Research Open

Cancer Studies and Therapeutics
Volume 9 Issue 3

Research Article

Exploring the Potential of Exosomal miRNA as Prognostic Biomarkers in Glioma

Syed Sultan Beevi[1]*, Manas Kumar Panigrahi[2], Vinod Kumar Verma[1]* and Radhika Chowdary[3]

[1]Cancer Biology Division, KIMS Foundation and Research Centre, KIMS Hospital, Minister Road, Secunderabad, Telangana, India
[2]Department of Neurosurgery, Krishna Institute of Medical Sciences, Minister Road, Secunderabad, Telangana, India
[3]Diagnostics Division, Krishna Institute of Medical Sciences, Minister Road, Secunderabad, Telangana, India

***Corresponding authors:** Syed Sultan Beevi PhD, Vinod Kumar Verma PhD, KIMS Foundation and Research Center KIMS Hospitals 1-8-31/1, Minister Road , Secunderabad 500 003 Telangana, India, Tel: 91 40 44885056, Fax: 91 40 27840980

Received: August 01, 2024; **Accepted:** August 05, 2024; **Published:** August 10, 2024

Abstract

Gliomas are aggressive brain tumors characterized by high morbidity and mortality. Recent advances in the field of exosome biology have opened new avenues for non-invasive diagnostics and therapeutic strategies in glioma management. Exosomes, small extracellular vesicles found in body fluids, carry a diverse array of molecular contents, including microRNAs (miRNAs), which reflect the biological state of their cells of origin. This review explores the potential of exosomes as liquid biopsies and the role of exosomal miRNAs in glioma progression, tumor recurrence, and drug resistance. We summarize current knowledge on how exosomal miRNAs can serve as biomarkers for early detection, prognosis, and real-time monitoring of gliomas. Exosomal miRNAs such as miR-21, miR-221/222, and miR-10b are highlighted for their association with tumor aggressiveness and poor patient outcomes. The mechanisms by which these miRNAs contribute to glioma growth, angiogenesis, metastasis, and therapeutic resistance are examined, underscoring their importance in tumor biology. Additionally, we discuss the challenges in exosome isolation and miRNA detection, emphasizing the need for standardized protocols and advanced analytical techniques. The review also addresses the potential of integrating exosomal miRNA analysis with other biomarkers and imaging methods to provide a comprehensive approach to glioma management. In conclusion, the application of exosomal miRNAs as liquid biopsies holds great promise for improving glioma diagnosis, monitoring disease progression, and guiding personalized treatment strategies. Further research and clinical validation are essential to fully realize the potential of exosomal miRNAs in transforming glioma care.

Keywords: *Exosomes; microRNAs; glioma recurrence; liquid biopsy; non-invasive prognostics; real-time monitoring*

Introduction

Gliomas are a diverse group of tumors originating in the glial cells of the brain and spinal cord. These tumors are classified based on the type of glial cells involved, their genetic characteristics, and their grade of malignancy [1]. The primary types of gliomas include glioblastomas, astrocytomas, oligodendrogliomas, and ependymomas. They have the third-highest cancer-related mortality and morbidity rates worldwide [2]. Despite aggressive treatment involving surgery, radiation, and chemotherapy, the majority of gliomas are nearly universally fatal within 5 to 7 years [3].

Advances in genomic and molecular profiling have led to the identification of distinct molecular markers such as IDH1/2, EGFR, p53, BRAF, TERT promoter mutations, 1p/19q co-deletion and MGMT promoter methylation as diagnostic, prognostic and therapeutic indicators in glioma management [4]. However, tumor recurrence in glioma is a major hurdle in the effective management of the disease. Tumor recurrence in glioma is significantly influenced by several factors. Surgical resection often cannot remove all tumor cells, particularly those infiltrating the surrounding brain tissue, leaving residual cells that can proliferate and cause recurrence [5]. Furthermore, glioma cells can develop resistance to therapies such as chemotherapy and radiation due to genetic mutations, epigenetic changes, or adaptive responses to treatment [6]. Additionally, a subpopulation of glioma cells with stem-like properties, known as cancer stem cells, can survive initial treatments and drive tumor regrowth [7]. These cancer stem cells are often more resistant to conventional therapies, further complicating the management of glioma recurrence.

Post-operative evaluation for disease burden is primarily conducted through MRI or other radiological investigations. However, these imaging techniques often fail to accurately correlate with the actual neoplastic disease burden, inadequately addressing the micro-infiltrative disease beyond the borders depicted radiologically [8]. Furthermore, MRI interpretation post-treatment can be challenging due to inflammation and necrosis caused by radiation, chemotherapy, or immunotherapy. Treatment-related inflammation, known as "pseudo-progression," frequently results in false positives, complicating clinical interpretation [9]. Furthermore, reliable biomarkers for early detection of recurrence are lacking, making it hard to monitor disease progression effectively [10]. Invasive and serial tumor biopsies for histological analyses are not only impractical and dangerous but also ineffective in providing adequate information about the tumor due to its heterogeneous nature. This highlights the

need for non-invasive procedures capable of detecting unique features that precisely reflect tumor status, enabling continual assessment of patients to monitor disease progression and supervise therapeutic response.

In this review, we summarized the recent understanding of exosomes as liquid biopsies and the role of different exosomal miRNAs in glioma progression, tumor recurrence, and drug resistance. We discussed how exosomes can serve as liquid biopsies, providing valuable molecular and genetic information that reflects the current state of the tumor. Further we highlighted the multifaceted role of exosomal miRNAs in glioma, emphasizing their potential as biomarkers for diagnosis, prognosis, and therapeutic targets.

Exosomes as Liquid Biopsy in Glioma

Exosomes, small extracellular vesicles secreted by cells, have emerged as a promising tool for liquid biopsy in glioma [11]. These vesicles carry a variety of biomolecules, including [12]. Cancer cells actively produce, release, and utilize exosomes to promote tumor growth and progression. These tumor-derived exosomes carry molecular and genetic information that can alter the phenotypic and functional attributes of recipient cells [13]. By transferring oncogenic proteins, RNAs, and other bioactive molecules, exosomes can reprogram recipient cells into active contributors to various processes crucial for tumor development [14]. For instance, they can enhance angiogenesis, which is the formation of new blood vessels to supply the growing tumor with nutrients and oxygen [15]. They can also promote thrombosis, creating a pro-coagulant environment that facilitates tumor cell survival and dissemination [16]. Moreover, exosomes contribute to immunosuppression by modulating the immune response, helping the tumor evade detection and destruction by the body's immune system [17].

In the context of brain tumors, exosomes have a unique advantage. The blood-brain barrier (BBB) is a selective barrier that typically prevents most molecules from entering or exiting the central nervous system (CNS). However, exosomes can cross the BBB, making them detectable in body fluids such as blood and cerebrospinal fluid [18]. This ability is particularly significant for brain cancer management because it allows for the non-invasive monitoring of tumor dynamics. The inability of brain tumor cells to exit the CNS combined with exosomes' capacity to cross the BBB and carry tumor-specific information into the systemic circulation underscores their potential as powerful biomarkers. This capability facilitates the early detection of brain tumors, monitoring of disease progression, and assessment of treatment response, making exosomes a valuable tool for liquid biopsy in the management of glioma.

Exosomal MicroRNAs in Glioma

Exosomes are rich in various RNA molecules such as mRNA, long non-coding RNAs (IncRNAs), circular RNAs (circRNAs) and miRNAs, with miRNAs being the most prevalent [19]. MicroRNAs (miRNAs) are a class of small, non-coding RNA molecules, typically about 22 nucleotides in length, that play a crucial role in regulating gene expression [20]. They function primarily by binding to complementary sequences on target messenger RNA (mRNA) transcripts, usually resulting in gene silencing through translational repression or mRNA degradation [21]. This regulatory function is crucial in numerous biological processes and disease states, including cancer [22].

According to the Exocarta database, which catalogs molecules identified in exosomes, 2,838 miRNAs have been detected in exosomes from various biological sources [23]. Among the thousands of miRNAs identified in exosomes, approximately 26 have been closely associated with gliomas [24]. These miRNAs are involved in various aspects of glioma biology, including tumor growth, invasion, angiogenesis, and immune evasion. Their presence in exosomes allows them to influence the tumor microenvironment and facilitate intercellular communication within the brain [25].

The miRNA content in exosomes is notably higher than in their source cells, suggesting a selective enrichment process [26]. Studies have shown that miRNAs are preferentially incorporated into exosomes before other RNA molecules, resulting in their elevated expression levels in exosomes compared to the originating cells [27]. This selective sorting of miRNAs into exosomes is critical for intercellular communication within the tumor microenvironment and plays a vital role in glioma biology [28]. The ease of access, abundance, and stability of exosomal miRNAs in biofluids make them ideal biomarkers for gliomas, offering significant potential for non-invasive disease monitoring.

Several miRNAs have been identified as significant prognostic biomarkers in glioma. Among them, miR-21 is extensively studied and typically overexpressed in high-grade gliomas, correlating with poor prognosis, increased tumor aggressiveness, resistance to apoptosis, and enhanced invasion capabilities [29]. High levels of miR-21 are associated with shorter overall survival and disease-free survival. Similarly, the miR-221/222 cluster is upregulated in glioblastomas, promoting cell proliferation and inhibiting apoptosis by targeting tumor suppressor genes like p27 and p57, resulting in poor clinical outcomes and reduced patient survival [30]. miR-10b, significantly overexpressed in gliomas, is crucial for tumor invasion and metastasis, with high levels indicating poor prognosis and shorter survival times [31]. The miR-181 family, including miR-181a and miR-181b, is often downregulated in gliomas, with lower expression levels linked to poorer prognosis. These miRNAs regulate glioma cell proliferation, apoptosis, and differentiation [32]. miR-124, typically downregulated and acting as a tumor suppressor, is associated with advanced tumor grade and poor prognosis; its restoration inhibits glioma cell proliferation and induces apoptosis [33]. Lastly, miR-196a, overexpressed in gliomas, promotes cell proliferation, migration, and invasion, with high levels linked to shorter overall survival, highlighting its value as a prognostic marker [34].

Clinical Application of Exosomal MiRNA as Prognostic Biomarkers

Given the unique biological characteristics of exosomes, their collection from patient body fluids combined with the detection of related miRNAs offers significant promise in glioma management. The miRNAs contained within exosomes can reflect the molecular

landscape of their cells of origin, providing a non-invasive means to gain insights into the tumor's genetic and proteomic profile [35].

By analyzing exosomal miRNAs from body fluids such as blood, cerebrospinal fluid, or urine, clinicians can obtain valuable information about the current state of the glioma. Bioinformatics analysis and processing of this miRNA data can help identify specific miRNA signatures associated with treatment response, disease progression, and recurrence [36].

Systematic collection of exosomes from body fluids enables continuous, non-invasive monitoring of tumors, eliminating the need for invasive procedures like biopsies. This facilitates real-time assessment of treatment efficacy and early detection of changes in tumor behavior. By tracking changes in exosomal miRNA profiles, clinicians can evaluate the effectiveness of therapeutic interventions. A decrease in specific oncogenic miRNAs or an increase in tumor-suppressive miRNAs may indicate a positive response to treatment. Additionally, certain miRNA signatures in exosomes can serve as prognostic biomarkers, aiding in predicting patient survival and the likelihood of tumor recurrence. For example, elevated levels of specific miRNAs associated with aggressive tumor behavior can signal a higher risk of recurrence.

Thus the integration of exosome-based miRNA analysis with advanced bioinformatics holds great potential for improving the management of glioma patients. This innovative approach can enhance our ability to evaluate treatment effects, predict survival outcomes, and identify early signs of tumor recurrence, ultimately leading to more effective and personalized therapeutic strategies.

Opportunities and Challenges

Standardizing and improving the methods for isolating and purifying exosomes from body fluids is essential to ensure consistency and reliability. Establishing standardized protocols for exosome handling, storage, and analysis will ensure reproducibility across different laboratories. It is also crucial to address the inherent heterogeneity of exosomes, which can vary greatly between patients and even within the same patient over time. Enhancing the sensitivity and specificity of detection techniques to accurately measure miRNAs within exosomes is vital. Conducting large-scale clinical studies is necessary to validate the prognostic utility of exosomal miRNAs in glioma. Additionally, gaining a deeper understanding of the biological functions and mechanisms of exosomal miRNAs in glioma progression and treatment response is imperative.

Conclusion and Future Perspectives

Exosomal miRNAs present a promising frontier in glioma diagnosis, prognosis, and treatment. Advancing non-invasive diagnostic methods using exosomal miRNAs can minimize the need for surgical biopsies, significantly improving patient comfort and outcomes. Utilizing these miRNA profiles for early detection of glioma recurrence holds the potential for timely interventions, thereby enhancing patient survival rates. Personalized treatment plans based on unique exosomal miRNA signatures can tailor therapies to individual patient needs, ensuring more effective and targeted treatment strategies. Routine profiling of exosomal miRNAs allows for real-time monitoring of disease progression and treatment response, providing continuous and up-to-date information on the patient's condition.

Combining exosomal miRNA analysis with other biomarkers and imaging techniques can offer a more comprehensive approach to glioma management, integrating various data sources for a holistic understanding of the disease. Predictive models incorporating exosomal miRNA data can forecast disease recurrence, guiding follow-up care and improving long-term outcomes. Finally, leveraging bioinformatics and machine learning to analyze complex exosomal miRNA data will uncover new insights into glioma biology and treatment, driving the field forward and opening new avenues for research and clinical application. These advancements collectively highlight the transformative potential of exosomal miRNAs in the comprehensive management of glioma, paving the way for more precise, personalized, and effective cancer care.

Author Contributions

SSB conceived the idea, wrote and edited the manuscript. MKP and VKV provided guidance throughout the preparation of this manuscript. RCD reviewed and made significant revisions to the manuscript. All authors contributed to the articles and approved the submitted version.

Conflict of Interest

Authors declare there is no conflict of interest to declare.

References

1. Lapointe S, Perry A, Butowski NA (2018) Primary brain tumors in adults. *Lancet* 392: 432-436. [crossref]

2. Smith HL, Wadhwani N, Horbinski C (2022) Major features of the 2021 WHO classification of CNS tumors. *Neurotherapeutics* 19: 1691-1704. [crossref]

3. Kamiya-Matsuoka C, Gilbert MR (2015) Treating recurrent glioblastoma: an update. *CNS Oncology* 4: 91-104. [crossref]

4. Verdugo E, Puerto I, Medina MA (2022) An update on the molecular biology of glioblastoma, with clinical implications and progress in its treatment. *Cancer Communications* 42: 1083-1111. [crossref]

5. Putavet DA, de Keizer PLJ (2021) Residual disease in glioma recurrence: A dangerous liaison with senescence. *Cancers (Basel)* 13: 1560. [crossref]

6. Ou A, Yung WKA, Majd N (2021) Molecular mechanisms of treatment resistance in glioblastoma. *International Journal of Molecular Sciences* 22: 351. [crossref]

7. Xie XP, Laks DR, Sun D, Ganbold M, Wang Z, Pedraza AM, et al. (2022) Quiescent human glioblastoma cancer stem cells drive tumor initiation, expansion and recurrence following chemotherapy. *Developmental Cell* 57: 32-46. [crossref]

8. Walker AJ, Ruzevick J, Malayeri AA, Rigamonti D, Lim M, Redmond KJ, et al. (2014) Post-radiation imaging changes in the CNS: How can we differentiate between treatment effect and disease progression? *Future Oncology* 10: 1277-1297. [crossref]

9. Young JS, Al-Adli N, Scotford K, Cha S, Berger MS (2023) Pseudoprogression versus true progression in glioblastoma: what neurosurgeons need to know. *Journal of Neurosurgery* 139: 748-759. [crossref]

10. Kan LK, Drummond K, Hunn M, Williams D, O'Brien TJ, Monif M (2022) Potential biomarkers and challenges in glioma diagnosis, therapy and prognosis. *BMJ Neurology Open* 2: e000069. [crossref]

11. Skouras P, Markouli M, Kalamatianos T, Stranjalis G, Korkolopoulou P, Piperi C (2023) Advances in liquid biopsy analysis for glioma diagnosis. *Biomedicines* 11: 2371. [crossref]

12. Yokoi A, Ochiya T (2021) Exosomes and extracellular vesicles: Rethinking the essential values in cancer biology. *Seminars in Cancer Biology* 74: 79-91. [crossref]
13. Whiteside TL (2016) Tumor-derived exosomes and their role in cancer progression. *Advanced Clinical Chemistry* 74: 103-141. [crossref]
14. Yang E, Wang X, Gong Z, Yu M, Wu H, Zhang D (2020) Exosome-mediated metabolic reprogramming: the emerging role in tumor microenvironment remodeling and its influence on cancer progression. *Signal Transduction and Targeted Therapy* 5: 242. [crossref]
15. Ribeiro MF, Zhu H, Millard RW, Fan GC (2013) Exosomes function in pro and anti-angiogenesis. *Current Angiogenes* 2: 54-59. [crossref]
16. Wortzel I, Dror S, Kenific CM, Lyden D (2019) Exosome-mediated metastasis: communication from a distance. *Developmental Cell* 49: 347-360. [crossref]
17. Olejarz W, Dominiak A, Żołnierzak, Kubiak-Tomaszewska G, Lorenc T (2020) Tumor-derived exosomes in immunosuppression and immunotherapy. *Journal of Immunology Research* 2020: 6272498. [crossref]
18. Ramoz-Zaldivar HM, Polakovicova I, Salas-Huenuleo E, Corvalan AH, Kogan MJ, Yefi CP et al. (2022) Extracellular vesicles through the blood-brain barrier: a review. *Fluids and Barriers of the CNS* 19: 60. [crossref]
19. Dai J, Su Y, Zhong S, Cong L, Liu B, Yang J, et al. (2020) Exosomes: key plays in cancer and potential therapeutic strategy. *Signal Transduction and Targeted Therapy* 5: 145.
20. O'Brien J, Hayder H, Zayed Y, Peng C (2018) Overview of microRNA biogenesis, mechanisms of actions and circulation. *Frontiers in Endocrinology* 9: 402. [crossref]
21. Ying SY, Chang DC, Lin SL (2008) The microRNA (miRNA): Overview of the RNA genes that modulate gene function. *Molecular Biotechnology* 38: 257-268. [crossref]
22. Suzuki HI (2023) Roles of microRNAs in disease biology. *Journal of JMA* 6: 104-113.
23. Keerthikumar S, Chisanga D, Ariyaratne D, Al Saffar H, Anand S, Zhao K, et al. (2015) Exocarta: A web-based compendium of exosomal cargo. *Journal of Molecular Biology* 428: 688-692. [crossref]
24. Aili Y, Maimaitiming N, Mahemuti Y, Qin H, Wang Y, Wang Z (2021) *Frontiers in Oncology* 11: 686369.
25. Beyer S, Fleming J, Meng W, Singh R, Haque SJ, Chakravarti A (2017) The role of miRNAs in angiogenesis, invasion and metabolism and their therapeutic implications in gliomas. *Cancers (Basel)* 9: 85. [crossref]
26. Zhang D, Lee H, Zhu Z, Minhas JK, Jin Y (2017) Enrichment of selective miRNAs in exosomes and delivery of exosomal miRNAs in vitro and in vivo. *American Journal of Physiology Lung Cellular and Molecular Physiology* 312: L110-L121. [crossref]
27. Janas T, Janas MM, Sapan K, Janas T (2015) Mechanisms of RNA loading into exosomes. *FEBS Letters* 589: 1391-1398. [crossref]
28. Nail HM, Chiu CC, Leung CH, Ahmed MMM, Wang HMD (2023) Exosomal miRNA-mediated intercellular communications and immunomodulatory effects in tumor microenvironments. *Journal of Biomedical Science* 30: 69. [crossref]
29. Aloizou AM, Pateraki G, Siokas V, Mentis AFA, Liampas I, Gazopoulos G, et al. (2020) The role of miRNA-21 in gliomas: Hope for a novel therapeutic intervention. *Toxicology Reports* 7: 1514-1530. [crossref]
30. Quintavalle C, Garofalo M, Romano G, Zanca C, Laboni M, De Caro MDB, et al. (2011) MiR-221/222 overexpression in human glioblastoma increases invasiveness by targeting the protein phosphate PTP. *Oncogene* 31: 858-868. [crossref]
31. Makowska M, Smolarz B, Romanowicz H (2023) MicroRNAs (miRNAs) in glioblastoma multiforme (GBM) -Recent literature review. *International Journal of Molecular Sciences* 24: 3521. [crossref]
32. Xu CH, Xiao LM, Zeng EM, Chen LK, Zheng SY, Li DH, Liu Y (2019) MicroRNA-181 inhibits the proliferation, drug sensitivity and invasion of human glioma cells by targeting selenoprotein K (SELK) *American Journal of Translational Research* 11: 6632-6640. [crossref]
33. Cai S, Shi CJ, Lu JX, Wang YP, Yuan T, Wang XP (2021) MiR-124-3p inhibits the viability and motility of glioblastoma multiforme by targeting RhoG. *International Journal of Molecular Medicine* 47: 69. [crossref]
34. Qu S, Qiu O, Huang J, Liu J, Wang H (2021) Upregulation of hsa-miR-196a-5p is associated with MIR196A2 methylation and affects the malignant biological behaviors of glioma. *Genomics* 113: 1001-1010. [crossref]
35. Jafari A, Karimabadi K, Rahimi A, Rostaminasab G, Khazaei M, Rezakhani L, et al. (2023) The emerging role of exosomal miRNAs as biomarkers for early cancer detection: A comprehensive literature review. *Technology in Cancer Research and Treatment* 22: 15330338231205999. [crossref]
36. Otoukesh B, Abbasi M, Gorgani HL, Farahini H, Moghtadaei M, Boddouhi B, et al. (2020) MicroRNAs signatures, bioinformatics analysis of miRNAs, miRNA mimics and antagonists and miRNA therapeutics in osteosarcoma. *Cancer Cell International* 20: 254. [crossref]

Citation:

Beevi S, Panigrahi MK, Verma VK, Chowdary R, et al. (2024) Exploring the Potential of Exosomal miRNA as Prognostic Biomarkers in Glioma. *Cancer Stud Ther J* Volume 9(2): 1-4.