Chapter 1
The Therapeutic Role of MicroRNAs in Human Gliomas

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1 Introduction

Central nervous system (CNS) tumors are classified based on their cell of origin and are graded based on standard histopathological features. The World Health Organization (WHO) classification, the most widely employed grading system for brain tumors, divides CNS tumors by predominant cell type and grade. The histopathological grading of gliomas accounts for presence of nuclear atypia, cellularity, mitotic activity, endothelial proliferation, necrosis, and proliferative index [1]. Tumors of the CNS can be broadly divided into primary brain tumors and brain metastases. With improved treatment and survival of cancer patients, there has been an increasing incidence of metastatic disease in the brain over the last decade. Primary brain tumors can arise from all cell types within the nervous system. Gliomas comprise a heterogeneous group of neuroectodermal tumors with unique clinical, histological, and molecular characteristics. Gliomas are the most common type of primary brain tumors and are broadly categorized into low-grade (WHO grade I and II) and high-grade (WHO grade III and IV) gliomas. Other common primary brain tumors include meningiomas, ependymomas, choroid plexus papillomas, medulloblastomas, pituitary adenomas and vestibular schwannomas.

Glioblastoma (GBM) is the most aggressive type of glioma and the most common malignant brain tumor. It is characterized by increased proliferation,

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robust angiogenesis and extensive invasion into surrounding brain tissue, with partial or complete disruption of the blood–brain barrier (BBB) [2, 3]. Although there is no specific set of symptoms that are diagnostic of brain tumors, one of the principal indicators that a brain tumor is presence of a leaky BBB, which can be detected by contrast-enhanced MRI or CT scan. The Cancer Genome Atlas Research Network has identified four subtypes of GBM: mesenchymal, classical, proneural and neural subtypes [4]. Proneural GBMs make up a large fraction of brain tumors.

Adding to the complexity of brain tumors is the highly infiltrating nature of malignant gliomas; these tumor invariably recur locally despite aggressive multimodality treatment with surgery followed by adjuvant chemoradiation therapy. As such, the prognosis of malignant gliomas remains extremely poor [2]. The median survival time after initial diagnosis of GBM is 14 months [5], and the 5-year survival rate is less than 10 % [6]. In combination with radiation therapy, the oral alkylating agent temozolomide (TMZ) is often given and has shown promise in improving the prognosis of GBM patients [7, 8]. TMZ crosses the BBB, and can help inhibit proliferation and induce apoptosis in glioma cells. In general, malignant gliomas are very infiltrative effectively negating the possibility of complete surgical resection. This highly infiltrative nature also explains the high rate of local tumor recurrence despite maximal multimodal treatment. Recurrent glioma cells, believed to arise from the infiltrating glioma stem cells (GSC), are highly resistant to both ionizing radiation and alkylating chemotherapeutic agents [2]. Tumor infiltration and presence of resistant GSCs are the major reasons for tumor recurrence. As such, considerable effort has been made to identify more effective ways to counter the invasiveness of gliomas. Recent studies have alluded to the hypothesis that GBM are maintained by a small population of GBM stem cells, which retain stem cell properties, are highly tumorigenic, and display increased resistance to radiation and chemotherapy [5]. Further complicating the problem, GSCs share a core developmental program with normal stem cells making them difficult to target [9]. Future studies should focus on finding molecular targets that regulate GBM stem cells while sparing normal stem cells, as well as identifying different biomarkers for early detection of tumor progression.

2 MicroRNAs in Gliomas

While the underlying causes of brain tumors remain largely unknown, some progress has been made in our understanding of gliomagenesis. Environmental factors that may induce tumorigenesis include exposure to vinyl chloride or ionizing radiation [10]. Genetic causes include overexpression of tumor oncogenes and mutations or deletions of tumor suppressor genes [11]. Moreover, there is mounting evidence that well-conserved, small non-coding segments of RNA called microRNAs (miRNAs) are involved in the transcriptional and post-transcriptional genetic regulation of these genes. These miRNAs are approximately 20–22

nucleotides in length and bind to the 3′ untranslated region (UTR) of multiple target messenger RNAs (mRNAs), resulting in genetic silencing of genes via translational repression or target degradation [12]. They are also known to play an important role in epithelial to mesenchymal transitions (EMT) required for embryonic development and cancer metastasis [13]. Thus, the impact of miRNAs in tumorigenesis has garnered considerable interest in recent years [14]. Since their discovery in 1993, research has exponentially increased on the impact of miRNAs in a variety of disease processes. Currently there are thousands of known miRNAs and many more continue to be discovered.

Deregulation of miRNA expression has been associated with many pathological states, including various cancers. Specific miRNAs have been reported to play vital roles in tumor initiation, proliferation, migration and invasion. Since malignant neoplasms can develop from either a reduction or deletion of a tumor suppressor miRNA or from amplification or overexpression of an oncogenic miRNA, we can divide miRNAs as either oncogenic or tumor suppressors. Overexpression of tumor suppressor miRNAs in GBM stem cells inhibits cell proliferation and induces neural differentiation [5]. Conversely, inhibition of tumor oncogenic miRNAs may result in decreased glioma growth and cell proliferation, and increased apoptosis [15–17]. Each miRNA can have hundreds of targets and therefore regulate a large number of diverse cellular functions [2]. Since every miRNA has many different targets, it is possible to regulate multiple gene networks by targeting a single miRNA. This demonstrates the vast potential of miRNAs in cancer therapy, and establishes a strong reason to investigate the use of miRNAs in glioma therapy [18, 19]. Tables 1.1 and 1.2 outline the oncogenic and tumor suppressor miRNAs involved in gliomagenesis, respectively. In the next sections, we will review in detail the role of some of the main miRNAs involved in gliomas.

3 Oncogenic miRNAs

3.1 miR-21

miR-21 is one of the most extensively studied miRNAs in cancer biology. It is highly expressed in embryonic and newborn central nervous system [28], and plays an important role during cerebral development. Its levels are often elevated in a variety of malignancies, including breast, colon, liver and pancreatic cancer [15–17]. miR-21 targets multiple components and plays an anti-apoptotic function in gliomas. Uncontrolled expression of miR-21 contributes to malignant transformation of glial cells, increases drug resistance, and is a major cause of tumor recurrence in high-grade gliomas [17]. Previous studies have confirmed that presence of miR-21 in cerebrospinal fluid (CSF) can be used to detect malignant gliomas [3]. However, CSF can only be collected by invasive methods and as such is not an ideal source for evaluation of miRNAs. Thus, the development of accurate blood

Table 1.1 Oncogenic miRNAs in glioma and their reported effects

miRNA	Target	Effects	Reference
miR-10b		In orthotopic human glioma mouse model, inhibition of miR-10b diminishes invasiveness, angiogenicity and growth of mesenchymal-like glioma cells and prolongs survival of glioma-bearing mice. Suppresses TP53, FOXO3, CYLD, PAX6, PTCH1, HOXD10 and NOTCH1	[4]
miR-10b	CSMD1	Upregulated in glioblastoma stem cells, compared to normal neural stem cells	[5]
miR-10b		Significantly elevated in glioblastoma	[20]
miR-17	PTEN, MDM2	Increases survival under nutrition-deproved conditions. Promotes cell motility and invasion	[21]
miR-19a/19b	PTEN	Overexpressed in glioma tumors and cell lines, and correlate positively with tumor grade	[22]
miR-20a	TGFβR2	Regulates TGF-β signaling and plays role in p53-Quaking pathway	[23]
miR-20a		Upregulated in pediatric brainstem glioma, compared to adult subtype	[24]
miR-21		Plasma levels significantly altered in glioblastoma patients compared to normal controls. Also, plasma levels in patients treated by operation and chemo-radiation almost revived to normal levels	[3]
miR-21	STAT3	Reduction of miR-21 decreases expression of hTERT and represses STAT3 expression and STAT3 phosphorylation; knockdown of miR-21 inhibits growth and diminishes expression of STAT3 in xenograft model	[25]
miR-21		Overexpression of PDGF-B in U87 glioblastoma and F98 rat glioma cells resulted in decreased miR-21 expression and overall increased cell proliferation	[15]
miR-21		Four-fold increase observed in the plasma of glioblastoma patient	[26]
miR-21		Inhibition of miR-21 sensitizes human glioblastoma U251 stem cells to chemotherapeutic drug temozolomide, enhancing apoptosis	[27]
miR-21		Circulating miR-21 in glioblastoma significantly higher than controls	[16]
miR-21		Chronic temozolomide exposure results in acquired temozolomide-resistance and elevated miR-21 expression. Concomitant treatment with miR-21 inhibitor and temozolomide resulted in a significantly higher apoptotic rate than temozolomide treatment alone	
miR-21		Significantly elevated in glioblastoma	[20]
miR-21		miR-21 and SOX2 upregulated in RCAS/tv-a generated mouse brain tumor specimens. Upon irreversible depletion of miR-21, expression of SOX2 strongly	[28]

(continued)

Table 1.1 (continued)

miRNA	Target	Effects	Reference
		diminished in both mouse primary glioma cultures and human glioma cell lines	
miR-21	PDCD4	Downregulation of miR-21/overexpression of PDCD4 inhibits metastasis via silencing of hnRNPC, resulting in suppressed Akt activation	[17]
miR-21	Tap63	High expression levels needed to maintain TRAIL-resistant phenotype. Impairs TRAIL-dependent apoptosis by inhibiting the expression of key functional proteins	[29]
miR-21		Expression found only in tumor cells and tumor-associated blood vessels, whereas no expression observed in adjacent normal brain parenchyma. miR-21 levels correlated significantly with histologic grade	[30]
miR-23a	PTEN	Oncogenic CREB (cAMP response element-binding protein) induces miR-23a which, in turn, suppresses PTEN	[31]
miR-23a	APAF1	High expression in tumor tissues. Inhibition results in suppression of proliferation and invasion	[32]
miR-23b	VHL	Downregulation of miR-23b triggers growth inhibition, induces apoptosis, and suppresses invasion of glioma *in vitro*. miR-23b deletion decreases HIF-1α/VEGF expression and suppresses β-catenin/Tcf-4 transcription activity by targeting VHL	[33]
miR-23b	Pyk2	Reduced expression of miR-23b enhances glioma cell migration *in vitro* and invasion ex vivo via modulation of Pyk2; increased expression of miR-23b results in decreased Pyk2 expression	[34]
miR-24-3p miR-27a-3p	MXl1	Overexpression of miR-24-3p and miR-27a-3p promotes cell proliferation, miR-23a~27a~24-2 and miR23b~27b~24-2 work synergistically to regulate MXl1	[35]
miR-27a		Stable expression reduces proliferation and increases the accumulation of glioma cells in sub-G1 arrest	[36]
miR-27a		Upregulated in glioma tissues and cell lines, potentially through adherens junction, focal adhesion, the neurotrophin pathway, MAPK signaling pathway, TGF-β pathway, cytokine-cytokine receptor pathway, or the p53 pathway	[37]
miR-30b/c	caspase-3	High expression levels needed to maintain TRAIL-resistant phenotype. Impairs TRAIL-dependent apoptosis by inhibiting the expression of key functional proteins	[29]
miR-30a-5p	SEPT7	Knockdown results in inhibition of cell growth and invasion in glioblastoma cells and induction of SEPT7 with downregulation of PCNA, cyclin D1, Bcl2, MMP2 and MMP9	[38]
miR-92b	NLK	Induces wnt/β-catenin signaling resulting in increased proliferation and invasion	[39]

(continued)

Table 1.1 (continued)

miRNA	Target	Effects	Reference
miR-106b		Upregulated in pediatric brainstem glioma compared to adult subtype	[24]
miR-106b	RBL2	Overexpressed in gliomas; antisense suppresses proliferation of glioma cells and xenograft tumors	[6]
miR-106b-5p	RBL1, RBL2, CASP8	Significantly high in glioma tumors and correlates with tumor grading	[40]
miR-125b	MMP9	Levels significantly higher in highly invasive glioma stem cell and progenitor cell lines	[41]
miR-125b	MAZ	Downregulated in glioblastoma associated endothelial cells, resulting in increased expression of MAZ, a transcriptional factor that regulates VEGF	[42]
miR-128		Overexpression of PDGF-B in U87 glioblastoma and F98 rat glioma cells results in decreased miR-21 expression and overall increased cell proliferation	[15]
miR-128		Plasma levels significantly altered in glioblastoma patients compared to normal controls. Also, plasma levels in patients treated by operation and chemo-radiation almost revived to normal levels. Positively correlated with histopathologic grades of glioma	[3]
miR143/145		Overexpressed in invasive subpopulation	[43]
miR-155	FOXO3a	Regulates Akt signaling and induces proliferation and invasiveness	[44]
miR-182	CYLD	Overexpressed in a set of gliomas. TGF-β induces miR-182 expression, leading to prolonged NF-κB activation both *in vitro* and *in vivo*.	[45]
miR-182		3.1 times high in glioma patients, compared to healthy persons	[46]
miR-183	IDH2	Upregulated in the majority of high-grade gliomas and glioma cell lines compared with peripheral, non-tumorous brain tissue. Downregulates IDH2 levels and upregulates HIF-1α levels	[47]
miR-183/96/182 cluster		Inhibition of cluster induced ROS-mediated AKT/survival, induced p53/apoptosis signaling independent of target genes FGF9, CPEB1 and FOXO1. Knockdown also enhanced the anticancer effect of temozolomide on glioma cells	[48]
miR-196b		Overexpressed; confers a poor prognosis via promoting cellular proliferation in glioblastoma	[49]
miR-221	TIMP3	Significantly increased in high-grade gliomas compared with low-grade gliomas. Overexpression increases cell invasion. Increased expression levels in high-grade gliomas confer poorer overall survival.	[50]
miR-222	TIMP3	Significantly increased in high-grade gliomas compared with low-grade gliomas. Overexpression increases cell invasion and confers poorer overall survival.	[50]

(continued)

Table 1.1 (continued)

miRNA	Target	Effects	Reference
miR-222	DKK2	Activates Wnt/β-catenin signaling and promotes tumorigenesis	[51]
miR-342-3p		Plasma levels significantly altered in glioblastoma patients. Plasma levels in patients treated by operation and chemo-radiation almost revived to normal levels. Positively correlated with histopathologic grades of glioma	[3]
miR-372		Upregulated in glioma tissues. Cumulative overall survival of glioma patients with advanced histologic grades significantly worse for high miR-372 expression group than for low miR-372 expression group	[52]
miR-376a*	RAP2A/ AMFR	Clinically, a significant correlation between accumulation of unedited miR-376a* and the extent of invasive tumor spread	[53]
miR-650		Possible prognostic marker with high expression in high grade gliomas	[54]

For miRNAs with multiple reports, major findings of reports are listed individually. The 'target' column is left blank in case no target was reported/validated in the study

miRNAs biomarkers will likely provide a less invasive and more practical way to diagnose gliomas, monitor therapeutic response, and detect tumor recurrence. A recent study showed that miR-21 may be used as a biomarker to detect GBM [3, 16]. Compared to control subjects, plasma levels of miR-21 were significantly higher in patients with malignant gliomas and correlated to histologic grade of glioma [16]. In addition, it was observed that the levels of miR-21 decreased after chemoradiation.

miR-21 works by targeting multiple genes. One study found that miR-21 inhibited cell growth in U87 and LN229 human GBM cell lines, accompanying a decrease in human telomerase reverse transcriptase (hTERT) mediated by signal transducer and activator of transcription 3 (STAT3) transcription [25]. This study showed that knockdown of miR-21 resulted in a significant increase in apoptosis and an induction of cells in cell cycle arrest. In addition, it showed that hTERT is necessary for cell survival, as it works to prevent the shortening of telomeres thereby delaying cell senescence. Furthermore, the study confirmed that STAT3 is critical for hTERT regulation of miR-21. These findings were also validated using a LN229 malignant glioma xenograft model [25].

Another study found that miR-21 works by regulating the Bax/Bcl-2 and caspase-3 activity [27]. Pro-apoptotic Bax and anti-apoptotic Bcl-2 proteins are known to regulate apoptosis in glioma cells. Bcl-2 poses one of the biggest obstacles to radiation and chemotherapy. It has been observed that GBM patients have a low Bax/Bcl-2 ratio [27]. Treatment of U251MG cells with a miR-21 inhibitor resulted in an increase of Bax and a decrease of Bcl-2 expression, dramatically improving the Bax/Bcl-2 ratio. Caspase proteins, especially caspase-3, are known to work downstream of Bax/Bcl-2, and play a vital role in GBM apoptosis. The authors noted that

Table 1.2 Tumor suppressor miRNAs in glioma and their reported effects

miRNA	Target	Effects	References
miR-7	EGFR	Enhanced levels induce apoptosis, inhibit proliferation migration and invasion, and antagonize ERK, Akt and Stat3. Plasmid-mediated gene therapy with miR-7 resulted in glioma xenografts growth arrest	[12]
Let-7a	K-Ras	Inhibits cell growth *in vitro* as well as *in vivo*.	[55]
miR-15b	NRP-2	Decreases cell invasiveness and *in vitro* tube formation	[56]
miR-16-1	Zyxin	Lower in glioma cells than normal brain tissues. Inhibits migration and invasion	[57]
miR-23b		miR-23b is epigenetically downregulated (through increased methylation), and restoration of miR-23b can effectively suppress cell growth in GSCs, induce cell cycle arrest and inhibit proliferation	[58]
miR-23b	TFAM	Inhibits PI3K/Akt signaling leading to reduced cell proliferation and migration	[59]
miR-24	ST7L	Inhibits proliferation and invasion, and induces apoptosis. Deletion of miR-24 suppresses β-catenin/Tcf-4 transcription activity	[60]
miR-25	MDM2 and TSC1	Overexpression results in p53 accumulation by directly targeting MDM2 and TSC1, leading to inhibited cell proliferation through cell cycle arrest *in vivo*	[61]
miR-32	MDM2 and TSC1	Overexpression results in p53 accumulation by directly targeting MDM2 and TSC1, leading to inhibited cell proliferation through cell cycle arrest *in vivo*	[61]
miR-34a		Tumor suppressor in U87 GSCs. Downregulated in CD133-positive cells. Suppresses cell proliferation and induces apoptosis in GSCs	[62]
miR-34a	PDGF-R	Downregulated by PDGF signaling pathway activation	[63]
miR-34c		Downregulated in glioma patients and cell lines. Overexpression reduces Notch, leading to cell cycle arrest and induction of apoptosis	[64]
miR-106a	SLC2A3	Low levels correlate with poor prognosis. Inhibits glucose uptake and cell proliferation	[65]
miR-107	Notch2	Downregulated in glioma tissues and cell lines, overexpression leads to inhibition of migratory and invasive ability of glioma cells via direct targeting of Notch2	[66]
miR-107	CDK6 and Notch 2	Inhibits proliferation and cell cycle, specifically p53 mutated U251 and A172	[67]
miR-107		Inhibits growth and invasion of glioma cells by Targeting Notch2 and stem cell markers	[68]
miR-124	NRAS, PIM3	Downregulated in glioblastoma stem cells, compared to normal neural stem cells	[5]

(continued)

Table 1.2 (continued)

miRNA	Target	Effects	References
miR-124	Slug, Twist, Vimentin	Cell differentiation agent-2 (CDA-2) inhibits cell growth and induces differentiation of glioma cells through upregulation of miR-124, accompanied with decreased expression of SLUG, Twist and Vimentin	[69]
miR-124	SOS1	Regulates Ras/Raf/Erk pathway and inhibits proliferation	[70]
miR-124		Inhibits STAT3 signaling	[71]
miR-124	CLOCK	Regulates proliferation and migration through targeting of NF-κB	[72]
miR-125b	E2F2	Overexpression of miR-125b inhibits the proliferation of CD133 positive glioma stem cells and reduces the expression of stemness marker	[73]
miR-128	P70S6K1	Levels decreased in gliomas; overexpression suppresses p70S6K1 and its downstream targets, HIF-1 and VEGF	[74]
miR-128	EphB2	Promotes cell-cell adhesion and inhibits cell migration	[75]
miR-128a		Negative regulator of mesenchymal signaling -CD44, vimentin, YKL-40	[76]
miR-134	Nanog	Reduces proliferation and invasion, induces apoptosis	[77]
miR-136	AEG-1, Bcl-2	Downregulated in human glioma, and promotes apoptosis of glioma cells induced by chemotherapy. Restoration of AEG-1 and Bcl-2 suppresses miR-136 enhanced apoptosis	[78]
miR-137	COX2	Levels downregulated in gliomas; ectopic expression inhibited cell proliferation and invasion	[79]
miR-137	RTVP-1	Promotes neural differentiation and suppresses stem cell markers	[80]
miR-138	EZH2, CDK6	High levels correlate with longer progression free survival. Induces cell cycle arrest	[81]
miR143/145	CTGF	Low in astrocytic tumors compared to normal brain specimens, low expression results in poor prognosis	[2]
miR-145	ADAM17	Significantly downregulated in glioma cell lines compared to normal brain tissue and negatively regulates tumorigenesis. Restoration inhibits proliferation, migration and invasion via silencing of ADAM17	[82]
miR-145	Sox9, Adducin3	Negatively correlates with tumor grade	[83]
miR-146b	MMP16	Inhibits migration and invasion of glioma cells	[84]
miR-146b		Exosomes expressing miR-146b inhibit glioma xenograft growth	[85]
miR-149	Akt1, PCNA, cyclinD1, MMP-2	Reduces proliferation and invasion, and induces cycle arrest	[86]

(continued)

Table 1.2 (continued)

miRNA	Target	Effects	References
miR-152	MMP-3	Decreases cell invasiveness	[56]
miR-153		Downregulated in glioma tissues	[87]
miR-155	GABRA1	Decrease in miR-155 expression restores expression of GABRA1, making glioglastoma cells sensitive to signals and inhibit cell proliferation mediated by GABRA1	[88]
miR-181b	IGF1R	Modulates PI3K/Akt and MAPK/ERK1/2 pathways leading to suppression of proliferation, invasion and tumorigenesis	[89]
miR-181b	MEK1	Modulates sensitivity to temozolomide	[90]
miR-181d	MGMT	A predictive marker of temozolomide response	[91]
miR-193a	Mcl-1	Induces apoptosis	[92]
miR-195	Cyclin D1, Cyclin E1	Inhibits proliferation and anchorage-independent growth, downregulates pRB and PCNA	[93]
miR-196b		Low expression associated with occurrence of preoperative seizures in low-grade gliomas, and may predict seizure prognosis in patients without preoperative seizures	[94]
miR-200b	CREB1	Suppresses proliferation and colony formation	[95]
miR-203		Reduced in high grade gliomas, low levels associated with poor prognosis	[96]
miR-204	SOX4, EphB2	Downregulated in glioma and neural stem cells. Suppresses self-renewal, stem cell-associated phenotype and migration of glioma cells. Restoring via promoter hypermethylation suppresses tumorigenesis	[97]
miR-206	Otx2	Ectopic expression inhibits cell proliferation and promotes apoptosis; miR-206 inhibitor upregulates expression of Otx2	[98]
miR-211	MMP-9	Inhibits glioma cell invasion and migration via epigenetic silencing and suppression of MMP-9. Activates intrinsic mitochondrial/Caspase-9/3-mediated apoptotic pathway in both glioma cells and CSCs. Increases drug retention capacity	[99]
miR-218	ECOP	Overexpression induces glioma cell apoptosis and inhibits viability, proliferation and tumorigenicity. miR-218 sensitizes glioma cells to apoptosis by regulating ECOP-mediated suppression of NF-κB activity	[100]
miR-218	LEF1, MMP-9	Expression low in glioma tissues, especially in glioblastoma. Inverse correlation in 60 GBM tissues between the levels of miR-218 and MMP mRNAs (MMP-2, -7 and -9)	[101]
miR-219	EGFR	Downregulated in gliomas. Inhibits anchorage independent growth, proliferation and migration	[102]

(continued)

Table 1.2 (continued)

miRNA	Target	Effects	References
miR-223	NF1A	Negatively regulate tumorigenesis via regulation of p21	[103]
miR-329	E2F1	Interferes with cell cycle progression and inhibits cell proliferation	[104]
miR-375		Expression significantly decreased in glioma tissues with ascending histopathologic grade. Loss of miR-375 expression effectively predicted the decreased overall survival	[105]
miR-383	IGF1R	Downregulated in gliomas and inversely correlates with glioma grade. Regulates Akt signaling	[106]
miR-410	MET	Inhibits proliferation and invasion of glioma cells	[107]
miR-483-5p	ERK1	Significantly downregulated in gliomas; overexpression suppresses cell proliferation and induces cell cycle arrest	[108]
miR-504		Negative regulator of mesenchymal signaling	[76]
miR-524-5p	Jagged-1, Hes-1	miR-524-5p behaves as a tumor suppressor by negatively targeting Jagged-1 and Hes-1	[109]
miR-708		Induces apoptosis by affecting multiple pathways	[110]
miR-1275	Claudin-11	Consistently downregulated during GSC differentiation, along with the upregulation of its target, CLDN11.	[111]
miR-6165	Pkd1, DAGLA	Induces apoptosis	[112]

For miRNAs with multiple reports, major findings of reports are listed individually. The 'target' column is left blank in case no target was reported/validated in the study

miR-21 inhibitor in combination with TMZ resulted in an increase of caspase-3 activity, thereby improving the effectiveness of apoptosis after chemotherapy and decreasing the likelihood of glioma recurrence [27].

In addition to Bax/Bcl-2 and hTERT, miR-21 targets programmed cell death 4 (PDCD4) and phosphatase and tensin homolog (PTEN), which are frequently downregulated in GBM with a marked increase in miR-21 expression [17]. PDCD4 is a protein that is upregulated during apoptosis and suppresses tumorigenesis. One way to regulate PDCD4 is phosphorylation by Akt, leading to ubiquitination and degradation of PDCD4. PTEN is a tumor suppressor that negatively regulates the PI3K/Akt signaling pathway. This study also found that in T98G GBM cell lines, downregulation of miR-21 or overexpression of PDCD4 or PTEN can inhibit metastasis via silencing of heterogeneous nuclear ribonucleoprotein C1/C2 (hnRNPC), resulting in suppressed Akt activation [17]. Suppressed Akt results in inhibited migratory and invasive activities, while silenced hnRNPC results in reduced proliferation and enhanced apoptosis. hnRNPC is involved in mRNA metabolism, including pre-mRNA processing, mRNA transport, mRNA stabilization, and can also enhance translation of proteins [17]. Further studies need to investigate the mechanism by which hnRNPC regulates miR-21 biogenesis.

Another interesting aspect of miR-21 is its connection to tumor necrosis factor (TNF) and tumor necrosis factor-related apoptosis-induced ligand (TRAIL). Novel research on TRAIL shows promise because it only induces apoptosis in cancer cells while sparing normal, healthy cells [113]. Many human cancers, including some gliomas, are TRAIL-resistant and do not respond to normal signals for programmed cell death [29]. One study found that miR-21 is markedly upregulated in TRAIL-resistant glioma cells (TB10 and LN229) and is downregulated in TRAIL-sensitive glioma cells (T98G and LN18) mainly by targeting the 3′ UTR region of Tap63, a member of the p53 family [29]. Sensitization of cancer cells to apoptosis is a valuable strategy to design novel treatment options. Thus, the relationship between miR-21 and TRAIL needs to be further elucidated as it may provide a mechanism for overcoming resistance to apoptosis.

Platelet derived growth factors (PGDF) are a vast family of pro-oncogenic growth factors. Alterations in the PGDF family, including overexpression of PGDF-A and B ligands on their receptors, are commonly observed in high-grade gliomas [15]. However, the connection between PGDF signaling and miRNAs remains to be elucidated. Interestingly, one study found that the expression of oncogenic miR-21 can be downregulated by activating PDGF-B, inducing GBM tumorigenesis and enhancing tumor proliferation [25]. In human U87 and rat F98 GBM cell lines, prolonged exposure of PDGF-B promoted downregulation of miR-21 expression [25]. Furthermore, small interfering RNA (siRNA)-mediated PGDF-B silencing increases the levels of miR-21 in U87 cells, confirming the relationship between PGDF-B signaling and miR-21 [25]. These findings conflict with the majority of studies on miR-21 and further demonstrate the complex balance of miRNAs in gliomas and the need for additional work to help clarify these intricate relationships.

Researchers are now investigating the effectiveness of miR-21 in synergy with other miRNAs and other drugs. One study found the combination of a miR-21 inhibitor and a miR-10b inhibitor could be an effective therapeutic strategy for controlling GBM growth [20]. Another study focused on the use of TMZ and a miR-21 inhibitor, finding that only the combination of both agents is effective in promoting GSC apoptosis thereby limiting the potential of tumor recurrence after chemotherapy [27]. This study observed that U251MG cells are normally resistant to TMZ alone, and the use of a miR-21 inhibitor or the use of TMZ alone had no effect on the stem cell population. The synergistic effects of miR-21 in combination with drugs and other miRNAs show great promise for glioma therapy and needs further investigation.

3.2 miR-182

A key regulator of cell fate is nuclear factor-κB (NF-κB), which mediates the inflammation pathway. The role of inflammation in promoting cancer is widely known and well documented [114–118]. Inflammation starts with the recruitment of

leukocytes by endothelial cells and their migration from plasma into tissue, caused by pro-inflammatory cytokines, protein kinase C activation, viruses or oxidants [117]. Any of these events can activate tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β), which in turn activate NF-κB and cyclooxygenase-2 (COX-2). NF-κB functions as a transcription factor for COX-2 and also activates many genes that cause inflammation in a feed-forward loop. NF-κB is a heterotrimer with three subunits (p50, p65 and IκBα). Upon activation of the complex, IκBα undergoes phosphorylation, ubiquitination, and eventually degradation, thus releasing the p50 and p65 heterodimer for translocation into the nucleus as the active NF-κB [115].

This pathway is also controlled by feedback mechanisms regulated by the anti-inflammatory cytokines IL-4, IL-10, transforming growth factor β (TGF-β), peroxisome proliferator activated receptor γ (PPAR-γ), manganese superoxide dismutase, glutathione, and catalase among others [117]. In response to pro-inflammatory cytokines such as TNF-α and IL-1, NF-κB activates the transcription of inhibitory Smad7, which in turn suppresses the TGF-β pathway [118]. Uncontrolled inflammatory responses via increased levels of NF-κB are associated with a number of neoplasms, including breast, prostate, ovarian, lung, colon and pancreatic cancer, head and neck cancer, melanoma and lymphoma [45, 118]. Investigating the multiple levels of NF-κB regulatory processes, as well as the crosstalk between NF-κB and TGF-β, may provide ways to prevent or treat cancers, including gliomas.

miR-182 is another oncogenic miRNA that is overexpressed in malignant gliomas [45, 46], with one study reporting 3-fold higher levels in glioma patients when compared to healthy control subjects [46]. Another study noted that miR-182 directly targets and suppresses cylindomatosis (CYLD) [45]. CYLD de-ubiquinates NF-κB, and acts as a negative regulator of the NF-κB pathway resulting in increased apoptosis. The authors noted a significant inverse correlation between CYLD levels and glioma tumor grade, which was also associated with shorter overall survival in GBM patients [45]. Restoration of CYLD resulted in inhibited glioma tumorigenesis, and inhibited glioma growth and angiogenesis *in vivo*. Suppressed CYLD resulted in ubiquitin conjugation of NF-κB and sustained NF-κB activity, which caused glioma cells to become more aggressive both *in vitro* and *in vivo*. In addition, suppression of miR-182 resulted in inhibited NF-κB activity. Furthermore, the authors found that TGF-β induced miR-182 expression and led to prolonged NF-κB activation, alluding to a possible regulatory mechanism by which NF-κB and TGF-β crosstalk. This study is critical for the development of more effective glioma therapies, as it discovered a possible mechanism for sustained NF-κB activation in malignant gliomas. Finding a way to regulate the NF-κB pathway will undoubtedly prove to be a powerful instrument in designing novel therapies for glioma patients.

3.3 *miR-10b*

miR-10b belongs to the tumor-oncogene family, and was one of the earliest discovered miRNAs. It is known to be upregulated in GSCs compared to normal neural stem cells [5, 20], as well as in GBM tissues with one study finding an average increase of 142-fold [5]. In U87-2M1 cells, an invasive type of the U87 subline that resembles the mesenchymal GBM cells, it was demonstrated that inhibition of miR-10b resulted in a distinct increase in apoptosis, with suppression of both glioma cell invasion and angiogenesis *in vitro* and *in vivo* [4]. After silencing miR-10b, invasive proteins such as MMP-13, MMP-2, CTNNB1 and HGF were downregulated. This finding was due to the suppression of multiple tumor suppressor genes, including TP53, FOXO3, CYLD, PAX6, PTCH1, HOXD10 and NOTCH1. Specifically, miR-10b targets genes HOXD10, NOTCH1, TP53 and PAX6, which may all regulate invasiveness of GBM via suppression of the proteins MMP-2 and CTNNB1 [4]. Additional studies should focus on the role of miR-10b in the invasion and angiogenesis of the other subtypes of GBM, and future mesenchymal glioma therapies should focus on silencing miR-10b.

In addition, miR-10b also targets tumor suppressor gene CSMD1 [5]. CSMD1 maps to chromosome 8p23, a region that is deleted in many tumor types. miR-10b binds to the predicted 3′ UTR region of CSMD1, resulting in a repression of the tumor suppressor gene. CSMD1 works in a complex regulatory framework centered on miR-10b in GBM stem cells and tissues. miR-10b is also known to be upregulated in breast cancer, leukemia, and pancreatic cancer, and promotes tumor invasion and metastasis in breast cancer. Combined with the information gathered on miR-10b in GBM, we can speculate that miR-10b functions as a global oncogene to stimulate tumorigenesis in multiple tumor tissue types [5].

3.4 *miR-106b*

miR-106b is a tumor oncogenic miRNA. Its levels are found to be overexpressed in the majority of gliomas, and its expression is significantly correlated to tumor grade [6]. One study found a 1.74-fold and 2.2-fold increase in miR-106b expression for WHO grade III and IV gliomas, respectively, when compared to low-grade tumors [6]. This was confirmed using three human malignant glioma cell lines: U251, LN229 and TJ905. When these cell lines were transfected with a miR-106b antisense oligonucleotide (ASON), cell proliferation was suppressed and cells were arrested in G0/G1. However, cell cycle arrest was only significant in the U251 and TH905 cell lines. Furthermore, tumor growth in a miR-106b ASON nude mouse xenograft model was significantly impaired; validating the claim that miR-106b is tumor oncogenic [6]. While previous studies have shown miR-106b to target the cyclin-dependent inhibitor p21/CDKN1A, this study proposed the cell

cycle regulator RBL2 as a direct target of miR-106b. It was found that cells are significantly shifted into S phase when RBL2 expression was suppressed. This study added to the growing body of evidence that miR-106b is tumor oncogenic, and proposes a pathway by which miR-106b affects cell cycle regulation.

In another study, the role of miR-106b in pediatric brainstem gliomas was investigated. It was found that the levels of miR-106b were significantly higher in pediatric brainstem gliomas and correlated with malignancy [24]. Brainstem gliomas are common in pediatric patients and the prognosis of these young children remains dismal. The importance of miR-106b in cell cycle regulation and its role in the development of malignancies cannot be overlooked as we continue to explore the potential role of miRNAs in glioma therapy.

3.5 miR-20a

Closely related to miR-106b, miR-20a is also tumor oncogenic and works in a complex pathway to affect tumorigenesis. Recently it was discovered that Quaking (QKI) is directly regulated by p53 and works to activate and stabilize miR-20a [23]. QKI is a tumor suppressor gene that is often deleted in GBM, resulting in an unstable miR-20a. miR-20a regulates TGF-β receptor 2 (TGF-βR2), the TGF-β signaling network and overall cell proliferation and differentiation. When miR-20a is unstable, it contributes to tumorigenesis and results in uncontrolled cell proliferation [23]. This p53-QKI-miR-20a-TGF-β pathway adds to the growing body of evidence that miRNAs can regulate tumorigenesis, and further shows the importance of proper regulation of miRNAs.

miR-20a also seems to play a causative role in malignant tumor progression of pediatric brainstem gliomas similar to miR-106b. Interestingly both these miRNAs are a part of the miR-17 family, which also is the precursor for miR-91 and miR-103. This group of miRNAs plays a crucial role in the development of breast cancer, further demonstrating the universal power of miRNAs in tumorigenesis and the global oncogenic effects of miR-20a and miR-106b [119]. Appropriate regulation of these miRNAs may prevent tumorigenesis, and may serve to be a powerful therapy for patients with gliomas.

3.6 miR-183

miR-183 is also upregulated in the majority of high-grade gliomas as well as U251, U87 and A172 malignant glioma cell lines [47]. This increase is associated with a decrease in isocitrate dehydrogenase (IDH) 2, which has complementary sequences to miR-183 in its 3′ UTR. Isocitrate dehydrogenases (IDHs) are a group of enzymes involved in the conversion of isocitrate to α-ketoglutarate during oxidative decarboxylation and IDH1 and IDH2 are known mutational targets in human cancers.

This is important because tumor cells obtain energy from aerobic glycolysis, with a defect in mitochondrial respiration. Recent studies have demonstrated that IDH1 and IDH2 mutations are frequently present in low-grade and anaplastic gliomas and represent a favorable prognostic biomarker [120]. Tanaka et al. noted that IDH2 is a direct target of miR-183, allowing the investigators to speculate that miR-183 might induce the mitochondrial dysfunction apparent in tumor cells [47]. Furthermore, the authors found that miR-183 upregulation resulted in an increased expression of HIF-1α and two downstream targets of HIF-1α, vascular epithelial growth factor (VEGF) and glucose transporter 1 (GLUT1). Both these targets were also upregulated as a result of miR-183. HIF-1α plays a role in angiogenesis, metabolism and survival in tumor cells, and the overexpression of its targets may affect tumorigenesis. This study identified a plausible mechanism by which miR-183 affects the way tumor cells get energy, and sheds light on another possible way to interfere with tumorigenesis of gliomas.

4 Tumor Suppressor miRNAs

4.1 miR-34a

miR-34a was originally identified as a likely tumor suppressor miRNA and a downstream transcriptional target of p53 [121, 122]. Prior reports have shown that miR-34a is downregulated in GBM compared to normal brain tissue, and that it inhibits cell proliferation, survival and invasion in adherent glioma cell lines [63, 123]. It works by targeting c-Met, Notch-1, Notch-2, and CDK6. The c-Met pathway is frequently expressed in gliomas and medulloblastomas, and overexpression of the c-Met pathway in tandem with the HGF pathway significantly correlates with poor prognosis. Notch signaling is a conserved pathway that controls differentiation, proliferation, EMT and migration, and consists of four members (Notch-1–4). The Notch pathway plays a critical role in glioma cell survival and cell proliferation [123]. CDK6 is a cell cycle regulator involved in cell proliferation, differentiation and transformation of many cancers including gliomas. It accelerates the transition of cells from the G0/G1 to S phase of the cell cycle. Its levels are often elevated when compared to normal brain tissue, and elevated levels again significantly correlate to poor prognosis. These downstream targets demonstrate the multiple pathways by which miR-34a can affect tumorigenesis, and the potential of miR-34a in glioma therapy.

A recent study found that the pathogenesis of proneural GBM is strongly linked to dysregulated PDGF signaling, another direct downstream target of miR-34a [63]. This study confirmed that miR-34a is downregulated by oncogenic PDGF signaling via PDGF receptors (PDGFRs), and that miR-34a inhibits growth in proneural GBM cells both *in vitro* and *in vivo*. Additionally, expression of miR-34a was negatively correlated with histologic grade [63]. While miR-34a

was originally discovered to be a downstream transcriptional target of p53, this study demonstrated that the regulation of miR-34a expression by PDGF signaling likely works independently of the p53 pathway. Again, this shows the multiple and complex pathways by which miR-34a functions as a tumor suppressor in glioma development. The advantage of a broad range of miRNA targets provides support for further research on miR-34a RNAs as therapy for high-grade gliomas.

4.2 miR-25 and miR-32

Overexpression of miR-25 and miR-32 result in p53 accumulation by directly targeting Mdm2 and TSC1, respectively, which are negative regulators of p53 and mammalian target of rapamycin (mTOR) [61]. This leads to inhibited cell proliferation through cell cycle arrest and inhibited growth of GBM in mouse brain *in vivo*. It was also found that miR-25 and miR-32 repress p53 through two feedback regulatory transcriptional factors E2F1 and MYC, respectively. In addition, it was found that p53 accumulates when Mdm2 is silenced resulting in GBM growth arrest. Mdm2 regulates p53 by negatively affecting ubiquitination degradation, and its levels are inversely correlated to GBM tissue in patients. It is well accepted that an active mTOR pathway can suppress PI3K-Akt signaling, which in turn affects the p53 activity via Akt-mediated phosphorylation of Mdm2 [124]. This crosstalk is important in growth and development, and consequently plays an integral role in tumorigenesis. miR-32 was also found to directly target TCS1, causing elevated TSC1 levels and p53 activation along with an increase in mTOR activity [61]. This was confirmed using MYC and E2F1 knockdown models, adding compelling evidence to the claim that miR-32 can stabilize p53 through activation of mTOR by targeting TSC1. Both miR-25 and miR-32 affect the very important p53 pathway whose deregulation plays one of biggest roles in tumorigenesis of all cancers, including gliomas.

4.3 miR-107

miR-107 is another tumor suppressor miRNA that has been shown to be downregulated in glioma tissues as well as U87, U251 and A172 glioma cell lines [66]. Conversely, overexpression of miR-107 lead to inhibited migration and invasive ability of glioma cells [66]. miR-107 works by directly targeting the 3′ UTR sequence of Notch-2, which is known to transactivate Tenascin-C, MMP-12 and COX-2. Tenascin-C, a large extracellular matrix of glycoprotein that acts as a tumor-specific antigen, is often upregulated in gliomas and Tenascin-C invasion is mediated by MMP-12. Knockdown of Notch-2 suppresses glioma cell invasion in U87 and A172 glioma cell lines, suggesting that Notch-2 is involved in glioma

invasion and that miR-107 exerts its anti-invasive tumor suppressive activity through Notch-2 signaling pathways.

Another study suggested that miR-107 targets CDK6 to induce cell cycle G1 arrest and inhibit invasion, in addition to targeting Notch-2 [67]. This study indicated that miR-107 is a transcriptional target of p53, and that miR-107 is downregulated particularly in p53-mutant U87 and A172 glioma cell lines. Moreover, the transfection of wild-type p53 into glioma cells stimulated miR-107 expression, and miR-107 expression inhibited cell proliferation and arrested cells in G0/G1 by targeting CDK6 and Notch-2. CDK6 is a cell cycle regulator involved in cell proliferation, differentiation and transformation of many cancers including gliomas, acting as an oncogene [125]. Proper regulation of CDK6 and Notch-2 is essential in controlling gliomas, showing the potential of miR-107 in glioma therapy.

4.4 miR-124

miR-124 is involved in the differentiation of brain tumor stem cells, making it an ideal target for therapy [5, 126]. The levels of miR-124 increase during differentiation of mouse embryonic stem cells. One study found that its levels are considerably decreased in glioma cell lines compared to normal neural stem cells, possibly by epigenetic modification such as promoter sequence hypermethylation [126]. miR-124 also induces differentiation in adult mouse neural stem cells, mouse oligodendroglioma-derived stem cells as well as in human GBM-derived U87 stem cells. Moreover, it can inhibit proliferation and induce G0/G1 cell cycle arrest in GBM-derived stem cells. This study also concluded that CDK6 is a downstream target of miR-124, and that its expression is inhibited by miR-124 in U251 cells [126]. This is another example of how miRNAs work in complex pathways, and how pathways can be targeted by different miRNAs. The ability to detect and regulate glioma stem cells will serve as early biomarkers for the disease providing better patient outcomes, and the role of miR-124 in early tumorigenesis cannot be overlooked.

Another study revealed two downstream targets of miR-124: NRAS and PIM3 [5]. NRAS is a small guanine-nucleotide binding protein and is one of the three RAS isoforms that play a crucial role in cell proliferation, differentiation and survival. The 3′ UTR region of NRAS is targeted by miR-124, and its levels are significantly increased in GBM stem cells. PIM3 is a proto-oncogene with serine/threonine kinase activity known to promote tumor cell growth through modulating cell cycle regulators. miR-124 represses PIM3 expression through directly targeting its 3′ UTR region. This shows the dual tumor suppressive activity of miR-124 and adds to the multiple pathways by which miR-124 works.

Adding to the body of evidence on miR-124, another study found for the first time that cell differentiation agent-2 (CDA-2) induces cell differentiation through suppressing Twist and SLUG in glioma cells [69]. miR-124 was found to be

upregulated by CDA-2. CDA-2, extracted from human urine, has shown promise in improving chemotherapy responses in many tumors including gliomas and has high anti-cancer properties. It was shown to suppress proliferation in U251 and SWO-38 glioma cells *in vitro*, and also promotes proper differentiation into mature astrocytes. Twist and SLUG are transcriptional repressors that are involved in both embryonic development and cancer metastasis. These repressors recruit histone deacetylases to condense chromatin and repress expression. It was found that inhibition of miR-124 upregulated levels of SLUG and Twist proteins in U251 glioma cells, and partially eliminated the function of CDA-2 on mesenchymal markers. This provides concrete evidence that miR-124 and CDA-2 regulation are correlated, which will prove to be valuable as we continue to discover better treatment options for glioma patients.

4.5 miR-218

miR-218 is also often downregulated in gliomas [100, 101]. One study found that overexpression of miR-218 induces glioma cell apoptosis and inhibits glioma cell viability, proliferation and tumorigenicity [100]. This study identified epidermal growth factor receptor-coamplified and overexpressed protein (ECOP) as a downstream target of miR-218, which can regulate the transcriptional activity of NF-κB and its associated apoptotic response. This study suggested that miR-218 sensitizes glioma cells to apoptosis by regulating ECOP suppression of NF-κB. Another study found lymphoid enhancer binding factor 1 (LEF1) and MMP-9 as downstream targets of miR-218 [101]. LEF1 is an oncogenic transcription factor involved in the Wnt signaling pathway, and affects cell proliferation and migration. This study showed that miR-218 directly targets LEF1, resulting in a reduced synthesis of MMP-9. Again, the multiple downstream targets of miR-218 demonstrate the high variability of miRNAs in glioma therapy, and further validate future research on multi-targeting miRNAs.

5 Conclusions

The role of miRNAs in gliomas is still vastly unclear, but research perseveres to discover the complex regulatory mechanisms by which miRNAs affect glioma tumorigenesis. The multiple pathways by which miRNAs work render them ideal therapeutic targets. Possible treatments for gliomas include overexpression of tumor suppressive miRNAs (e.g. miR-34a, -25, -32, -107, -124 and -218), as well as inhibition of tumor oncogenic miRNAs (e.g. miR-21, -182, -10b, -106b, -20a and -183). It is interesting to note that some miRNAs, such as miR-23b, miR-27a, miR-125b, miR-128, miR-143, miR-145 and miR-196b have reported oncogenic as well as tumor suppressor functions (Tables 1.1 and 1.2). This suggests a

context-dependent complex functionality of miRNAs which requires further elaborate studies. The importance of identifying all of the downstream targets to these miRNAs and further elucidating the complex mechanisms in these regulatory networks may be the key to developing novel drug therapies to be used in combination with radiation and chemotherapy. In addition to helping to regulate tumor initiation, invasion, growth, proliferation, metastasis and apoptosis, many miRNAs may function as early biomarkers for developing gliomas. The role of some miRNAs, such as miR-21, miR-124, miR-10b and miR-106b, in brain stem cell development make these miRNAs suitable targets for therapy. This will provide glioma patients with earlier diagnosis, in hopes of achieving improved prognosis and reduced incidence of tumor recurrence. Moreover, identifying global oncogenic miRNAs and global tumor suppressive miRNAs will offer targeted therapies for many different tumor types in addition to malignant gliomas. Future studies will further validate the profound effect that miRNAs have on glioma tumor development and, thus, prevention. Researchers continue to focus on miRNAs in gliomas, as well as in other cancers, since miRNAs play a multifaceted role in cancer stem cell development, early diagnosis, therapeutic treatment, and ultimately aiming to improve the prognosis of patients.

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