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REVIEW

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Exploring the clinical implications and applications of exosomal miRNAs in gliomas: a comprehensive study

Liang Yang[1†], Zhen Niu[1†], Zhixuan Ma[1], Xiaojie Wu[1], Chi Teng Vong[3,4], Ge Li[2*] and Ying Feng[1*]

Abstract

Gliomas are aggressive brain tumors associated with poor prognosis and limited treatment options due to their invasive nature and resistance to current therapeutic modalities. Research suggests that exosomal microRNAs have emerged as key players in intercellular communication within the tumor microenvironment, influencing tumor progression and therapeutic responses. Exosomal microRNAs (miRNAs), small non-coding RNAs, are crucial in glioma development, invasion, metastasis, angiogenesis, and immune evasion by binding to target genes. This comprehensive review examines the clinical relevance and implications of exosomal miRNAs in gliomas, highlighting their potential as diagnostic biomarkers, therapeutic targets and prognosis biomarker. Additionally, we also discuss the limitations of current exsomal miRNA treatments and address challenges and propose future directions for leveraging exosomal miRNAs in precision oncology for glioma management.

Keywords Exosomal microRNAs, Glioma, Diagnosis, Treatment, Prognosis

Introduction

The World Health Organization (WHO) CNS5 classification of central nervous system tumors categorizes gliomas into grades I to IV, with higher grades indicating higher malignancy [1–3]. Grades I and II gliomas are classified as low-grade gliomas, while grades III and IV are classified as high-grade gliomas. Low-grade brain gliomas primarily refer to diffuse astrocytomas, oligodendrogliomas, and oligoastrocytomas. High-grade brain gliomas primarily refer to anaplastic astrocytomas, anaplastic oligodendrogliomas, glioblastomas, and diffuse midline gliomas. Gliomas, the most common and malignant primary brain neoplasms, originate from glial or precursor cells in the central nervous system (CNS) neuroectoderm [4, 5]. They are characterized by their undesirable prognosis and poor survival rate, encompassing astrocytomas, oligodendrogliomas, and ependymomas [6, 7], posing a serious threat to human health and lives. While computed tomography (CT) and magnetic resonance imaging (MRI) are routine techniques for diagnosing disease stages and monitoring tumor growth and therapeutic response, they are often cumbersome and expensive. Conventional surgical, radiation, and chemotherapy treatments can delay tumor progression but are often ineffective and do not provide significant improvement [8]. Therefore, there is an urgent need for a

†Liang Yang and Zhen Niu are co-first authors.

*Correspondence:
Ge Li
lige@gdph.org.cn
Ying Feng
fengy8@scut.edu.cn
[1] School of Medicine, South China University of Technology, Guangzhou, Guangdong, China
[2] Guangdong Provincial Key Laboratory of Pathogenesis, Targeted Prevention and Treatment of Heart Disease, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou 510100, China
[3] State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macau, China
[4] Macau Centre for Research and Development in Chinese Medicine, University of Macau, Macau, China

new method that can both diagnose and treat gliomas, as well as detect the prognosis of gliomas. Recently, increasing evidence suggests that diagnostic biomarkers, such as exosomal miRNAs, would be clinically meaningful for the early detection of the tumor and for cases in which surgery is contraindicated or biopsy results are inconclusive [9, 10].

Exosomes, small vesicles with round or cup shapes, were first isolated from sheep erythrocyte supernatant in 1983 by JohnStone et al. during a study on the transformation of immature erythrocytes to mature erythrocytes [11]. These vesicles, which have a diameter of 40–160 nm, originate from endosomes and consist of lipid bilayer membranes [12, 13]. They are actively released by most cells, circulating stably in body fluids [14, 15]. Besides their roles in cell-to-cell communication and tumorigenesis, exosomes safeguard the substances they carry, including DNA, RNA, lipids, and proteins, from degradation [16–20], while also regulating the activity of recipient cells and influencing the tumor microenvironment by transporting nucleic acids [21].

Exosomal miRNAs, a subset of circulating miRNAs, have gained attention for their characteristics as endogenous, double-stranded, non-coding small molecule RNAs, typically 18–25 nucleotides in length, with over 1000 different exosomal miRNAs identified through RNA sequencing [22, 23]. The discovery of the first miRNA dates back to 1993 when *Lee and Ambros* identified one in *Caenorhabditis elegans*, and their presence in exosomes was first demonstrated by Valadi et al. in 2007 [24–27]. Originating from single-stranded miRNA gene transcripts, they are processed by the ribonuclease III enzyme, Dicer, integrated into the RNA-induced silencing complex, enabling them to repress the translation of target RNA by binding to partially complementary sequences in the 3′ untranslated region (UTR) of messenger RNA (mRNA) [28–30] (Fig. 1). Exosomal miRNAs may play roles in gene activation in certain contexts, affecting biological processes, exerting significant influence on cell differentiation, proliferation, and survival, exhibiting both tumor-suppressive and oncogenic effects [31–34]. Notably, Calin et al. observed a loss or downregulation of miR-15/16 cluster expression in chronic lymphocytic leukemia in 2002, highlighting the potential role of miRNAs in tumorigenesis [35]. Studies have also demonstrated the effectiveness of exosomal miRNAs as potential biomarkers in liquid biopsy for cancer diagnosis, treatment monitoring, and prognosis prediction, emerging as valuable disease markers [36–43]. Notably, the effects of exosomal miRNAs on gliomas primarily involve the inhibition or promotion of their downstream target genes, thereby exerting their respective biological functions (Tables 1, 2).

In this review, we summarize the latest findings on the fundamental roles of exosomal miRNAs implicated in the diagnosis, treatment, and prognosis of gliomas, considering the complex molecular mechanisms and the expanding research field. We also discuss the research limitations and provide future perspectives.

Exosomal miRNAs and the occurrence and development of gliomas

Exosomal miRNA biogenesis is tightly regulated temporally and spatially, with dysregulation implicated in glioma development [44–49]. Current research suggests that dysregulation of exosomal miRNAs could be pivotal in glioma growth, angiogenesis, metastasis, and cell migration. For example, several studies have reported that miR-375 inhibits proliferation and invasion in glioblastoma, while miR-16-1 inhibits migration and proliferation in glioma cells [50, 51]. Additionally, Li et al. demonstrated that microglial exosome miR-7239-3p promotes glioma progression by regulating Circadian genes [52]. These research findings indicate a close association between exosomal miRNAs and the occurrence and development of gliomas, suggesting their potential application in clinical diagnosis, treatment, and prognosis.

Application of exosomal miRNAs in the diagnosis of gliomas

A variety of circulating biomarkers are present in the blood of glioma patients, including circulating tumor cells, nucleic acids, and proteins [53]. Among these, exosomal miRNAs have garnered considerable attention due to their significant distinctions between glioma patients and healthy counterparts. Lu et al. conducted a systematic analysis of 217 mammalian miRNAs across 334 samples, revealing a prevailing downregulation of miRNAs in tumors compared to normal tissues [54]. Their findings enabled the successful classification of poorly differentiated tumors using miRNA expression profiling, highlighting the diagnostic potential of miRNA analysis in cancer. Furthermore, Wang et al. discovered significantly higher levels of miR-766-5p and miR-376b-5p in the serum of patients with high-grade glioma compared to healthy controls, suggesting their potential as auxiliary diagnostic biomarkers [55].

Glioblastoma (GBM), or glioblastoma multiforme, is the most malignant and common type of glioma. It is classified as a Grade IV glioma, characterized by its rapid growth, high invasiveness, and poor prognosis. Dong et al. identified elevated expressions of miR-576-5p, miR-340, and miR-626, alongside decreased expressions of miR-320, miR-7-5p, and let-7g-5p in the peripheral blood of GBM patients compared to normal subjects using gene microarray analysis [56]. In another study by Manterola,

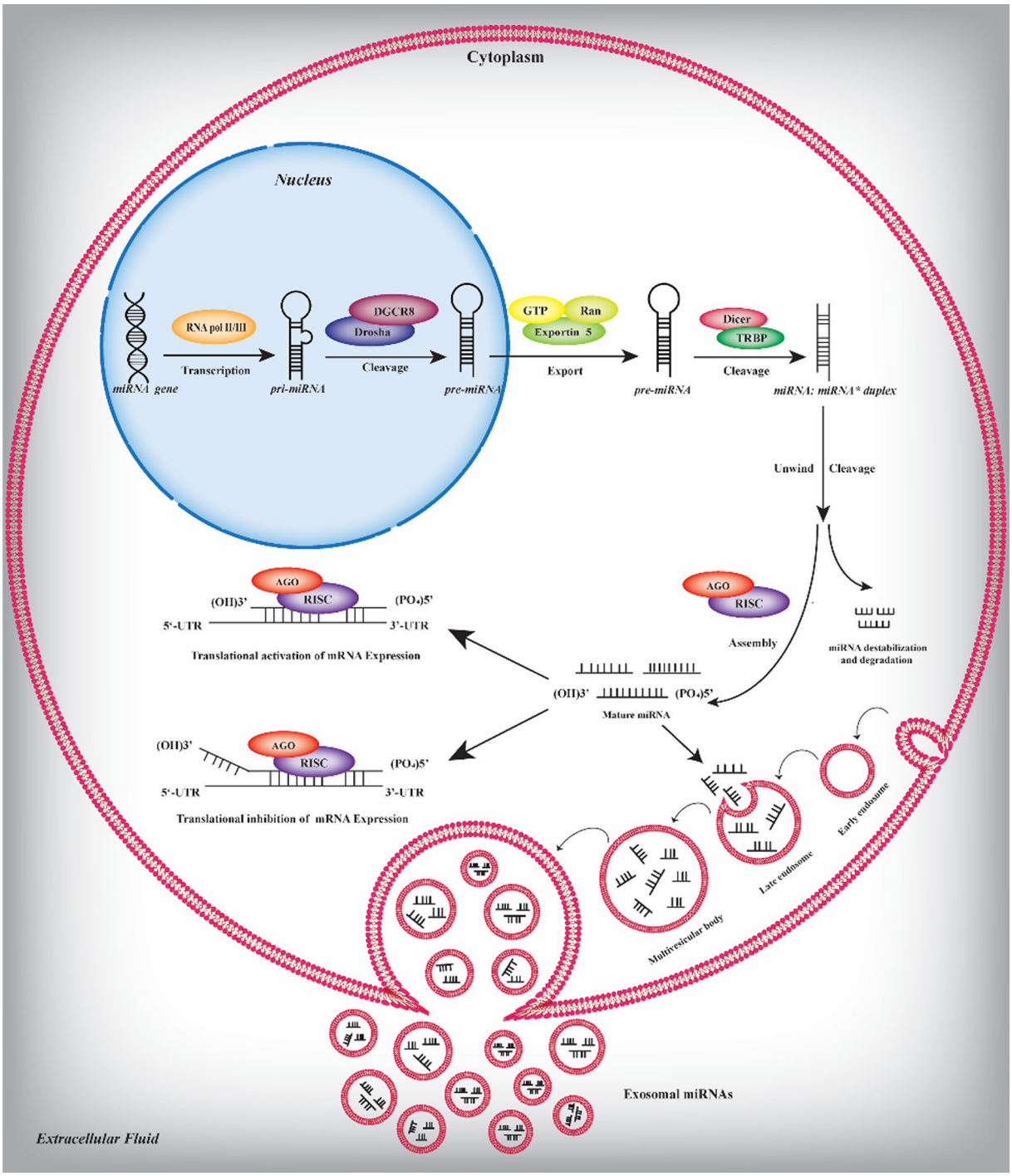

Fig. 1 The process of production and functions of mature exosomal miRNAs in animals. Mature miRNA is secreted out of the cells after entering endosomes formed by the cell membrane, thus resulting in the formation of exosomal miRNA. Mature miRNAs are produced in two stages: in the nucleus, genes encoding miRNAs are transcribed into pri-miRNAs by the action of RNA polymerase RNA pol II, which are then processed by Drosha RNase III nucleic acid endonuclease into 60-70 nt stem-loop intermediates, i.e. pre-miRNAs (miRNA precursors). Subsequently, pre-miRNA is transported into the cytoplasm by Exportin-5 bound to Ran-GTP, and the stem-loop structure is cleaved away by Dicer RNase III nuclease, leaving two incompletely paired strands called miRNA:miRNA* complexes, where miRNA is the mature miRNA and miRNA* is the relative arm with a short lifetime. Then, the double strand is loaded onto the argonaute protein, and nucleotide base pairing between the miRNA in the double strand and the complementary sequence in the 3′ untranslated region (3′ UTR) of the target mRNA forms the miRNA effector miRNA-induced silencing complex (miRISC) to inhibit translation and/or promote mRNA degradation, while miRNAs are released and degraded

Table 1 Exosomal miRNAs that are down-regulated, their target genes and biological functions, and their roles in glioma diagnosis, treatment and prognosis

MicroRNA	Target genes/pathway	Dysregulation	Mechanism/biological function	Diagnostic significance	Clinic treatment	Prognostic significance	Ref
MiR-1	ANXA2/MET	Downregulated in human GBM	Reducing the tumorigenicity, angiogenesis, invasion and progression of glioblastoma multiforme	Promising	Potential	Unclear	[34]
MiR-7	EGFR	Downregulated in GBM	Decreasing invasiveness of GBM and enhancing the sensitivity of GBM to TRAIL	Unclear	Potential	Unclear	[131, 132]
MiR-15a	CCND1	Downregulated	Suppressing migration and invasion of glioma	Unclear	Potential	Unclear	[102]
MiR-15b	CCNE1/NRP-2	Downregulated	Inhibiting angiogenesis and proliferation of gliomas cells	Unclear	Potential	Unclear	[133, 134]
MiR-29a-3p	ROBO1	Downregulated in glioma cells	Inhibiting migration and vasculogenic mimicry formation in glioma	Unclear	Potential	Unclear	[98]
MiR-29c	SP1	Downregulated in glioma	Increasing temozolomide sensitivity by targeting MGMT	Unclear	Potential	Unclear	[135]
MiR-34a	PDGFRA/c-Met/Notch/MYCN	Downregulated in glioma	Inhibiting proliferation and tumorigenesis in glioma cells	Unclear	Potential	Unclear	[79, 80, 136, 137]
MiR-101	EZH2	Downregulated in GBM	Inhibiting proliferation, migration, and angiogenesis of GBM	Unclear	Potental	Unclear	[138]
MiR-106a	E2F2	Downregulated in glioma	Inhibiting growth of glioma cells	Potential	Potential	Unclear	[139]
MiR-124	CDK6/STAT3	Downregulated in glioma	Suppressing proliferation, migration and increasing chemosensitivity to TMZ	Potential	Potentail	Unclear	[91, 94]
MiR-124a	IQGAP1/LAMC1/ITGB1/FOXA2	Downregulated in GBM	Suppressing migration and invasion in GBM	Unclear	Potential	Unclear	[95, 140]
MiR-125b	E2F2	Downregulated in CD133 positive GSCs	Inhibiting the proliferation of glioblastoma stem cells	Unclear	Potential	Unclear	[141]
MiR-128	RTK	Downregulated in glioma	Blocking GBM stem cells self-renewal and growth	Unclear	Potential	Potential	[142]
MiR-133b	Wnt	Downregulated in glioma	Suppressing proliferation, invasion and migration in glioma cells	Unclear	Potential	Unclear	[143]
MiR-136	AGE1/Bcl2	Downregulated in glioma cell	Promoting the apoptosis of glioma cells	Unclear	Potential	Unclear	[144]
MiR-137	CDK6	Downregulated in high-grade glioma	Inhibiting the proliferation of glioblastoma multiforme cells	Unclear	Potential	Unclear	[145]

Table 1 (continued)

MicroRNA	Target genes/ pathway	Dysregulation	Mechanism/ biological function	Diagnostic significance	Clinic treatment	Prognostic significance	Ref
MiR-139	Mcl-1	Downregulated in GBM	Suppressing the proliferation and enhancing temozolomide-induced apoptosis	Unclear	Potential	Unclear	[146]
MiR-143	N-RAS	Downregulated in glioma	Suppressing growth and enhancing temozolomide-induced apoptosis in glioma	Potential	Potential	Unclear	[147]
MiR-146b	EGFR	Downregulated in glioma cells	Suppressing the invasion and migration in glioma	Unclear	Potential	Unclear	[148]
MiR-152	MMP-3	Downregulated in glioma cells	Reducing invasion and angiogenesis in glioma	Unclear	Potential	Unclear	[134]
MiR-199a	AGAP2	Downregulated in glioma tissue	Enhancing chemosensitivity to TMZ in glioma	Unclear	Potential	Unclear	[89]
MiR-302–367	Cyclin D1/CyclinA/ E2F1/CXCR4	Downregulated	Suppressing migration, proliferation and chemosensitivity of GBM	Unclear	Potential	Unclear	[149, 150]
MiR-410	MET	Downregulated in glioma cells	Inhibiting proliferation and invasion of glioma	Unclear	Potential	Unclear	[151]
MiR-433	HMGB3	Downregulated in glioma tissue	Inhibiting the proliferation ability of glioma cells	Unclear	Potential	Unclear	[152]
MiR-451	AMPK/c-Myc/PI3K/ AKT	Downregulated	Promoting proliferation and immunosuppression in glioma cells	Unclear	Potential	Unclear	[153–156]
MiR-454-3p	ATG12	Downregulated in glioma cells	Inhibiting cell proliferation, migration, invasion, and autophagy in glioma	Yes	Unclear	Yes	[113]
MiR-483-5p	ERK1	Downregulated in glioma	Suppressing the proliferation of glioma cells	Unclear	Potential	Unclear	[157]
MiR-491	CDK6	Downregulated in GBM	Inhibiting the proliferation of glioma cell lines	Unclear	Potential	Unclear	[158]
MiR-512-5p	JAG1	Downregulated in glioblastoma	Suppressing glioblastoma proliferation	Unclear	Potential	Unclear	[159]
MiR-520/302	AKT1/PIK3CA/SOS1	Downregulated	Enhancing glioblastoma cell susceptibility to tyrosine kinase inhibitors	Unclear	Potential	Unclear	[160]
MiR-580-3p	WEE1	Downregulated in GBM	Suppressing the proliferation and drug resistance of glioma cells	Unclear	Potential	Unclear	[161]
MiR-584	PTTG1IP/CYP2J2	Downregulated in glioma	Inhibiting cancer cell proliferation, invasion and migration	Unclear	Potential	Unclear	[99, 162]

Table 1 (continued)

MicroRNA	Target genes/ pathway	Dysregulation	Mechanism/ biological function	Diagnostic significance	Clinic treatment	Prognostic significance	Ref
MiR-584-5p	CYP2J2/MMP-2/Bcl-2 and Bax	Downregulated	Suppressing metastasis, proliferation, migration and inducing glioma cells apoptosis	Unclear	Potential	Unclear	[99]
MiR-873	Bcl-2	Downregulated in glioma tissue	Decreasing the resistance of the glioma cells to cisplatin	Unclear	Potential	Unclear	[163]
MiR-885-5p	MMP9	Downregulated in glioma	Inhibiting cellular invasion in glioma cells	Unclear	Potential	Unclear	[164]
MiR-944	VEGFC	Downregulated	Suppressing proliferation, migration and angiogenesis in glioma	Unclear	Potential	Unclear	[165]
MiR-2276-5p	Rab13	Downregulated in glioma	Inhibiting the growth glioma cells	Potential	Unclear	Potential	[117]
MiR-4686	Unclear	Downregulated by exo-ROR1AS1	Suppressing the progression glioma cells	Unclear	Potential	Unclear	[166]
MiR-4709-3p	GRB14/PDGFRα	Downregulatede in glioblastoma	Enhancing glioblastoma progression and radioresistance	Unclear	Potential	Unclear	[167]

analysis of exosomal miRNAs from 161 GBM patients and 110 healthy subjects revealed that the combination of miR-320/miR-574-3p/RNU6-1 (RNA, U6 Small Nuclear 1) serves as promising biomarker candidates for distinguishing between GBM patients and healthy controls [57]. Similarly, elevated levels of miR-103 and miR-125 were detected in the serum of GBM patients [58].

Numerous studies have reported a significant upregulation of exosomal miR-21 expression in the serum of glioma patients, a dysregulation that may contribute to the initiation and progression of GBM by influencing various cellular and molecular targets [59, 60]. Santangelo et al. observed that post-surgery, levels of exosomal miR-21 isolated from patient serum were notably higher in individuals with high-grade glioma compared to those with low-grade glioma [61]. They further identified three serum exosome-associated miRNAs (miR-21, miR-222, miR-124-3) that could aid in glioma detection and grading through the analysis of 141 serum samples and accompanying clinical data [40]. The utilization of these three miRNA-based diagnostics was demonstrated to enhance diagnostic efficiency for high-grade glioma patients. Additionally, Akers et al. noted significantly elevated levels of miR-21 in the cerebrospinal fluid of GBM patients during their examination of cerebrospinal fluid from both healthy subjects and GBM patients for miRNA analysis [62]. Consequently, exosomal miR-21 emerges as a reliable biomarker for the diagnosis of glioma patients.

In addition to exosomal miR-21, several exosomal miRNAs have shown potential as biomarkers for glioma diagnosis. MiR-10, which is absent in normal brain tissue but elevated in gliomas, has been linked to tumor cell stasis, apoptosis, and autophagy [63]. MiR-449 and miR-5194 are promising for GBM diagnosis, while miR-210 is already confirmed as a biomarker for GBM patients [64]. Additionally, miR-221 was found to be significantly upregulated in GBM tissues, while miR-128 and miR-181 expressions were decreased, suggesting that elevated miR-221 expression could serve as a potential diagnostic biomarker for glioma [65, 66].

Tumor metastasis is a critical stage of tumor progression and a major therapeutic challenge. Exosomal miRNAs play an important role in the development of distant metastasis of primary tumor cells [67]. Studies have demonstrated a significant elevation in miR-148a levels in both the serum and tumor tissues of GBM patients. Furthermore, miR-148a has been implicated in promoting glioma metastasis, proliferation, and migration by targeting Cell Adhesion Molecule 1(CADM1), Mitogen-inducible gene 6(MIG6), and Epidermal growth factor receptor (EGFR) [68, 69]. Additionally, Teplyuk et al. also observed significant elevations in miR-10b and miR-21 levels in the cerebrospinal fluid of GBM patients, whereas miR-200 levels were notably increased in the cerebrospinal fluid of patients with glioma metastases [70]. Furthermore, Emilliya and colleagues discovered that miR-491 not only differentiates glioma brain metastasis but also exhibits

Table 2 Exosomal miRNAs that are upregulated, their target genes and biological functions, and their roles in glioma diagnosis, treatment and prognosis

MicroRNA	Target genes/ pathway	Dysregulation	Mechanism/ biological function	Diagnostic significance	Clinic treatment	Prognostic significance	Ref
MiR-9	COL18A1/THBS2/ PTCH1/PHD3	Upregulated in human glioma	Promoting tumorigenesis, angiogenesis and enhancing chemosensitivity, proliferation of glioma cells	Unclear	Potential	Unclear	[90, 168, 169]
MiR-10a	Rora/IkBa/NF-kB	Upregulated in H-GDEs	Promoting the expansion and function of myeloid-derived suppressor cells	Unclear	Potential	Unclear	[104]
MiR-10b	BCL2L11/TFAP2C/ CDKN1A/CDKN2A	Upregulated in human GBM	Reducing growth and inhibiting the proliferation of glioblastoma	Unclear	Potential	Potential	[63, 115]
MiR-10b-5p	TFAP2A	Upregulated in H-GDEs	Inducing glioma migration and invasion	Potential	Potential	Potential	[107]
MiR-21	VEGF/PTEN	Upregulated in GBM	Promoting proliferation, migration, nvasion and angiogenesis of glioma	Potential	Potential	Unclear	[47, 60, 104]
MiR-21-5p	SPRY1	Upregulated in GBM	Unclear	Yes	Unclear	Yes	[116]
MiR-9-5p	NAP1L1/FREM2	Upregulated in GBM stem cell	Unclear	Yes	Unclear	Yes	[116]
MiR-23a	PTEN	Upregulated in glioma	Promoting gliomagenesis	Unclear	Potential	Unclear	[170]
MiR-23b	VHL	Upregulated in glioma cells	Promoting proliferation and invasion of glioma	Unclear	Potential	Unclear	[171]
MiR-24	ST7L	Upregulated in glioma cells	Promoting proliferation, invasion and inducing apoptosis in glioma	Unclear	Promising	Unclear	[172]
MiR-25-3p	FBXW7	Upregulated in GBM	Promoting the proliferation and temozolomide resistance of glioblastoma	Potential	Unclear	Unclear	[88]
MiR-26a	RB1	Upregulated in glioma cells	Promoting the proliferation and angiogenesis in glioma cells	Unclear	Yes	Unclear	[173–175]
MiR-92b	NLK	Upregulated in glioma cells	Promoting invasion, growth and inhibiting apoptosis in glioma cells	Unclear	Potential	Unclear	[176]
MiR-145	srGAP1	Upregulated in IM3 cell lines	Regulating the invasion of glioblastoma cells	Unclear	Potential	Unclear	[177]
MiR-148a	CADM1/MIG6/BIM/ EGFR	Upregulated in GBM cells	Promoting proliferation, invasion and migration in glioma cells	Yes	Potential	Unclear	[68, 69]
MiR-148a-3p	ERRFI1	Upregulated in glioma cells	Promoting angiogenesis and proliferation	Unclear	Potential	Unclear	[178]
MiR-151a	XRCC4	Upregulated in glioma tissue	Enhancing chemosensitivity to TMZ in drug-resistant glioblastoma	Unclear	Potential	Unclear	[179]

Table 2 (continued)

MicroRNA	Target genes/ pathway	Dysregulation	Mechanism/ biological function	Diagnostic significance	Clinic treatment	Prognostic significance	Ref
MiR-181b/d	MGMT	Upregulated in GBM patients	Stimulating the cell proliferation, migration, and invasion	Yes	Unclear	Yes	[110]
MiR-182-5p	KLF2/4	Upregulated in glioma cells	Promoting glioblastoma angiogenesis and leading to the accumulation of VEGFR	Potential	Potential	Potential	[112, 180]
MiR-195	SIAH1/WEE1/RANBP3	Upregulated in GBM cells	Enhancing temozolomide resistance in glioblastoma multiforme cells	Unclear	Potential	Unclear	[181]
MiR-210	PTBP3	Upregulated in GBM patients serum	Involving survival, differentiation, angiogenesis, metabolism and cell cycle control	Yes	Potential	Yes	[182]
MiR-214-5p	CXCR5	Upregulated in GBM	Promoting cell proliferation and migration	Unclear	Potential	Yes	[183]
MiR-221	DNM3/PUMA	Upregulated in GBM	Promoting temozolomide resistance and progression in glioma	Yes	Yes	Unclear	[65, 66]
MiR-222	PUMA/PTPμ/AKT	Upregulated in HGG patients	Associating with glioma progression	Yes	Potential	Yes	[40, 184]
MiR-223	PAX6	Upregulated in GBM	Promoting the growth and invasion of tumor cells	Unclear	Potential	Unclear	[48]
MiR-301a	TCEAL7	Upregulated in glioma tissue	Promoting radiation resistance, proliferation and invasion in glioma cells	Yes	Unclear	Yes	[106]
MiR-328	SFRP1	Upregulated in glioma cells	Promoting the invasion of glioma cells	Unclear	Potential	Yes	[185]
MiR-381	LRRC4	Upregulated	Promoting the proliferation of glioma cells	Promising	Potential	Unclear	[186]
MiR-423-5p	FOXP4	Upregulated in MB patients exosomes	Inhibiting MB tumorigenesis, proliferation, migration and invasion	Unclear	Potential	Unclear	[187]
MiR-603	MGMT	Upregualted	Enhancing the TMZ sensitivity of GBM	Unclear	Potential	Unclear	[188]
MiR-634	CYR61	Upregulated	Decreasing the proliferation and growth of glioblastoma cells	Unclear	Potential	Unclear	[189]
MiR-889	Notch/Jak-STAT	Upregulated	Promoting glioma proliferation and radiation resistance	Unclear	Potential	Unclear	[190]
MiR-1238	CAV1/EGFR	Upregulated in GBM patients	Promoting resistance to TMZ and enhancing anti-apoptosis	Yes	potentail	Unclear	[87]
MiR-1298-5p	MSH2/Setd7	Upregulated	Promoting immunosuppressive effects of MDSCs and suppressing the progression in glioma	Unclear	Potential	Unclear	[103]
MiR-1587	NCOR1	Upregulated	Increasing the tumorigenicity of glioma stem-like cells	Unclear	Potential	Unclear	[93]

Table 2 (continued)

MicroRNA	Target genes/ pathway	Dysregulation	Mechanism/ biological function	Diagnostic significance	Clinic treatment	Prognostic significance	Ref
MiR-5096	Kir4.1	Upregulated	Promoting the invasiveness of glioma cells	Unclear	Potential	Unclear	[191]
MiR-7239-3p	Bmal1	Upregulated	Promoting proliferation and invasion in glioma	Unclear	Potential	Unclear	[52]
MiR-7239-4p	Bmal2	Upregulated	Promoting proliferation and invasion in glioma	Unclear	Potential	Unclear	[52]

lower expression in high-grade gliomas compared to low-grade gliomas [71]. Meanwhile, the findings of Bao et al. indicate that elevated expression of miR-155-5p in the plasma of glioma patients is positively correlated with glioma grading [72]. These studies suggest that miRNAs in exosomes have the potential to serve as diagnostic markers for glioma metastasis and to distinguish between different grades of gliomas, such as low-grade and high-grade gliomas.

Application of exosomal miRNAs for the treatment of gliomas

Traditional glioma treatments, like surgical resection and chemotherapy with radiotherapy, often lead to significant side effects and poor prognosis [73, 74]. For example, temozolomide (TMZ), a primary antitumor agent in clinical chemotherapy, induces DNA damage in glioma cells while also causing a multitude of chemotherapy side effects [75]. Furthermore, the limitations of traditional treatments underscore the urgent need for alternative therapeutic approaches. Nucleic acid therapy, currently promising in various human diseases, has attracted attention. Research accumulation indicates potential utilization of exosomal miRNAs in treating malignant tumors. [76, 77]. These exosomal miRNAs regulate gene expression post-transcriptionally and intricately connect with the glioma microenvironment through targeting multiple signaling pathways such as EGFR, Phosphatidylinositide 3-kinases/protein kinase B (PI3K/AKT), p53, Notch, and others [78–81].

Targeted therapy refers to a treatment strategy that specifically targets molecules or molecular pathways involved in the growth, progression, or spread of diseases such as cancer. Unlike traditional chemotherapy, which can affect both cancerous and healthy cells, targeted therapies are designed to interfere with specific molecules that play crucial roles in disease development. Meanwhile, exosomal miRNAs possess dual characteristics, with both tumor suppressive and oncogenic activities, endowing them with potential for tumor therapy [82–84]. Dysregulation of exosomal miRNAs significantly impacts glioma tumorigenesis, proliferation, migration, invasion, angiogenesis, immunosuppression, and drug resistance, suggesting a potentially innovative clinical treatment approach for glioma (Fig. 2).

Exosomal miRNAs for drug-resistant glioma treatment

Glioma resistance to clinical chemotherapy drugs often results in frequent disease recurrence and a poor prognosis [85]. Numerous studies have demonstrated the involvement of exosomal miRNAs in glioma chemotherapy drug resistance, including alkylating drug TMZ, suggesting a novel treatment approach to enhance drug sensitivity by regulating the expression of exosomal miRNAs [86].

Yin et al. identified high expression of miR-1238 in TMZ-resistant GBM cells and tissues, suggesting the miR-1238/CAV1 (Caveolin 1) axis as a potential target for future anti-tumor drugs [87]. Additionally, Wang et al. demonstrated that miR-25-3p promotes glioma development and resistance to TMZ by downregulating F-Box And WD Repeat Domain Containing 7(FBXW7) [88]. Furthermore, overexpression of miR-199a enhances chemosensitivity to TMZ and inhibits glioma progression by downregulating ArfGAP With GTPase Domain, Ankyrin Repeat And PH Domain 2(AGAP2) [89]. Moreover, Munoz et al. demonstrated that targeted delivery of exosome-derived functional anti-miR-9 from bone marrow stem cells enhances sensitivity of GBM to TMZ [90]. Meanwhile, Sharif et al. discovered that exogenous miR-124 delivered through Wharton's Jelly-derived MSCs (WJ-MSCs) efficiently affects cell migration and proliferation in GBM cells, increasing sensitivity to TMZ, suggesting a potential combination therapy for GBM [91].

Although the above studies have shown that exosomal miRNAs can enhance the sensitivity of glioma to chemotherapy drugs, most experiments are currently limited to

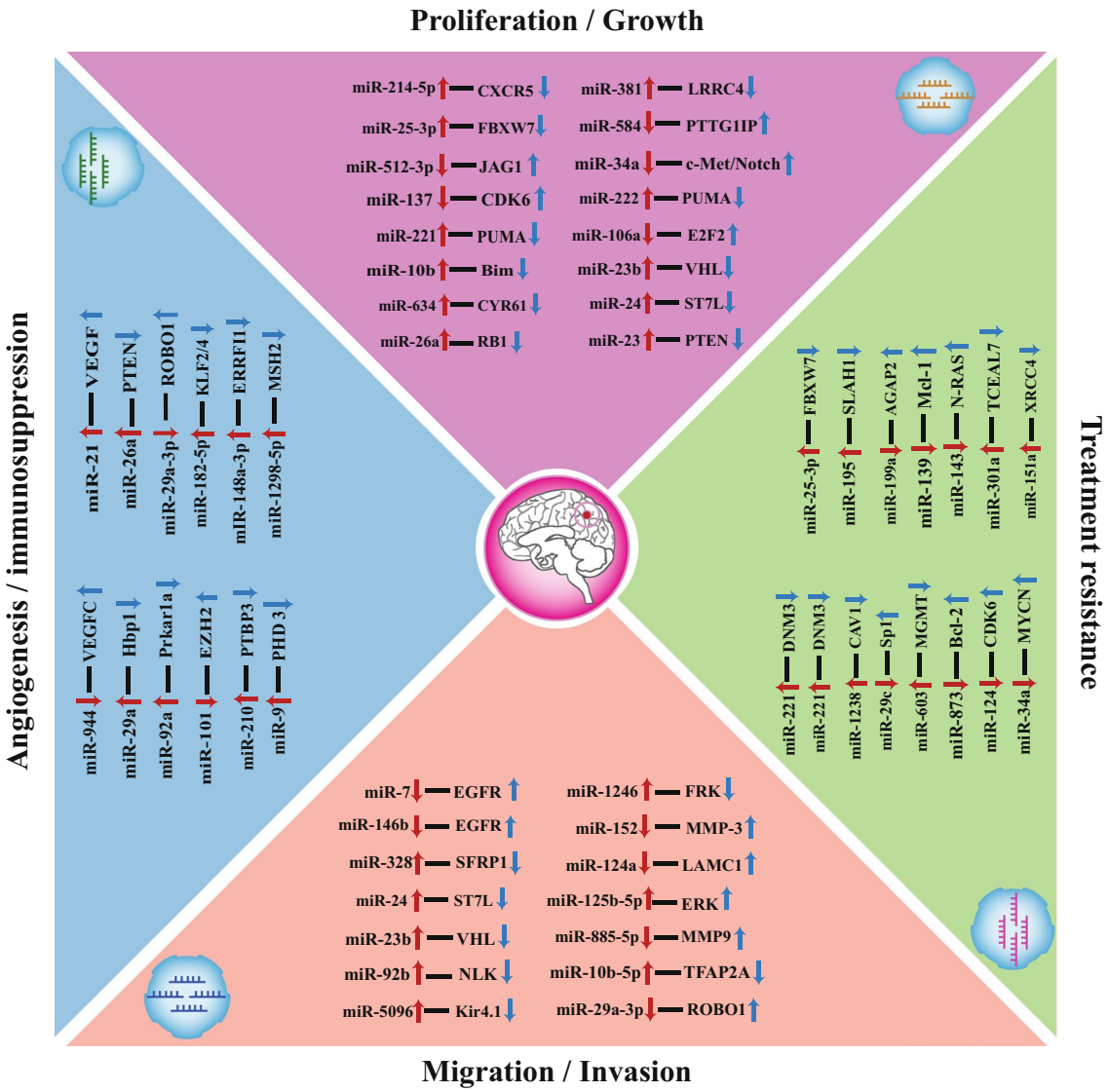

Fig. 2 The relationship between exosomal miRNAs, their target genes and biological functions. Exosomal miRNAs mediate their biological effects by targeting downstream genes, playing a pivotal role in shaping the glioma microenvironment. These effects include influencing glioma angiogenesis, progression, proliferation, invasion, migration, and the development of treatment resistance

the cell level. Whether it has the same effect in living animals and clinical trials still requires further exploration and research.

Stem cell-derived exosomal miRNAs for the treatment of gliomas

Stem cell-derived exosomal miRNAs are pivotal in glioma, affecting tumor growth, drug resistance, and treatment outcome [92, 93].They regulate gene expression and cell behavior, influencing tumor progression and treatment outcomes. Ongoing research aims to pinpoint specific miRNAs, elucidate their mechanisms, and explore their potential as biomarkers and therapeutic targets for improved glioma management [94, 95].

Glioma stem cells (GSCs) play a pivotal role in GBM, with GSC-derived exosomes (GSC-Exs) shown to enhance endothelial cell angiogenic ability via the miR-21/VEGF/Vascular Endothelial Growth Factor(VEGFR2) signaling pathway [96]. Jiang et al. demonstrated that GSC-derived exosomal miR-944 suppresses Vascular Endothelial Growth Factor C(VEGFC) expression and the AKT/ERK signaling pathway, inhibiting glioma growth, progression, and angiogenesis, offering potential for GBM therapeutic targeting [97]. Additionally,

targeting Roundabout Guidance Receptor 1(ROBO1), miR-29a-3p delivered via exosomes from engineered human mesenchymal stem cells suppresses tumor migration and vasculogenic mimicry in glioma, presenting potential for anti-VM (Vasculogenic mimicry) therapy and as supplements for anti-angiogenic therapy [98]. Kim et al. found that exosomal miRNA-584 inhibits glioma metastasis, suggesting MSC-derived exosomal miRNAs as an alternative strategy for malignant glioma treatment [99].

Although stem cell-derived exosomal miRNAs are closely related to the therapeutic application of glioma, further research is still needed to understand their precise mechanisms, ensure effective delivery, and verify safety. These include optimizing miRNA-based therapies, using advanced delivery systems, conducting rigorous preclinical and clinical evaluations, and combining these methods with existing treatment modalities to improve their efficacy and targeting accuracy.

Type II macrophage-derived exosomal miRNAs for the treatment of gliomas

It has been shown that M2-type macrophages promote glioma proliferation and migration [100, 101]. Yao et al. found that miR-15a and miR-92a, lowly expressed in M2 macrophage-derived exosomes, inhibit glioma metastasis and infiltration by binding to Cyclin D1(CCND1) and RAP1B (RAP1B, Member Of RAS Oncogene Family) to activate the PI3K/AKT/mTOR (mammalian target of rapamycin) signaling pathway [102]. This suggests that miR-15a and miR-92a might be a novel biomarker for GBM diagnosis in the glioma patients, and targeting miR-15a or miR-92a could contribute to anti-tumor immunotherapy.

At present, the specific mechanism of action of M2-type macrophage-derived exosomal miRNAs in glioma is not fully understood and has been less studied. At the same time, their detection methods need to improve sensitivity and specificity, and their biological functions need to be further verified. In addition, there are also verification and safety issues in the transformation process from the research stage to actual clinical application.

Cellular hypoxia-derived exosomal miRNAs for the treatment of gliomas

Myeloid-derived suppressor cells (MDSCs) constitute a heterogeneous population of bone marrow-derived cells crucial for tumor immune escape mechanisms due to their ability to significantly suppress immune cell responses [103]. Meanwhile, hypoxia has been reported to play a critical role in miRNA release from exosomes and the differentiation progression of MDSCs.

Gou et al. conducted miRNA sequencing, revealing upregulation of miR-10a and miR-21 expressions in Hypoxia-induced glioma exosomes (H-GDEs) compared to normoxia [104]. These miRNAs enhanced MDSC proliferation by targeting Rora and PTEN genes, respectively. Knockdown experiments of miR-10a and miR-21 in glioma cells further confirmed these findings. Guo et al. demonstrated that hypoxia-induced glioma cell exosomes stimulated the differentiation of functional MDSCs by transporting miR-29a and miR-92a, targeting Hbp1 and Prkar1a, respectively [105]. This promoted MDSC proliferation, thereby regulating the immunosuppressive tumor microenvironment.

Additionally, hypoxic glioma cells secrete exosomal miR-301a, which activates the Wnt/β-catenin signaling pathway and enhances radiation resistance by targeting Transcription Elongation Factor A Like 7(TCEAL7). The exo-miR-301a/TCEAL7-signaling axis presents a novel target for cellular resistance to cancer therapeutic radiation in GBM patients [106]. Furthermore, exosomal miR-1246 and miR-10b-5p from hypoxic glioma directly target Fyn Related Src Family Tyrosine Kinase(FRK) and Transcription Factor AP-2 Alpha(TFAP2A), respectively [107]. These miRNAs are delivered to normoxic glioma cells, promoting cell migration and invasion, thus offering a new avenue for antitumor therapy development.

Application of exosomal miRNAs in the prognosis of gliomas

Recent research highlights the crucial role of exosomal miRNAs in determining glioma prognosis. Their expression levels serve as potential biomarkers for predicting clinical outcomes and guiding therapeutic strategies.

For example, Guessous et al. analyzed TCGA data and found that miR-10b levels were negatively correlated with the prognosis of glioma patients. Shi et al. observed an association between elevated exosomal miR-21 levels in the cerebrospinal fluid of glioma patients and poor prognosis [108]. In addition, serum exosomal miR-301a levels were significantly elevated in glioma patients compared to healthy controls. After surgical resection of the primary tumor, serum exosomal miR-301a levels decreased, but increased again upon tumor recurrence [109]. Hence, serum adventitial miR-301a expression may serve as a novel potential biomarker for predicting prognosis in advanced glioma cases. Furthermore, Stakaitis et al. reported that high levels of miR-181b were linked to shorter postoperative survival, and that exosomal miR-181 levels decreased during glioma progression [110]. This suggests that exosomal miR-181 may serve as a potential biomarker for prognosis in glioma patients.

Studies have identified several exosomal miRNAs as potential prognostic markers for glioblastoma GBM.

In GBM patients, an inverse relationship was observed between miR-125b/miR-182-5p and nestin expression, which correlated with overall survival and implied their utility as a potential biomarker for predicting GBM prognosis [111, 112]. High expression of miR-454-3p/miR-10b in exosomes or miR-628-3p downregulation in GBM patients' blood suggests its potential as a poor prognosis biomarker [113–115]. Zottel et al. found that GBM patients with high miR-5p and miR-138-5p expressions, particularly with Isocitrate dehydrogenase (IDH) mutations, had significantly shorter median survival and worse prognosis [116]. Additionally, Sun et al. observed that miR-2276-5p was significantly lower in GBM patients compared to non-glioma individuals, correlating with poorer survival, while its target gene RAB13 (RAB13, Member RAS Oncogene Family) was elevated and associated with worse outcomes [117]. Moreover, Qiu et al. conducted bioinformatics analysis on 480 GBM samples, revealing strong associations between high levels of miR-326/-130a and low levels of miR-323/329/155/210 with long overall survival and progression-free survival in GBM patients [118]. These findings suggest that these miRNAs could serve as valuable prognostic biomarkers for GBM.

Conclusion

Gliomas, a type of brain tumor, can be broadly classified into two categories: localized gliomas, which are typically benign and often amenable to complete removal through surgical resection, and diffuse gliomas, which are malignant and carry a generally poor prognosis, posing significant challenges in post-surgery treatment [119]. As medical science progresses, the pursuit of such innovative approaches becomes crucial in enhancing patient care and outcomes in glioma cases. Exosomal miRNAs, small non-coding RNAs pivotal in regulating gene expression, have emerged as key players in various biological processes, including the pathogenesis of cancers, notably gliomas [120, 121]. Exosomal miRNAs present promising prospects for glioma research and treatment, offering potential for early diagnosis and prognostic assessment through liquid biopsies [53]. However, challenges include potential immune responses, off-target effects, and cytotoxicity, which could impact normal cells. In addition, the financial costs are substantial, encompassing isolation, extraction, and detection expenses, with overall development and clinical trials potentially costing several million dollars. Despite these hurdles, their value in glioma diagnostics, treatment and prognosis underscores their significance in ongoing research and clinical applications.

As the same time, the integration of big data analysis in exosomal miRNAs detection offers a groundbreaking perspective on gliomas [122]. With rapid advancements in bioinformatics and computational biology, big data analytics enable a deeper understanding of the intricate roles of exosomal miRNAs in glioma, driving the progress of personalized medicine [123]. For example, distinct exosomal miRNA patterns could serve as diagnostic markers, allowing physicians to diagnose and subtype gliomas via blood tests without invasive surgeries [124, 125]. Furthermore, in-depth analysis of miRNA expression patterns can inform treatment decisions, offering patients more personalized therapy options.

Additionally, exosomal miRNAs are prepared using various techniques, including ultracentrifugation, density gradient centrifugation, and immunoaffinity capture. Extraction is typically performed with commercial RNA kits, and detection is conducted using methods such as qRT-PCR and next-generation sequencing [126, 127]. These miRNAs are promising as non-invasive biomarkers for early cancer detection and prognosis, including gliomas, due to their ability to reflect tumor biology and facilitate liquid biopsy [128, 129]. However, several challenges persist, including the lack of standardized methods, ensuring high specificity and sensitivity, validating biomarkers across diverse patient cohorts, and addressing issues related to delivery and safety [130]. Future research should aim to standardize protocols, improve detection technologies, validate biomarkers through extensive clinical trials, and advance exosome engineering to enhance therapeutic applications. Collaboration among researchers, clinicians, and industry stakeholders will be essential for overcoming these challenges and advancing personalized medicine.

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Author contributions

LY wrote the manuscript. LY and ZN analyzed the data and drafted the manuscript. ZXM and XJW analyzed the data. YF, GL and CTV reviewed and edited the manuscript. All authors participated in the conception of this manuscript and approved the final version of this manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

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