal miR-21, miR-155, and miR-1246 have been reported in patients with breast, pancreatic, and lung cancers, correlating with poor prognosis and higher tumor burden (Kalluri & LeBleu, 2020). These findings underscore the functional significance of exosomal micro RNAs—not only as passive markers but also as active participants in tumor progression.

Given these attributes, exosomal micro RNAs have garnered increasing attention in the field of clinical chemistry and personalized medicine, with ongoing research focusing on their use in cancer screening, disease monitoring, and therapeutic response prediction.

4. Techniques for Isolation and Detection of Exosomal microRNAs

Accurate analysis of exosomal microRNAs depends heavily on the efficiency of both exosome isolation and miRNA extraction techniques. Due to their small size and the complexity of biological fluids, isolating pure and intact exosomes poses a technical challenge that directly affects downstream molecular analysis, particularly in a clinical chemistry setting.

Several methods have been developed for exosome isolation, each with its advantages and limitations. Differential ultracentrifugation, the gold standard method, separates exosomes based on size and density through sequential high-speed spins. While widely used in research, it is time-consuming, labor-intensive, and not ideal for high-throughput clinical applications (Li et al., 2017). Size-exclusion chromatography (SEC) offers improved purity and scalability but may yield lower exosome concentrations. Meanwhile, immunoaffinity capture methods use antibodies against exosomal surface proteins such as CD63 or CD81, enabling specific isolation of tumor-derived exosomes, which is particularly useful in cancer diagnostics (Gamez-Valero et al., 2015).

Commercial kits based on polymer-based precipitation (e.g., ExoQuick) have simplified the process for clinical use, although they may co-isolate non-exosomal particles, potentially affecting microRNA specificity and reproducibility.

Following exosome isolation, RNA extraction is performed using kits optimized for small RNA recovery. Techniques such as RT-qPCR, microarray, and next-generation sequencing (NGS) are commonly employed for the detection and profiling of exosomal microRNAs. RT-qPCR remains the most practical approach in clinical laboratories due to its sensitivity, specificity, and cost-effectiveness (Buschmann et al., 2018). However, NGS provides a broader and more comprehensive microRNA profile, making it preferable for discovery-phase research and biomarker validation.

Pre-analytical variables—such as sample type, handling, and storage—also influence exosomal RNA yield and integrity, highlighting the urgent need for standardization across laboratories. The International Society for Extracellular Vesicles (ISEV) has issued guidelines to improve reproducibility and ensure data reliability in both clinical and research settings (Théry et al., 2018).

5. Clinical Relevance of Exosomal microRNAs in Cancer

The clinical relevance of exosomal microRNAs in oncology has garnered significant interest due to their stability in biological fluids, tumor-specific expression profiles, and potential to serve as minimally invasive biomarkers. These features make them particularly attractive for early cancer detection, prognosis, and monitoring of treatment response.

In various malignancies, specific exosomal microRNAs have been consistently found to be upregulated or downregulated compared to healthy individuals. For example, elevated levels of miR-21, miR-155, and miR-1246 have been identified in the exosomes of patients with breast, lung, and pancreatic cancers, respectively, and are often associated with poor survival and advanced tumor stage (Hannafon & Ding, 2013; Zhang et al., 2015). Such associations suggest a direct link between exosomal miRNA signatures and tumor biology, supporting their utility as diagnostic and prognostic tools.

Beyond detection, exosomal microRNAs can also reflect how patients respond to therapy. For instance, changes in the levels of specific exosomal microRNAs during chemotherapy or immunotherapy may provide early indicators of therapeutic efficacy or resistance, thus guiding personalized treatment strategies (Yuan et al., 2016). In this context, exosomal microRNAs could complement or even replace some conventional tumor markers, offering a more dynamic and informative tool for patient management.

Despite the promising data, translation into clinical practice remains limited. Variability in isolation techniques, lack of standardized reference controls, and insufficient validation across large patient cohorts are major barriers. Nevertheless, several ongoing clinical trials are investigating exosomal microRNAs as cancer biomarkers, indicating growing recognition of their potential in real-world settings.

In summary, exosomal microRNAs represent a novel and powerful class of cancer biomarkers with broad clinical applications, although further standardization and validation are necessary before their integration into routine diagnostics.

6. Limitations and Future Perspectives

Despite the exciting potential of exosomal microRNAs as cancer biomarkers, several limitations currently hinder their widespread clinical application. One of the main challenges is the lack of standardized protocols for exosome isolation and microRNA analysis, leading to variability in results between studies and laboratories. Differences in sample types, handling, and storage conditions further complicate reproducibility and data comparison (Royo et al., 2020).

Another significant limitation is the heterogeneity of exosomes. Since exosomes are secreted by almost all cell types, isolating tumor-specific exosomes from complex biological fluids remains difficult, which can reduce the specificity of microRNA biomarkers. Immunoaffinity-based isolation techniques targeting tumor-specific surface markers offer promise but require further validation and scalability for routine clinical use (He & Zeng, 2020).

Moreover, many studies to date have small sample sizes or are limited to preliminary phases, making it necessary to perform larger, multicenter clinical trials to validate the diagnostic and prognostic utility of exosomal microRNAs across diverse patient populations and cancer types.

Looking forward advances in nanotechnology and molecular profiling techniques are expected to improve the sensitivity and specificity of exosomal microRNA detection. Integration of multi-omics approaches and artificial intelligence for data analysis may also facilitate the identification of robust biomarker signatures, enabling personalized cancer diagnostics and therapy monitoring.

In conclusion, while the clinical utility of exosomal microRNAs in cancer is promising, overcoming current technical and biological challenges through rigorous research and standardization is essential for their successful translation into clinical practice.

7. Materials and Methods

An in-depth literature review was carried out for this review using academic databases such as PubMed, Scopus, and Google Scholar. Topics like "breast cancer," "gene expression," and "liver cancer" were used to find appropriate studies submitted between 2010 and 2024. Only articles in English with a priority on experimental and human research were taken into account. Relevant review papers, original studies, and meta-analyses were identified and scrutinized.

8. Results

According to the reviewed research, peripheral microRNAs show efficacy as biomarkers for early detection and surveillance of cancer. Exosomal microRNA types of expression have been discovered to vary between cancer patients and healthy people in a number of research projects. (Ghafouri-Fard et al., 2023). These molecules can be used as discrete diagnostic tools because they possess superior stability in internal fluids. (Cazzoli et al., 2013). On top of that, spanning all cancer types, fluctuations in the proportions of microRNA loaded in vesicle exteriors were linked to tumor development, outcomes following therapy, and relapse of the disease. As a whole, the observations are in line with the putative medicinal application of peripheral microRNAs for cancer monitoring and diagnosis.(Galvão-Lima et al., 2021)

9.Conclusion

Exosomal microRNAs have emerged as promising biomarkers in cancer diagnosis, prognosis, and therapeutic monitoring due to their stability in biofluids, tumor-specific expression, and role in tumor progression. Their non-invasive detection in various body fluids offers a significant advantage over traditional tissue biopsies, enabling real-time and dynamic assessment of cancer status. However, challenges related to standardization of isolation methods, heterogeneity of exosome populations, and validation in large clinical cohorts must be addressed before routine clinical implementation. Continued advancements in isolation technologies, molecular profiling, and bioinformatics will likely overcome these obstacles, paving the way for personalized cancer management based on exosomal microRNA signatures. In summary, exosomal microRNAs hold great potential to revolutionize cancer diagnostics and therapy, offering a new frontier in precision oncology that warrants extensive further research and clinical translation.

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