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Mini Review

# Role of Exosomes in the Progression, Diagnosis, and Therapy Targeting of Malignant Brain Gliomas

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## Abstract

Glioblastoma is the most common primary tumor of the central nervous system, characterized by an infiltrative growth pattern, which results in the most unfavorable prognosis. The average survival time of patients after diagnosis of this tumor is typically several months, with complete recovery from glioma being very rare. In recent years, significant involvement of exosomes in the development of cancer, including malignant brain tumors, has been discovered. Exosomes are extracellular vesicles that carry signaling molecules and participate in communication between cells. They influence cell survival, proliferation, migration, and increased neoangiogenesis, all of which significantly contribute to tumor recurrence. Molecules carried by exosomes are considered potential diagnostic markers, enabling early diagnosis of cancer and prompt implementation of appropriate treatment. Of particular diagnostic importance are microRNA molecules, which promote increased cell proliferation and inhibition of apoptosis. Equally important exosomal transmitters include proteins such as PSMD2 and EGFR, which enhance tumor invasiveness and resistance to chemotherapeutic agents. Recent studies suggest the possibility of using exosomes as carriers for new anticancer drugs, potentially improving the therapeutic treatment of cancers resistant to standard treatment methods. This review aimed to provide a comprehensive analysis of recent research on glioblastoma, the role of exosomes in its progression, the potential of exosomes as diagnostic biomarkers, and their use as therapeutic targets for patients who have not responded to conventional treatments.

## Introduction

Glioblastoma is an example of a primary brain tumor that tends to grow in an infiltrative pattern and accounts for 12–15% of all brain tumors. According to statistical data, the incidence of this tumor is 3.21 per 100,000 people in the United States, making it the most frequent primary brain tumor. Despite recent advancements in treatments, such as the use of temozolomide (TMZ) in conjunction with radiotherapy, the outcomes for patients remain quite unfavorable, with a median overall survival of nine to sixteen months following diagnosis.[1] For recurrent cases, the outlook is even bleaker, with a median survival of five to seven months, even with optimal treatment.[2] Glioblastoma is characterized by a wide range of genetic mutations, including *CDK4* amplification, *CDKN2A* deletion, and *IDH1/2* and *TP53* mutations. The methylation status of the MGMT promoter is a crucial diagnostic marker, as patients with methylation are known to have better survival outcomes.[3] Other molecular markers that have been identified include *ATRX*, *CIC*, *FUBP1*, *NOTCH1*, and the *TERT* promoter gene, all of which exhibit variability in glioblastoma.[4] Despite its frequency, glioblastoma is not the only tumor diagnosed in the central nervous system. Progress in genetics and molecular studies has made it possible to isolate specific biomarkers for different cancers, significantly improving diagnosis and tumor identification. Mutations in the *ATRX*, *IDH1/2*, and *TP53* genes characterize diffuse anaplastic astrocytomas, while mutated *IDH1/2* with a simultaneous deletion at the 1p19q position indicates the presence of oligodendroglioma. *BRAF* gene fusions are identified in low-grade gliomas. Finally, *TERT* promoter mutations, trisomy of chromosome 7 with loss of chromosomes 10 and 13, and focal amplifications of receptor tyrosine kinase genes point to glioblastoma.[5] Standard therapies for glioblastoma include surgery, chemotherapy, different types of radiotherapy, and tumor treating fields. However, despite the use of several treatment options, a cure is rarely achieved. As a result, there remains a need for the development of new therapeutic approaches. Over the last few years, exosomes have gained significant attention in cancer biology, especially in glioblastoma. These nanosized membrane-bound vesicles, which contain specific bio-

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**Table 1. Exosomal biomarkers in glioblastoma cells**

| Marker | Action |
|---|---|
| *ACTR3, ANXA1, APP, CALR, CTSD, ECM1, GAPDH, IGF2R, IPO5, ITGB1, MVP, PDCD6IP, PSAP, PSMD2* | Determination of tumor's invasive properties and increasing its invasiveness |
| miR-5096 | Stimulation of cell invasiveness and proliferation |
| miR-21, miR-23a, miR-29a, miR-30a, miR-92b, miR-222, miR-221, | Inhibition of apoptosis and support of cell proliferation |
| Mutated *PTEN* | Excessive cell proliferation |
| *EGFR/EGFR Viii* | Formation of resistance to apoptotic signals and chemotherapy, which is associated with poor prognosis |
| *PDGFR* amplification | Increased proliferation of cancer cells means an unfavorable prognosis for the patient |
| *TERT* promoter | Induction of cells' excessive proliferation |
| Ndfip1 | Repression of this protein increases the survival of cancer cells and their proliferation |

*ACTR3,* actin-related protein 3; *ANXA1*, annexin 1; *APP*, amyloid-beta precursor protein; *CALR*, calreticulin; *CTSD*, cathepsin D; *ECM1*, extracellular matrix protein 1; *EGFR*, epidermal growth factor receptor; *GAPDH*, glyceraldehyde 3-phosphate dehydrogenase; *IGF2R*, insulin-like growth factor 2 receptor; *IPO5*, importin 5; *ITGB1*, integrin beta-1; *MVP*, major vault protein; *PDCD6IP*, programmed cell death 6-interacting protein; *PDGFR*, platelet-derived growth factor receptor; *PSAP*, prosaposin; *PSMD2*, proteasome 26S subunit ubiquitin receptor, non-ATPase 2; *PTEN*, phosphatase and tensin homolog; *TERT*, telomerase reverse transcriptase.

active molecules, offer potential for both diagnosis and therapy. The objective of this review is to examine the current knowledge on the functions of exosomes in glioblastoma progression, evaluate their potential as biomarkers for diagnostic purposes, and assess their effectiveness as targets for therapeutic interventions, including in cases that have not responded to conventional therapies.

## Important role of exosomes in glioblastoma

Each exosome carries molecules involved in intercellular communication. Glioblastoma brain cells secrete exosomes that carry bioactive molecules specific to this tumor, including proteins and RNA. These biologically active molecules contained in exosomes contribute to the increased proliferation of cancer cells, their invasiveness, resistance to TMZ, and the initiation of angiogenesis in brain endothelial cells. Moreover, these molecules modulate the expression of specific genes and influence the functioning of various signaling pathways.[6] In general, glioblastoma-derived exosomes modulate immune evasion, the formation of a pre-metastatic niche, anti-apoptotic mechanisms, and resistance to anticancer drug therapy.[7] Exosomes involved in carcinogenesis have been found to be enriched with long non-coding RNA molecules (lncRNA). These lncRNAs have the ability to remodel the tumor microenvironment (TME), enabling further growth and development.[8–10] However, despite many studies, the function of oncogenic lncRNA-enriched exosomes in regulating chemoresistance in glioblastoma remains poorly understood.[11] Exosomes derived from glioma stem cells (GSCs) have a significant impact on shaping the TME. Exosomes from GSCs are key mediators in the transformation of the TME, which participates in the development of drug resistance. The remodeling of the microenvironment initiated by GSCs is associated with the polarization of M2-type tumor-associated macrophages. In addition, GSC-derived exosomes have significantly increased levels of miR-374b-3p molecules, which enhance the polarization of tumor-associated macrophages. This results in increased neoangiogenesis and, consequently, tumor progression. Furthermore, research indicates that miR-374b-3p interacts with the phosphatase and tensin homolog (PTEN) protein. miR-374b-3p molecules can reduce the expression of PTEN, leading to macrophage polarization toward the M2 phenotype and stimulation of angiogenesis.[12] The results of numerous studies highlight the significant role of exosomes in the carcinogenesis of brain tumors at various levels. Table 1 below shows the exosomal markers involved in the development of brain glioblastoma.

## Diagnostic importance

Detecting the presence of glioblastoma at an early stage of development is difficult due to the lack of specific biomarkers. In recent years, there has been hope for the use of exosomes as a source of marker molecules characteristic of the early stages of malignant tumor development. Determining the content of these molecules in patients would undoubtedly be a breakthrough method for early cancer diagnosis, providing a chance for full recovery. It is evident that accurate characterization of the tumor at the molecular level is necessary to implement therapy optimized for each specific patient. Previous research on glioblastoma markers has revealed the content of molecules in exosomes from tumor cells that can be successfully used for diagnostic purposes. For example, EGFRvIII expression imparts aggressive and proliferative properties to GBM cells and also acts in a non-cell-autonomous manner by deregulating pathways of intercellular communication.[13] Syndecan-1, in turn, is considered a biomarker enabling the differentiation of low- and high-grade gliomas.[10] Moreover, the level of microRNA (miRNA) is also of diagnostic importance—high concentrations of these molecules are associated with cancer progression, and increased expression of miR-21 indicates enhanced invasive abilities. Additionally, the content of miR-23a, miR-29a, miR-30a, miR-92b, miR-221, and miR-222 molecules increases the proliferation of cancer cells and inhibits the apoptosis process.[14] These markers primarily help determine the degree of malignancy of the tumor, which is crucial for planning appropriate treatment. Also characteristic of glioblastoma development is the overexpression of many proteins, which have been detected in exosomes isolated from various glioma cell lines. Comparative analysis of the proteomes of normal and cancer-affected glial cells showed overexpression of 13 proteins present in exosomes: ANXA1, ANXA2, COF1, ENO1, G3P, HS90B, KPYM, PRDX1, TPIS, TERA, VIM,

1433E, and NPM. These are therefore additional marker proteins present in glioma cell exosomes. Interestingly, the most useful biomarkers in the diagnosis of glioma, such as p53 and PCNA, are not found in exosomes.[15] The aforementioned exosomal lncRNA molecules also have diagnostic potential. Due to the high specificity and sensitivity of exosomal lncRNAs, they can be used as biomarkers for the early diagnosis of malignant brain tumors and as prognostic markers in monitoring a patient's response to chemotherapy.[16]

## Therapeutic possibilities

The main challenge for anticancer drugs in the treatment of brain tumors is their permeability through the blood-brain barrier. In recent years, extensive research has been carried out on the possibility of using exosomes in anticancer therapies, including the effective treatment of glioblastoma. The dynamic development of nanotechnology and the possibility of isolating exosomes from cells have enabled research into their therapeutic potential. Exosomes can be used as carriers of anticancer drugs or as carriers of factors that promote the apoptosis pathway in cancer cells. Studies using exosomes from the U87MG glioma cell line containing selumetinib showed that the exosome equipped with this drug has a targeted anticancer effect without damaging healthy cells, offering hope for the effective treatment of malignant brain tumors.[17] Furthermore, study results have also shown an association between the transfer of exosomal molecules, such as miR-151a, and the sensitivity of glioma cells to TMZ therapy. Increasing the expression of this molecule sensitizes drug-resistant tumor cells to TMZ by inhibiting DNA repair via XRCC4.[18] Consequently, it becomes possible to combine existing chemotherapy with the use of exosomes, which would significantly increase its effectiveness. Another potential approach concerns personalized anticancer therapy based on the transdifferentiation process, i.e., reprogramming somatic cells, in which exosomes are also involved. The results of subsequent studies suggest that exosomes from transdifferentiation-induced neural stem cells (Exo-iNSC) are an effective and promising option for the therapy of many brain tumors. It has been shown that genetically modified iNSC cells secrete exosomes containing the TRAIL protein, which is lethal to cancer cells and naturally penetrates them, arranging itself across the outer membrane (Exo-iNSC-TRAIL). Studies conducted under *ex vivo* conditions found that Exo-iNSC-TRAIL selectively accumulates within the tumor without damaging healthy cells and kills cancer cells faster than TRAIL in its free form. This method has proven effective both in combating primary malignant brain tumors and potential metastatic foci.[19] Therefore, personalized therapies using exosomes represent a promising breakthrough in oncology, providing hope for the effective treatment of even the most drug-resistant cancers, such as glioblastoma.

## Discussion

Brain gliomas originate from cells of the astrocytic layer, which play a central role in the exchange of metabolites in the blood-brain barrier. Cancer-affected glial cells exhibit significant resistance to alkylating drugs, such as TMZ, and the combination of chemotherapy with radiotherapy and surgery usually does not guarantee survival longer than several months. Every year, numerous studies are conducted to improve anticancer therapies. Standard chemotherapy drugs, which act non-selectively on the patient's body cells, are gradually being replaced by molecularly targeted drugs and immunotherapeutic agents. A new possibility in glioblastoma treatment has recently emerged. This involves the use of exosomes containing drug cargo to eliminate tumor cells. Recent studies have revealed that glioblastoma cells release numerous exosomes that facilitate tumor cell migration, invasion, and the stimulation of normal cells' malignant transformation.[14] However, their ability to modulate various cell functions can also be harnessed for therapy. Taking into account their nanosize, exosomes can easily cross the blood-brain barrier, making them a promising therapeutic target for glioblastoma.[20] Exosomes can carry various cargo particles, such as miRNA. Sakr *et al*.[21] demonstrated that exosomes transfected with miR-133a or miR-150-5p can suppress the expression of membrane-type 1 matrix metalloproteinases, subsequently inducing apoptosis in glioma cells.[18,21,22] Moreover, miRNA-containing exosomes present a promising treatment option for TMZ-resistant glioblastoma. Zeng *et al*.[18] investigated the influence of exosomal miR-151a on TMZ resistance. They proved that overexpression of this exosomal particle can sensitize resistant cells to TMZ by suppressing the XRCC4 DNA repair pathway.[18,23] Another advantage of exosomes is that they are a promising source of diagnostic markers. These exosomal markers can be used for early diagnosis of glioblastoma. Lai *et al*.[24] determined that miR-210 levels are increased in the serum of glioblastoma patients relative to healthy controls. Furthermore, miR-210 expression may be used as a biomarker for the diagnosis and prognosis of glioblastoma. However, high expression of this miRNA is associated with poor prognosis for patients.[24] According to these findings, exosomes offer numerous perspectives for the diagnosis and treatment of glioblastoma patients, providing hope for effective therapy against this highly aggressive brain tumor.

## Conclusions

Exosomes containing that carry various cargo molecules play one of the crucial roles in carcinogenesis and progression of human glioblastoma. They are also responsible for its resistance to TMZ therapy and poor prognosis. However, exosomes can be used as an useful source of glioblastoma's diagnostic biomarkers and become an excellent drug carrier.

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## Conflict of interest

The author has no conflicts of interest to declare in relation to the work presented in this review.

## Author contributions

PP is the sole author of the manuscript.

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