6 Noncoding RNAs in Glioblastoma

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Abstract: The vast majority of the human genome is transcribed into noncoding RNAs. Among these, microRNAs (miRNA) and long noncoding RNAs (lncRNA) are frequently deregulated in cancer, where they regulate a wide variety of functions. Glioblastoma (GBM) is the most common and the most deadly primary human brain tumor. This chapter reviews the deregulation, functions, mechanisms of action, and clinical applications of miRNAs and lncRNAs in GBM. miRNAs are short noncoding RNAs that broadly and profoundly regulate gene expression. Numerous miRNAs are deregulated in GBM, where their expression levels can serve as diagnostic and prognostic biomarkers. miRNAs can act as oncogenes or tumor suppressors in GBM by regulating the expression of numerous tumor-suppressive or oncogenic proteins. miRNAs regulate all GBM malignancy parameters including tumor cell proliferation, cell survival, invasion, angiogenesis, cancer stem cells, immune escape, and therapy resistance. miRNAs are also secreted in body fluids, where they can be used as biomarkers. Because of

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their deep involvement in GBM malignancy, efforts are under way to also exploit miRNAs as therapeutic agents or targets. lncRNAs are a diverse group of noncoding RNAs that are >200 nucleotides long. Several lncRNAs are deregulated in GBM, where their expressions can associate with clinical parameters. lncRNAs regulate GBM functions including tumor cell proliferation, survival, invasion, cancer stem cell differentiation, and therapy resistance. lncRNAs exert their actions via transcriptional, post-transcriptional, and epigenetic mechanisms that are only partly understood. Studying noncoding RNAs is important for the understanding, management, and development of future therapies for GBM.

Key words: Cancer stem cells; Glioblastoma; Glioma; Long noncoding RNA; microRNA

Introduction

The vast majority (>80%) of the human genome is transcribed into RNA. However, only ~2% of RNA is translated into proteins. Consequently, the vast majority of cellular RNAs are noncoding RNAs (ncRNAs). NcRNAs function as crucial regulators of biological, physiological, and pathological processes and are not evolutionary junk as previously thought. In the last decade, the small ncRNAs (microRNAs; 17–22 nucleotides) and long ncRNAs (lncRNAs; >200 nucleotides) have been extensively studied in cancer and have furthered our understanding and knowledge of cancer initiation and progression, and offered new therapeutic avenues. A large number of studies have shown that microRNAs and lncRNAs play important roles in almost every aspect of cancer, including tumor initiation, progression, and resistance to therapy, as well as providing biomarkers for diagnosis and prognosis and serving as therapeutic agents or targets. This chapter reviews the roles of microRNAs and LncRNAs in glioblastoma (GBM).

Glioblastoma

Gliomas are the most common and most malignant primary human brain tumors. They are extremely aggressive tumors that account for the majority of deaths due to primary brain neoplasms (1). Despite the most advanced treatment with combinations of surgery, radiotherapy, and chemotherapy, the most commonly diagnosed grade IV GBM is associated with an average life expectancy of only 14 months. The origin of gliomas is largely unknown, but there is increasing speculation that they might arise from glioma stem cells (GSCs), which might consist of transformed normal neural stem cells (NSCs). GBM malignancy is driven by the deregulation of molecules and pathways that control tumor cell proliferation, survival, invasion, and stem cell differentiation (2). The Cancer Genome Atlas (TCGA) classified these molecular deregulations as belonging to three major pathways: Receptor tyrosine kinase (RTK), p53, and Rb pathways (3). Factors responsible for GBM malignancy and poor prognosis include rapid cell proliferation, resistance to apoptosis, invasion of the surrounding brain, high levels of angiogenesis, immune evasion, and the existence of therapy-resistant GSCs.

MicroRNAs

MicroRNAs (miRNAs) are short, noncoding, endogenous RNAs (17–22 nucleotides) that post-transcriptionally regulate gene expression. More than 3,000 human miRNAs have been identified to date (4, 5). Around two-thirds of miRNA coding genes are located in introns (6, 7). One-third of miRNAs are transcribed as independent single transcriptional units or in clusters (6–8). MiRNA genes are transcribed by RNA polymerase II as pri-miRNA and then processed into pre-miRNA by the RNase III enzyme Drosha and its interacting partner DGCR8 or Pasha. The pre-miRNA is exported to the cytoplasm by exportin-5 and converted into a mature duplex by the Dicer complex (9–11). Mature miRNAs regulate their targets by incorporating into the RNA-induced silencing complex (RISC) and directing it to the targeted mRNA 3′ untranslated region (3′UTR) (12). MiRNAs directly cleave the mRNA or inhibit protein synthesis, according to the degree of complementarities with their targets' 3′ untranslated regions (3′ UTR) (Figure 1). Notably, single miRNAs can regulate the expressions of numerous genes and most genes are regulated by multiple miRNAs. Computational predictions of miRNA targets suggest that more than 60% of human protein expressions are regulated by miRNAs (13). miRNAs are frequently deregulated in human cancers via genetic, epigenetic, transcriptional, and processing mechanisms (14–19). Deregulation of miRNA expression has been associated with cancer initiation, progression, and metastasis (20, 21). By targeting the mRNAs of oncogenes or tumor suppressors, miRNAs can act as tumor suppressors or oncogenes, respectively. miRNAs regulate all aspects of cancer biology including cell cycle, proliferation, death, apoptosis, migration, invasion, metastasis, angiogenesis, tumor microenvironment, tumor immunology, and cancer stem cell biology (5) (Figure 2). Thus, correcting miRNA deficiencies by either antagonizing or restoring miRNA function may provide a therapeutic benefit.

miRNA DEREGULATION AND ASSOCIATION WITH CLINICAL PARAMETERS IN GBM

Several studies have shown that miRNA expression is deregulated in GBM. Recent reviews (22, 23) summarized the differentially expressed miRNAs in GBM and showed that 256 miRNAs were significantly overexpressed and 95 miRNAs were significantly downregulated in GBM as compared to the normal brain tissue. There follows a brief survey of select deregulated miRNAs in GBM.

MiR-21 was the first miRNA to be linked with glioma malignancy. Most reports describe miR-21 as an oncogenic miRNA. MiR-21 levels are elevated in human glioma cells and tissues as compared to normal glial cells and/or brain (24–26). In addition, miR-21 levels in gliomas correlate with tumor grade, and low miR-21 levels in human tumors are associated with slightly better survival according to the TCGA database (27, 28).

Several reports have implicated miR-221/222 in glioma malignancy. A screening study identified miR-221 as one of the most frequently upregulated miRNAs in human glioma tumors and cell lines (29). MiR-221 upregulation was confirmed in a subsequent study which also found that miR-221 levels are further increased

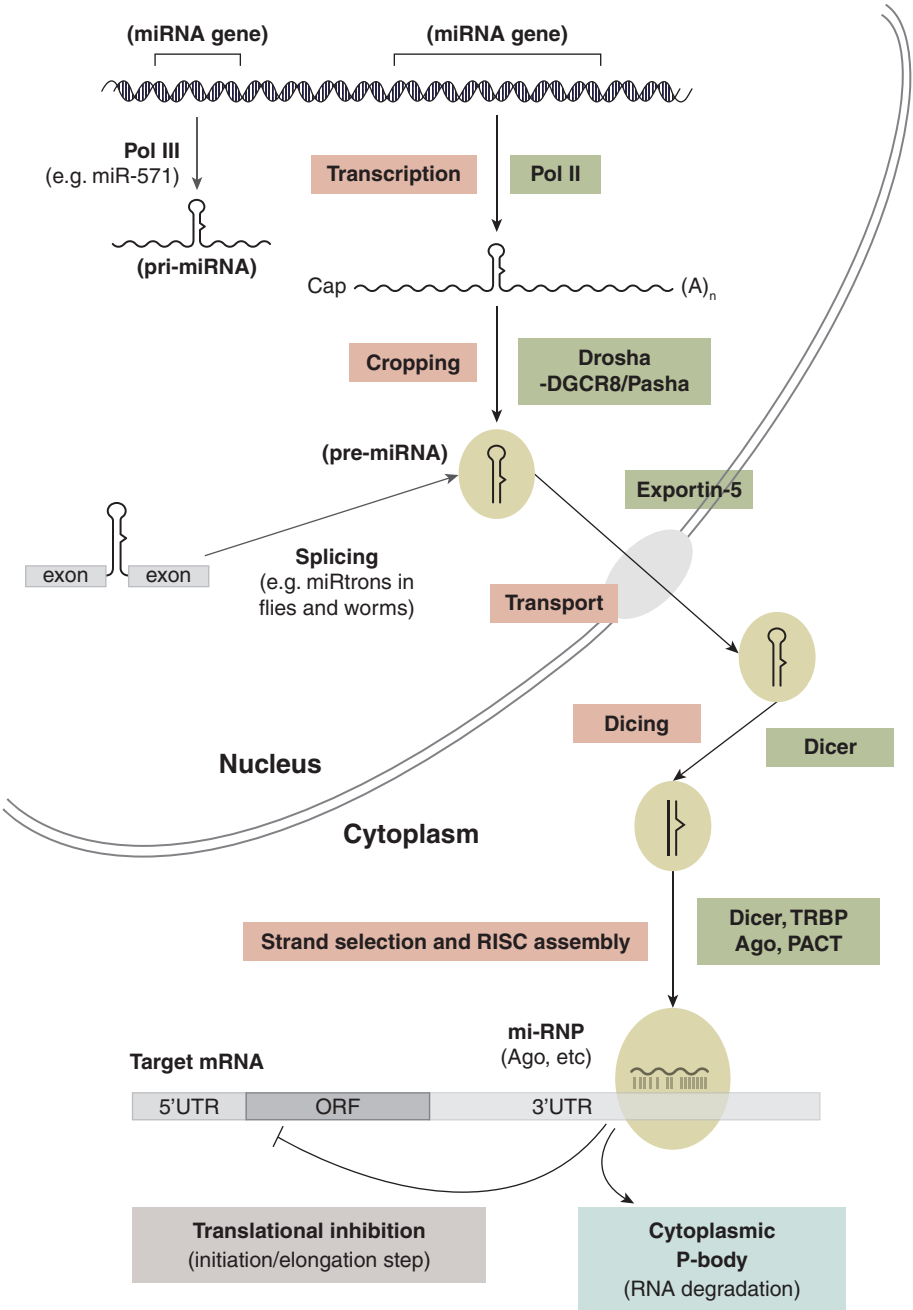

Figure 1 **miRNA biogenesis and functions.** Black lines indicate the canonical pathway, with minor pathways depicted in gray lines. Modified with permission from Lee and Dutta (5).

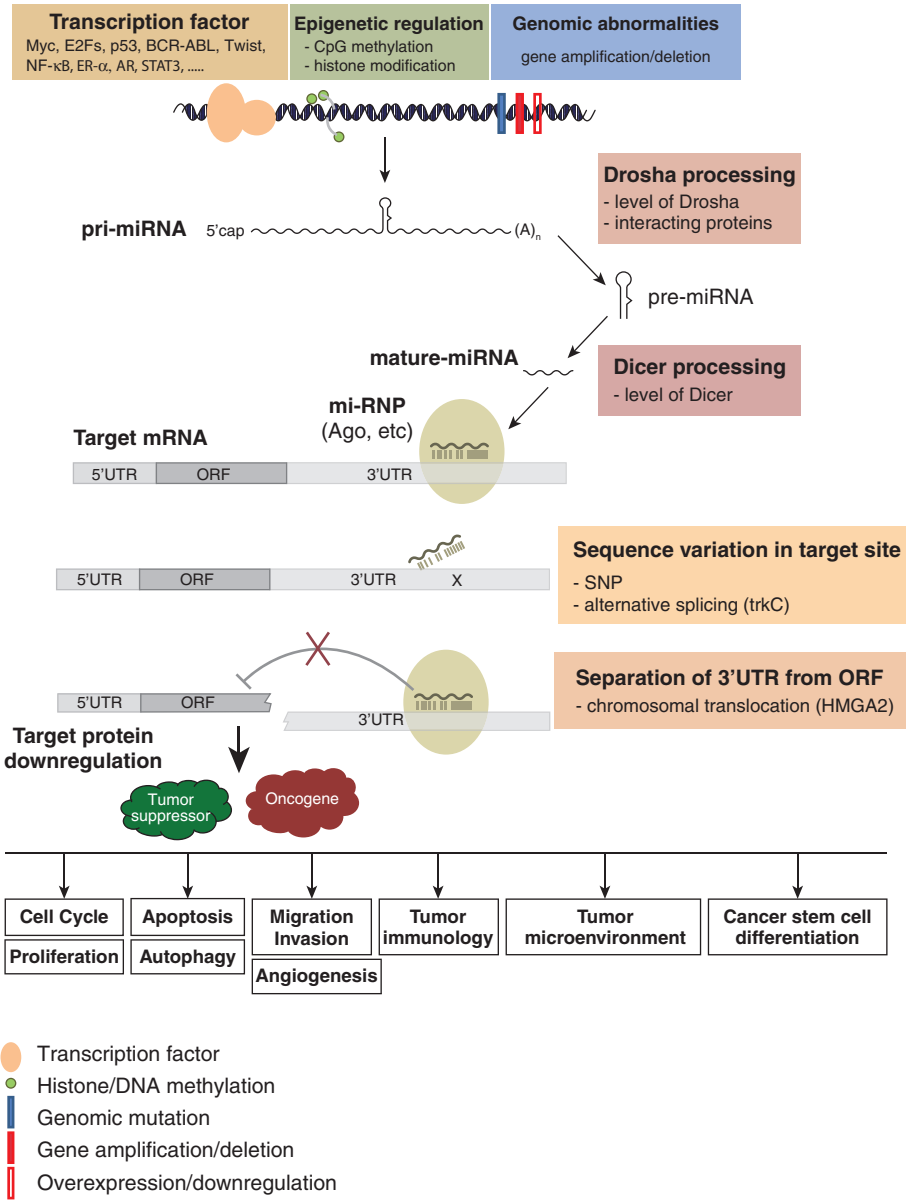

Figure 2 Mechanisms of miRNA deregulation in cancer. Modified with permission from Lee and Dutta (5).

in higher grade tumors (30). TCGA data show that miR-221/222 downregulation in human tumors is associated with a better patient prognosis.

MiR-181a, miR-181b, and miR-181c were reported to be downregulated in GBM cells and tumors (29). miR-181a and, to a greater extent, miR-181b were subsequently described as tumor suppressors (31). Moreover, miR-181b and miR-181c were significantly downregulated in patients who responded to radiation therapy and temozolomide (TMZ) in comparison to patients with progressive disease. It was therefore proposed that expression levels of miR-181b and miR-181c could serve as a predictive marker of response to therapy in GBM patients (32).

Two high-profile publications identified miR-26a as a regulator of the tumor suppressor PTEN in gliomas (33, 34). The first publication showed that miR-26a gene is frequently amplified in human gliomas and that this is associated with monoallelic PTEN loss. The second publication used a multidimensional genomic data set of GBM from TCGA to identify miR-26a as a cooperating component of a frequently occurring amplicon that also contains CDK4 and CENTG1, two oncogenes that regulate the RB1 and PI3K/AKT pathways, respectively.

Analysis of human specimens showed that miR-34a expression is downregulated in GBM tissues compared to normal brain and in mutant p53 gliomas as compared with wild-type p53 gliomas. MiR-34a was also downregulated in GBM cell lines compared to astrocytes. MiR-34a levels in human gliomas were inversely correlated to RTK MET, measured in the same tumors (35).

MiR-148a expression was elevated in human GBM specimens, cell lines, and GSC compared with normal human brain and astrocytes. High expression of miR-148a significantly correlated with survival in TCGA samples. Therefore, miR-148a can serve as a prognostic oncogenic miRNA in GBM (36).

MiR-10b expression was upregulated in glioma samples as compared to non-neoplastic brain tissues, and expression levels were associated with higher grade tumors. Several lines of evidence suggest that miR-10b plays a role in glioma invasion (37, 38).

A recent study identified miR-182 as a prognostic marker for glioma progression and patient survival (39). miR-182 was upregulated in glioma cell lines and primary glioma specimens as compared to normal brain. miR-182 expression levels in the tumors significantly correlated with tumor grade and clinical features. The 5-year survival rates of patients with low miR-182 levels were significantly better than the survival rates of patients with high miR-182 levels. Additional miRNAs that are differentially expressed in GBM are listed in Table 1.

SECRETED miRNAS AS GBM BIOMARKERS

GBM cells shed microvesicles with cytoplasmic contents including substantial quantities of miRNAs that are stably preserved to allow quantitation in patient serum and cerebrospinal fluid. The quantification of miRNAs in fluid samples would permit noninvasive determination of GBM features based on miRNA signatures (40, 41). Interestingly, microvesicle shedding by GBM cells enables them to "share" miRNAs with surrounding cells, modifying nearby stromal cells, and essentially terraforming their environment (42). There are many examples of miRNAs released from tumor cells that indicate the importance

TABLE 1 **Deregulated miRNAs with Their Correlations with Survival, Targets, and Functions in Glioblastoma**

miRNA	Expression in GBM (glioma)	Survival correlation	Targets	Function	
				Overexpression	Anti-miR
Let-7	Down		KRAS	Migration↓, Proliferation↓, *In vivo* tumor growth↓	
Hsa-miR-7	Down		FAK, EGFR, AKT *PI3K*, *RAF1*	Viability↓, Migration↓, Invasiveness↓, Proliferation↓, *In vivo* tumor growth↓, Radiosensitivity↓, GSC proliferation and invasion↓	
Hsa-miR-9	Up (Up in high-grade tumor)		CAMTA1		
Hsa-miR-10ab	Up (Up in TMZ-resistant tumor)	Y	HOXD10		
Hsa-miR-15a	Up (Up in high-grade tumor)				
Hsa-miR-15b	(Down in high-grade tumor)		CCNE1	Proliferation↑	Proliferation↓
Hsa-miR-16	Up (Up in high-grade tumor)				
Hsa-miR-17-92 cluster	Up (Disputed in high-grade tumor, CD133+ cells)		POLD2, TGFβ-RII, CTGF, CAMTA1, *ATG7*	Angiogenesis↑, Growth↑, GSC apoptosis↑, proliferation↓	Viability↓, Apoptosis↑, Proliferation↓
Hsa-miR-18a	Up (Up in low-grade tumor)		Smad4, CTGF	Angiogenesis↑, Growth↑	Viability↓, Apoptosis↑, Proliferation↓

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TABLE 1 **Deregulated miRNAs with Their Correlations with Survival, Targets, and Functions in Glioblastoma** (Continued)

miRNA	Expression in GBM (glioma)	Survival correlation	Targets	Function	
				Overexpression	Anti-miR
Hsa-miR-19a	Disputed (Up in high-grade tumor)		CTGF		Viability↓, Apoptosis↑, Proliferation↓
Hsa-miR-20a	Up (Up in high-grade tumor)		TGFβ-RII, CTGF	Angiogenesis↑, Growth↑	Viability↓, Proliferation↓
Hsa-miR-21	Up (Up in high-grade tumor)	Y	RECK, TIMP3, APAF1, NP32A, SMARCA4, Spry2, Caspases, PTEN, Cdc25A, HNRPK, TAp63, RRFIP1, PDCD4, p53	Invasiveness↑	Invasiveness↓, Apoptosis↑, Viability↓, Proliferation↓, *In vivo* tumor volume↓, Chemosensitivity↑, Radiosensitizes↑
Hsa-miR-23a	(Down in high-grade tumor)				
Hsa-miR-25	Up (Up in high-grade tumor)		Mdm2, TSC1	*In vivo* tumor growth ↓	
Hsa-miR-26a	Up	Y	PTEN, RB1 and MAP3K2/ MEKK2	*In vivo* tumor growth ↑	
Hsa-miR-28	Up (Up in high-grade tumor)				
Hsa-miR-30bc	Disputed		KRAS		
Hsa-miR-34a	Down (Down in GSCs, Down in proneural subtype)		SIRT1, MET,NOTCH1/2, Msi1, PDGFRA,	Viability↓, Proliferation↓ Apoptosis↑, Invasiveness↓, *In vivo* tumor growth ↓, Differentiation↑, GSC stem ness↓	

TABLE 1 **Deregulated miRNAs with Their Correlations with Survival, Targets, and Functions in Glioblastoma** (Continued)

miRNA	Expression in GBM (glioma)	Survival correlation	Targets	Function	
				Overexpression	Anti-miR
Hsa-miR-93	Up		Integrin-β8	Angiogenesis↑, Proliferation↑, *In vivo* tumor growth ↑	
Hsa-miR-96	Up		KRAS		
Hsa-miR-100	Down		ATM	Radiosensitivity↑	
Hsa-miR-124/137	Down	Y	PTBP1, STAT3	Proliferation↓, Migration↓, Invasiveness↓, Stemness↓, GSC differentiation↑	
Hsa-miR-125b	Down		Bmf, MAZ	Invasiveness↑, Apoptosis↓, Proliferation↑	
Hsa-miR-128	Down		WEE1, p70S6K1, Msi1, E2F3a, Bmi-1, EGFR, PDGFRα	Angiogenesis↓, Proliferation↓, *In vivo* tumor growth ↓, inhibition of GSC stemness and self-renewal↓	
Hsa-miR-130b	Up (Up in high-grade tumor)				
Hsa-miR-133a	(Down in high-grade tumor)				
Hsa-miR-134	Up		KRAS and STAT5B		

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TABLE 1 **Deregulated miRNAs with Their Correlations with Survival, Targets, and Functions in Glioblastoma** (Continued)

miRNA	Expression in GBM (glioma)	Survival correlation	Targets	Function	
				Overexpression	Anti-miR
Hsa-miR-135b	Up (Up in GSCs)				
Hsa-miR-137	Down (Down in late-stage tumor)		CDK6, Msi1, Cox-2	Proliferation↓, Invasiveness↓, Migration↓, *In vivo* tumor growth↓	
Hsa-miR-140	Up (Up in high-grade tumor)				
Hsa-miR-141	Disputed (UP in GSCs)				
Hsa-miR-146b-5p	Down		EGFR, MMP16	Invasiveness↓, Migration↓, Proliferation↓, *In vivo* tumor growth ↓	
Hsa-miR-148a	Up	Y		Proliferation↑, Apoptosis↓, Angiogenesis↑, *In vivo* tumor growth ↑	Proliferation↓, Apoptosis↑
Hsa-miR-150	Down in high-grade tumor				
Hsa-miR-153	Down		Bcl-2, Mcl-1, Irs-2	Proliferation↓, Viability↓, Apoptosis↑	
Hsa-miR-181abc	Down		Bcl-2	Proliferation↓, Apoptosis↑, Invasiveness↓, Chemosensitivity and Radiosensitivity↑	

TABLE 1 **Deregulated miRNAs with Their Correlations with Survival, Targets, and Functions in Glioblastoma** (Continued)

miRNA	Expression in GBM (glioma)	Survival correlation	Targets	Function	
				Overexpression	Anti-miR
Hsa-miR-182/183	Up (Up at late-stage tumor)	Y			
Hsa-miR-184	Down (Down in high-grade tumor)		Akt2	Apoptosis↑, Invasiveness↓	
Hsa-miR-193	Up		KRAS		
Hsa-miR-195	(Up in TMZ resistant)		CCND3, E2F3, CCND1	Proliferation↓, Invasiveness↓	Chemosensitivity, Viability↓
Hsa-miR-196ab	Up	Y			
Hsa-miR-197	(Down in high-grade tumor)				
Hsa-miR-200c	Up (High in GSCs)				
Hsa-miR-205	Disputed (High in GSCs)		VEGF-A	Proliferation↓, Apoptosis↑, Invasiveness↓	
Hsa-miR-210	Up (Up in high-grade tumor)	Y	HIF3α	Enhanced vasculogenesis	Reduced vascular density and tumor growth *in vivo*
Hsa-miR-218	Down (Down in mesenchymal subtype)		IKK-β, HIF2α	Invasiveness↓	
Hsa-miR-221/222	Up (Up in high-grade tumor, CD133+ cells)	Y	P27, Akt, PUMA, P57, PTPμ BIRC1, NIAP, ICAM-1	Proliferation↑, Invasiveness↑, *In vivo* tumor growth ↑, Apoptosis↓, Migration↑	Proliferation↓, Apoptosis↑, *In vivo* tumor volume↓ STAT1/2 upregulation

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TABLE 1 **Deregulated miRNAs with Their Correlations with Survival, Targets, and Functions in Glioblastoma** (Continued)

miRNA	Expression in GBM (glioma)	Survival correlation	Targets	*Function*	
				Overexpression	**Anti-miR**
Hsa-miR-296	Up				Reduced angiogenesis
Hsa-miR-297	Down				
Hsa-miR-301a	Up (Up in GSCs)				
Hsa-miR-326	Down		NOTCH 1/2, PKM2	Proliferation↓, Apoptosis↑, Viability↓, Invasiveness↓, *In vivo* tumor growth↓, GSC stemness↓	
Hsa-miR-328	(Up in invading cells)	Y	SFRP1,ABCG2	Invasiveness↑	Invasiveness↓
Hsa-miR-335	Up		Daam1	Viability↑, Invasiveness↑	Apoptosis↑, Invasiveness↓, *In vivo* tumor growth↓
Hsa-miR-339-5p	Down (Down in GSCs)		ICAM-1		
Hsa-miR-363	Up (Up in GSCs)		Bim, Caspase3	Proliferation↑, Apoptosis↓	Proliferation↓, Apoptosis↑
Hsa-miR-365a	(Down in GSCs)		KRAS, MAX	Proliferation↓, Invasiveness↓, Cell cycle↓	Proliferation↑, Migration↑
Hsa-miR-367-302	Up, (Up in GSCs)				
Hsa-miR-371-373	Up, (Up in GSCs)				

TABLE 1 **Deregulated miRNAs with Their Correlations with Survival, Targets, and Functions in Glioblastoma** (Continued)

miRNA	Expression in GBM (glioma)	Survival correlation	Targets	Function	
				Overexpression	Anti-miR
Hsa-miR-451	Disputed, (Up in GSCs)	High with poor survival Y	CAB39	Proliferation↓, Invasion↓, Stemness↓, Neurosphere formation↓, Sensitized cells to glucose deprivation	Migration↑
Hsa-miR-455	(Up in TMZ resistant)				
Hsa-miR-497	(Down in high-grade tumor)				
Hsa-miR-548b	(Down in high-grade tumor)				
Hsa-miR-582-5p	Up (Up in GSCs)		Caspase 3/9	Proliferation↑, Apoptosis↓	Proliferation↓, Apoptosis↑

of their roles in the modulation of the microenvironment in GBM (Table 2). MiR-21 is upregulated (43), while miR-205 is downregulated in patient plasma (44, 45). Many more miRNAs have been described as highly expressed in peripheral blood as compared to normal samples (46). MiR-454-3p was highly expressed in the plasma of GBM patients as compared to healthy controls and was lower in low-grade glioma. Furthermore, miR-454-3p expression in the postoperative plasma is markedly downregulated in comparison to preoperative plasma, and a correlation of worsening prognosis of glioma was observed with increasing miR-454-3p expression (47). MiR-29 levels in serum can serve to distinguish the progression of malignancy from stage I–II to stage III–IV (48). In addition, a huge increase in miR-210 expression was found in serum samples of GBM patients compared to controls and this was associated with tumor grade and poor outcome (48). A study of serum miRNA profiles found a significant difference of miRNA levels between untreated high-grade astrocytomas (grade III–IV) and controls in a genome-wide miRNA analysis. Seven miRNAs (miR-15b*, miR-23a, miR-133a, miR-150*, miR-197, miR-497, and miR-548b-5p) were markedly decreased in grade II–IV patients and showed high specificity (97.87%) and sensitivity (88.00%) for the prediction of malignant astrocytomas (48, 49).

miRNAS IN GSCS

GSCs are major contributors to therapy resistance in gliomas. It was shown that CD133+ tumor cells, presumably GSCs, represent the cellular population that confers glioma radioresistance and could be the source of tumor recurrence after radiation (50). It was hypothesized that GSCs originate from transformed NSCs. This hypothesis was recently supported by a study that found that gliomas display a miRNA expression profile reminiscent of neural precursor cells (51). Discussed below are select critical miRNAs that have been implicated in the regulation of GSCs (summarized in Figure 3 and Table 1). A study assessed the effects of miR-124 and miR-137 on the differentiation of mouse NSCs, mouse oligodendroglioma-derived stem cells, and human GSCs (26). Transfection of miR-124 or miR-137 induced morphological changes and marker expressions consistent with neuronal differentiation in mouse NSCs, mouse oligodendroglioma-derived stem cells derived from S100β-v-erbB tumors, and CD133+ human GBM-derived stem cells. This study therefore implicated miR-124 and miR-137 in the differentiation of NSCs and GSCs. A subsequent report examined the miRNA profiles of GSC and nonstem cell populations and found that several miRNAs including miR-451, miR-486, and miR-425 were upregulated in the GSCs (53). The expression of miR-451 is regulated by SMADs, which have been previously associated with GSC regulation, through binding to promoter region of miR-451 gene (54). Two studies uncovered critical roles of miRNA-34a in GSCs (35, 55). It was first shown that miR-34a is downregulated in human GBM and exerts potent tumor-suppressive effects in glioma cells and stem cells via direct inhibition of MET, NOTCH1, and NOTCH2 expressions. NOTCH is a critical regulator of normal and cancer stem cell maintenance (56–58). NOTCH pathway activation enhances the stemness, proliferation, and radioresistance of GSCs (57–60). These studies therefore implicated miR-34a in the regulation of GSCs partly via regulation of

TABLE 2 **Deregulated lncRNAs with Their Correlations with Survival, Targets/Mecahnisms of Action and Functions in Glioblastoma**

lncRNA	Expression in GBM (glioma)	Survival corelation	Targets/Mechanisms of action	Function	
				Overexpression	Under-expression
linc-RoR	Down		KLF4	Prolifereation↓, Sphere formation↓	Proliferation↑, Sphere formation↑,
ADAMTS9-AS2	Down	Y		Migration↓	Migration↑
CRNDE	Up	Y	polycomb repressive complex 2 and CoREST complexes, MiR-384, miR-186	Cell growth↑, Invasion↑, Apoptosis↓	
H19	(Up in high grade)			Invasion↑	
HOTAIR	Up	Y	EZH2, miR-148b-3p		Cell cycle↓, *in vivo* tumor growth↓
Xist				X-chromosome inactivation↓	
HOTAIRM1	Up				
MEG3	Down		p53	Proliferation↓, Apoptosis↑	
MALAT1	(Up at hypoxic conditions)		AIM1, LAYN, HMMR, SLC26A2, CCT4, ROD1, CTHRC1, and FHL1	Migragion↓	
MIR210HG	(Up at hypoxic conditions)			Invasion at hypoxia↑	Angiogenesis↓
GAS5			GR, GREs		Sensitivity GBM cells to erlotinib treatment↑
PNKY			PTBP1	Normal neuronal differentiation	

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TABLE 2 **Deregulated lncRNAs with Their Correlations with Survival, Targets/Mecahnisms of Action and Functions in Glioblastoma** (Continued)

lncRNA	Expression in GBM (glioma)	Survival corelation	Targets/Mechanisms of action	Function	
				Overexpression	Under-expression
NEAT1	Up		miR-449b-5p		Proliferation↓, Invasion↓, Migration↓
ASLNC22381	Up				GBM recurrence↑
ASLNC2081	Up				GBM recurrence↑
LOC000937	Up				
LINC00152	Up				
LOC04745	Up				
TUNAR	Down			Normal neuronal differentiation	
RP11-713C5.1	Down				
RP11-123M6.2	Down				
LINC00599	Down				
LOC27853	(Up in low grade tumor)				
RP-32L13.3	(Up in low grade tumor)				

TABLE 2 **Deregulated lncRNAs with Their Correlations with Survival, Targets/Mecahnisms of Action and Functions in Glioblastoma** (Continued)

lncRNA	Expression in GBM (glioma)	Survival corelation	Targets/Mechanisms of action	*Function*	
				Overexpression	Under-expression
MIAT	(Down in low grade tumor)				
RP11-677O4.6	(Down in low grade tumor)				
TMEM191A	(Down in low grade tumor)				
LINC01476	Down				
RP11-334C17		Y			
BTAT10		Y			
SOX2OT	(Down in migratory GBM cells)	Y			
LOC100192378	Up				
RP11-112J3.16	Up				
LOC100127888	Up				
HCG4	Down				
FLJ39609	Down				

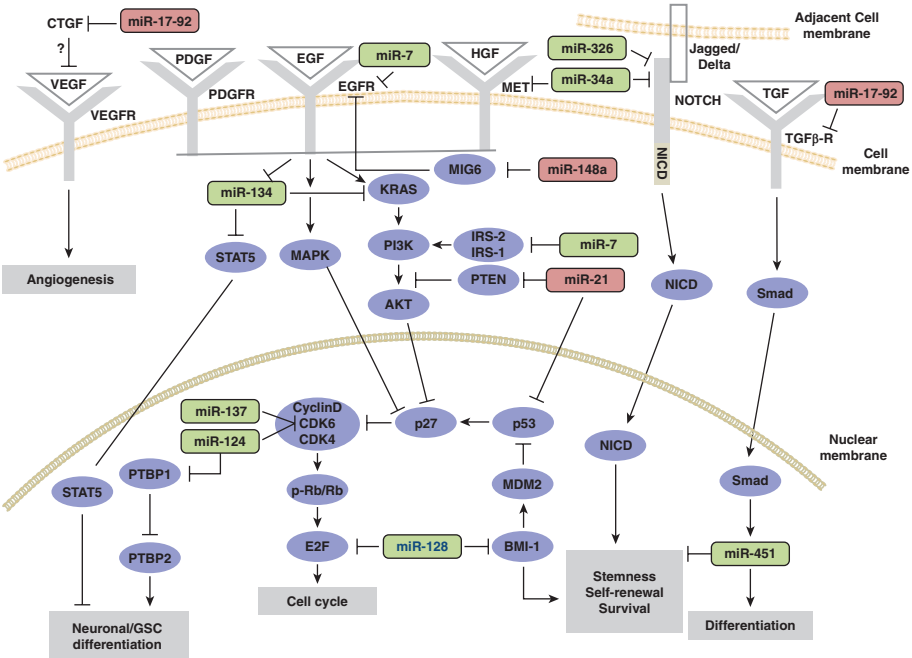

Figure 3 Regulation of glioblastoma stem cell targets and functions by miRNAs. Modified with permission from Zhang et al. (52).

NOTCH expression. The miR-17-92 cluster has been implicated in the regulation of GSC differentiation, apoptosis, and proliferation (61). It was first shown that expression of several members of miR-17-92 was significantly higher in primary astrocytic tumors than in the normal brain and significantly increased with tumor grade. A high-level amplification of the miR-17-92 locus was also detected in one GBM specimen, while inhibition of miR-17-92 induced apoptosis and decreased cell proliferation of GSCs.

Functions and Targets of miRNAs in GBM

CELL PROLIFERATION, VIABILITY, AND STEMNESS

One distinctive characteristic of GBM is uncontrolled proliferation and evasion of programed cell death. MiRNA deregulation is one mechanism for sustained proliferation and evasion of apoptosis through regulation of the cell cycle, apoptosis, and growth signaling pathways.

AP-1–induced miR-21 downregulates tumor suppressors PDCD4 and PTEN. Inhibition of PDCD4 contributes to an increase in AP-1 activity, revealing an AP-1 autoregulatory mechanism in RAS transformation (62). MiR-21 exerts antiapoptotic effects and enhances tumor formation through targeting of p53 and TGF-β signaling

and the mitochondrial apoptotic pathway (63). MiR-21 affects apoptosis and the cell cycle by inhibiting heterogeneous nuclear ribonucleoprotein K (HNPRK); the tumor suppressor homologue of p53 (Tap63); programmed cell death 4 (PDCD4); and possibly also EGFR, cyclin D, and Bcl2 (63–65), as well as ANP32A, SMARCA4, SPRY2, IGFBP3, and LRRFIP1 *(4, 66–68)*. MiR-21 is therefore an important miRNA in gliomas that exerts oncogenic effects by regulating cell proliferation and survival.

MiR-221/222 directly targets the tumor suppressor and negative regulator of the cell cycle, p27 (69, 70). miR-221/222 can inhibit apoptosis by targeting p53-upregulated modulator of apoptosis (PUMA), which acts to induce rapid cell death via binding to Bcl-2 and Bcl-xL. Therefore, overexpression of miR-221/222 and subsequent downregulation of PUMA enhance cell survival while knockdown of miR-221/222 induces apoptosis, thereby reducing tumor growth (71, 72).

MiR-26a regulates the major tumor suppressor PTEN in glioma (33, 34). It was shown that miR-26a can transform cells and promote GBM cell growth by decreasing PTEN, RB1, and MAP3K2/MEKK2 protein expression, thereby increasing AKT activation, promoting proliferation, and decreasing c-JUN N-terminal kinase-dependent apoptosis. Overexpression of miR-26a in PTEN-competent and PTEN-deficient GBM cells promoted tumor growth *in vivo* and increased growth in cells overexpressing CDK4 or CENTG1. MiR-335 is upregulated in GBM and acts to prevent apoptosis and promote cell growth and invasion of astrocytoma cells by targeting the potential tumor suppressor disheveled-associated activator of morphogenesis 1 (DAAM1), as well as regulating RB1 in a p53-dependent manner (73). Inhibition of miR-335 leads to effective suppression of growth and increased apoptosis of astrocytoma cells. Importantly, delivery of a miR-335 antagonist to rat glioma C6 cells prevented tumor growth, resulted in activation of apoptosis, and repressed invasion of astrocytoma xenografts (74).

MiR-34a is a downregulated miRNA in GBM that directly inhibits the expression of MET, NOTCH1, NOTCH2, CDK6, CCND1, and SIRT1 (35, 75–77). MET is a commonly overexpressed and activated RTK in GBM and is responsible for mediating multiple growth-signaling pathways. NOTCH is a critical regulator of cell fate and cancer stem cell maintenance (56–58). CDK6 and CCND1 are well-known cell-cycle regulators. By targeting these important molecules involved in cell proliferation, miR-34a inhibits cell survival, proliferation, and invasion, as well as GSCs self-renewal (35, 55).RTKs are co-deregulated in the majority of GBM. MiR-134 is upregulated in human tumors and GSCs and is regulated by the RTKs, MET, EGFR, and PDGFR (19). MiR-134 inhibits GSCs self-renewal, survival, and xenograft growth and induces GSC differentiation by directly binding to KRAS and STAT5B 3′ UTRs. MiR-134 therefore represents an RTK-regulated tumor-suppressive hub that mediates RTK effects on GBM malignancy.

Many more miRNAs, including the tumor-suppressive miR-181, miR-15b, miR-153, miR-184, miR-326, miR-218, and miR-451 (23, 78–80), inhibit proliferation and/or induce apoptosis in GBM. Additional upregulated oncogenic miRNAs that promote glioma cell viability and proliferation include miR-296 (81), miR-125b (82), miR-196a (83), miR-148a (36), miR-363, and miR-582-5p (84, 52).

MIGRATION AND INVASION

The lethality of GBM is partly attributed to extensive and diffuse tumor cell infiltration throughout the brain. The invasive growth of GBM is driven by the modulation of cell-to-cell and cell-to-matrix interactions, degradation, and remodeling of the extracellular matrix, cytoskeletal reorganization, and gain of migratory behavior (85). These processes are regulated by miRNAs. The oncogenic miR-21 promotes GBM invasiveness through suppression of the expression of matrix metalloprotease (MMP) inhibitors. MMPs are a family of enzymes that function in proteolysis of extracellular matrix components and are critical for the migration and invasion properties of tumor cells. By targeting multiple molecules, such as RECK, TIMP3, ANP32A, and SPRY2, miR-21 can induce the expression and activity of various MMPs, increase Ras/Raf binding, and activate ERK phosphorylation, thereby enhancing the invasive potential of GBM cells (27, 68, 86).Several studies reported that miR-146b and miR-10b can also promote GBM invasion (37, 87–89). MiR-146b inhibits MMP16 and leads the increased invasion in GBM, whereas MiR-10b can enhance GBM invasive growth by indirectly modulating MMP14 as well as uPAR and RhoC through direct binding and inhibits upstream target, HOXD10 (37, 88). When treated with antisense miR-10b, GBM cells display reduced growth, invasion, and angiogenesis, as well as enhanced cell death (38, 88, 89).The let-7 family of tumor-suppressive miRNAs is inhibited by Lin28A, which is normally expressed in development but is also found overexpressed in GBM by TCGA data analysis. There is a strong correlation in GBM between Lin28A expression and expression of the pro-invasive HMGA2 gene targeted by let-7 miRNAs, and an inverse correlation with let-7 family members. Overexpression of let-7g can reverse the invasive phenotype of Lin28A-expressing GSCs (90).

ANGIOGENESIS

One of the primary characteristics of GBM is its ability to create extensive microvasculature networks. New blood vessel growth orchestrates the growth of aggressive GBM by supplying a greater quantity of energy and nutrients, in addition to providing infrastructure for invasion. A number of miRNAs have been identified as important regulators of neovascularization in GBM (91). MiR-218 was shown to prevent GBM tumor angiogenesis and cell survival by targeting multiple components of RTK signaling pathways and the hypoxia-inducible factor, HIF2α (92). MiR-125b is downregulated in both human GBM-associated endothelium and in endothelial cells cultured with conditioned medium from GBM cells (82). Myc-associated zinc finger protein (MAZ), a transcription factor that regulates vascular endothelial growth factor (VEGF), is a target of miR-125b that is overexpressed in GBM-associated endothelium and is driven by VEGF. It was reported that miR-296 is a GBM angiogenic miRNA that is upregulated in tumor-associated endothelial cells. Augmented expression of miR-296 is associated with increased endothelial cell tube formation and enhanced vascularization of tumors, while knockdown of miR-296 results in reduced tumor angiogenesis (81).miR-210-3p is induced under hypoxic growth conditions and directly targets HIF3α, a negative regulator of hypoxic response that acts through downregulation of VEGF.

Therefore, miR-210-3p overexpression induces HIF, VEGF, and CA9 transcriptional activity, enhancing vasculogenesis, while inhibition of miR-210-3p under hypoxia inhibits HIF-mediated induction of VEGF and CA9, reducing vascular density and tumor growth *in vivo* (93).A member of the miR-17 family, miR-93, plays a role in GBM-associated angiogenesis by targeting integrin B8, a tumor suppressor and inhibitor of angiogenesis (94). MiR-93 was sufficient to enhance angiogenesis and tumor growth and drastically reduce survival in a xenograft model of GBM.

IMMUNE EVASION AND DRUG RESISTANCE

Increased antitumor immune responses have been linked to enhanced survival in many cancers, including GBM (95–101). MiRNAs regulate immune evasion. MiR-124 inhibits STAT3 to enhance T-cell-mediated immune clearance of glioma (102). Treatment of T cells isolated from GBM with miR-124 reversed a block in T-cell proliferation and also reduced expression of signal transducer and activator of transcription 3 and forkhead box P3—ultimately inhibiting the development of immune-suppressive regulatory T cells (102). MiR-124 delivery in mouse GBM xenograft models prolonged survival but only in immunocompetent mice. Dicer, miR-222, and miR-339 expressions were inversely associated with the expression of intercellular cell adhesion molecule (ICAM-1) and they enhanced the susceptibility of tumor cells to antigen-specific lysis by cytotoxic T-lymphocytes. MiR-222 and miR-339 contribute to GBM evasion of the immune system by targeting ICAM-1, which modulates T-cell responses (103).A major challenge of GBM therapy is the resistance to chemotherapy and/or radiotherapy. A number of miRNAs can influence therapeutic sensitivity by targeting multidrug resistance proteins (104). MiR-21 strongly reduces the effect of TMZ on apoptosis, which is mediated through inhibition of proapoptotic proteins Bax and caspase-3 as well as upregulation of antiapoptotic protein Bcl-2 (105). Inhibition of miR-21 can enhance the chemosensitivity of human GBM cells to TMZ and other drugs including paclitaxel, sunitinib, doxorubicin, and VM-26 (106–110). MiR-195, miR-455-3p, and miR-10a* were also implicated in TMZ resistance as they were upregulated in a TMZ resistant variant of the U251 GBM cell line (111). Knockdown of miR-195 was shown to significantly enhance the effectiveness of TMZ. Two studies examined the link between the miRNA levels (32) and TMZ resistance (112) in GBM. They found that miR-221, miR-222, miR-181b, miR-181c, and miR-128 were significantly downregulated in GBM, while miR-21 was overexpressed. MiR-181b and miR-181c had the strongest correlation with responsiveness to TMZ treatment, indicating their potential as predictive markers for response to TMZ therapy. MiR-125b-2 has also been shown to increase resistance of GSCs to TMZ, whereas peptide nucleic acid (PNA) miR-125b inhibitors increase TMZ-induced GSCs apoptosis via mediation of cytochrome c release from the mitochondria, caspase-3, and PARP activation (113). MiR-328 has been found to sensitize GSCs to chemotherapy through downregulating the expression of ATP-binding cassette subfamily G member 2 (ABCG2), a transporter that regulates shuttling of substrates across the cellular membrane (114). MiR-100 has been reported to increase the sensitivity of glioma cells to ionizing radiation through the downregulation of ataxia telangiectasia mutated (ATM) (115).

miRNA Therapeutics

Because miRNAs regulate all aspects of cancer, they represent promising therapeutic agents or targets. The goal of miRNA therapeutics is to replace tumor suppressor miRNAs or inhibit oncogenic miRNAs. There are a host of possible choices for both the therapeutic payload and the delivery vector. A number of reports in GBM describe preclinical efforts to characterize individual oncogenic and tumor-suppressive miRNA that can be targeted *in vitro*, with some evidence of efficacy in mouse models; however, none of them has moved on to clinical trials in GBM patients to date.

As described earlier in this chapter, numerous groups have reported oncogenic and tumor-suppressive miRNAs, affecting cell viability in GBM. Therapeutic efforts targeting oncogenic miRNAs have largely focused on delivering stabilized antisense oligonucleotides complementary to the miRNAs sequence. Preclinical studies with GBM tumor-suppressive miRNAs have consisted of forced overexpression of miRNA mimics. Among the GBM oncogenic miRNAs described in multiple studies, miR-21 and miR-10b figure prominently (38, 116–118). Several of these GBM miR-21 and miR-10b studies have demonstrated preclinical efficacy with delivery of miRNA antisense, some of which are dubbed "antagomiRs" (anti-miR); miR-10b may be an especially powerful oncogenic miRNA in GBM. One group has now shown preclinical efficacy in GBM models with a radically different approach to targeting miR-10b; viral delivery of CRISPR/Cas9 elements was used to eliminate miR-10b expression in GBM (119). Even more studies have identified tumor-suppressive microRNAs in GBM and shown their potential for therapeutic delivery. Among these translational studies of tumor-suppressive miRNAs and their therapeutic potential in GBM, miR-34a has received the most attention (35, 55). Others include miR-326, mir-297, miR-128, and miR-182 (120–124). Most of the published work with tumor-suppressive miRNAs in GBM has involved *ex vivo* transfection prior to GBM cell implantation in the mouse brain, but some studies have reached the higher bar of demonstrating *in vivo* efficacy with tumor-suppressive miRNA delivery to previously established orthotopic GBM in mice. A number of studies have also shown the potential of miRNA-based therapies to indirectly attack GBM, through its vasculature or through immunotherapeutic effects (82, 92, 94, 102, 103).

The problem of efficient delivery of miRNA-based therapies to GBM remains perhaps the biggest challenge. Numerous approaches tested preclinically have involved local delivery, sometimes with the addition of convection-enhanced delivery (CED) to drive better penetration of the agent into the tumor and the nearby brain. These local delivery approaches have typically used lentivirus, adenovirus, or one of a large variety of nanoparticles as vectors to transfect the GBM cells. While in the occasional report naked miRNA or anti-miRNA has been infused, it is typically more efficient to use a viral or nanoparticle vector to get substantial quantities of the payload into GBM cells. It should also be noted that intravenous delivery of miRNA-based therapeutic vectors might be a possibility for GBM; some reports describe approaches targeted to the brain vasculature or designed to pass through the blood–brain barrier or locally disrupt it (124, 125).

One key question for miRNA-based therapies directly targeting GBM cells is whether it is necessary for the therapeutic vector to reach all or nearly all of the

malignant cells to be highly effective. Some therapies might yield a bystander effect allowing for less-than-perfect delivery, but in general, it is likely that delivery will have to be highly efficient. However, this requirement might well be eased substantially by a biologic phenomenon found to be prominent in GBM cells—intercellular sharing of cytoplasmic contents through exosome shedding and uptake (126). This has been found in GBM cells to allow transduced cells to share cytoplasmic contents such as overexpressed miRNAs with adjacent GBM cells (42), which could dramatically reduce the need to reach the overwhelming majority of the GBM cells with any miRNA-based therapy.

Although there are numerous preclinical studies on miRNA-based therapeutic strategies for GBM, none has yet advanced to clinical trials in patients. However, miRNA-based therapeutics have entered clinical trial testing for other cancers, and GBM might not be far behind. A miRNA-34a therapeutic entered a Phase I trial for certain cancers (NCT01829971), enrolling 47 patients, yielding a partial response and four cases of stable disease, but it was marked by significant inflammatory side effects requiring immunosuppressive steroid premedication (127). This immune reaction may represent yet another challenge with miRNA therapeutics in the clinic, and it is hoped that valuable information will be gleaned from the analysis of this trial.

Long Noncoding RNAs

LncRNAs are nonprotein coding transcripts that are longer than 200 nucleotides (nt). LncRNAs are emerging as significant regulators of critical biological functions in human disease, including cancer and GBM (128–132). Over 50,000 human lncRNAs have been identified (133–135) and similar catalogs have been generated from various mouse tissues and model organisms (136–140). lncNRAs can regulate gene expression at the transcriptional, post-transcriptional, and epigenetic levels (141). Recent studies indicate that lncRNAs play important roles in glioma development (142, 143) by regulating several tumorigenic processes such as cellular proliferation and apoptosis (144). Differential expression of specific lncRNAs might correlate with disease progression and cancer malignancy and thus could potentially be used as therapeutic targets and biomarkers for prognosis (145–149).

lncRNA EXPRESSION AND CORRELATION WITH CLINICAL PARAMETERS IN GLIOMAS

One high throughput screening study of 1308 lncRNAs discovered 654 highly upregulated lncRNA in GBM compared to normal brain tissue (150), among which ASLNC22381 and ASLNC2081 were further investigated and found to be involved in GBM recurrence and malignant progression. Another study (145), using a microarray-mining approach, demonstrated aberrant lncRNA expression patterns in two large public cohorts (151, 152). They identified 127 lncRNAs that were differentially expressed between glioma and nontumoral brain tissues. Their analysis found that lncRNAs, CRNDE and HOTAIRM1, were significantly

upregulated in GBM while MEG3 was downregulated. In a clinical trial–based study, 80 GBM specimens were analyzed and 81 sets of lncRNAs were found to be deregulated (153). Another study found 37 lncRNAs that were upregulated and 44 lncRNAs that were downregulated in GBM specimens compared to nontumoral brain tissues based on the profiling analysis of 30 GBM patient samples and 5 GBM cell lines. They found that 147 out of 2448 lncRNAs were differentially expressed in tumor tissues compared to normal brain, and 213 lncRNAs were differentially expressed in tumor cell lines compared to normal astrocytes. Importantly, certain lncRNAs, including CRNDE, HOTAIRM1, and MEG3, were consistently differentially expressed, indicating that they may play a role early in GBM initiation and tumorigenesis (153, 154) (Table 2).

A recent comprehensive study of global lncRNA expression analyzed over 650 brain tumor and 70 normal brain tissues from TCGA and other public databases (155). A total of 611 induced and 677 repressed lncRNAs were identified in glial tumors relative to normal brains. One frequently reported oncogenic lncRNA, CRNDE, was confirmed to be upregulated over 40-fold in GBM. The lncRNA, TUNAR, was also identified as significantly downregulated (14-fold) in both GBM and LGG. Interestingly, TUNAR was found to act as a crucial positive regulator of neuronal development and differentiation in zebrafish, mice, and humans, suggesting that its downregulation is required for increased oncogenic potential and uncontrolled neuronal cell growth (138, 156).

Specific lncRNAs correlate with patient survival. From TCGA data analysis, approximately 500 lncRNAs were associated with poor prognosis, while 200 lncRNAs correlated with better survival outcomes (155). For example, patients displaying high expression of RP11-334C17.6 had a median survival time of 485 days, while patients with lower expression had a median survival time of 380 days (HR = 0.728, 95% CI = 0.6011–0.883, p = 0.00122). Patients with high versus low expression of BTAT10 had median survival time of 335 and 485 days, respectively (HR = 1.298, 95% CI = 1.0881–1.548, p = 0.00374).

Functions of lncRNAs in GBM

lncRNAs have been implicated in GBM development and malignancy by regulating cell proliferation, apoptosis, GSC self-renewal, differentiation, and response to hypoxic stress (see Table 2).

CELL PROLIFERATION AND APOPTOSIS

MEG3, a lncRNA that is significantly downregulated in GBM (144), acts as a tumor suppressor in GBM cells. Ectopic expression of MEG3 inhibits cell proliferation and via p53 activation. CRNDE, an oncogenic lncRNA in GBM (157) and other cancer types (158), promotes cell proliferation, migration, and invasion while inhibiting apoptosis in GBM cells and GSCs (157, 159, 160). HOTAIR has been shown to regulate cell cycle progression in glioma via interaction with EZH2 (161). Knockdown of HOTAIR or EZH2 leads to cell cycle arrest in GBM cells (161) and inhibition of HOTAIR represses orthotopic GBM tumor growth *in vivo* (162).

MIGRATION AND INVASION

MALAT1 is one lncRNA that was found to regulate cell migration in GBM and lung cancer (163). Although its mechanism in glioma is unclear, initial evidence suggests that MALAT1 regulates cell migration in lung cancer cells through the mediation of several motility-associated molecules, including AIM1, LAYN, HMMR, SLC26A2, CCT4, ROD1, CTHRC1, and FHL1 (164). LncRNA SOX2OT is also downregulated in migratory GBM cells, although its exact mechanism of action is unknown. Increased expression of SOX2OT in GBM correlates with better prognosis (165).

GSC DIFFERENTIATION

A study discovered 39 lncRNAs that were differentially expressed between GSCs and differentiated GBM cells (166), while another lncRNA screening study identified 33 lncRNAs that were expressed in a unique pattern between glioma cells and GSCs (167). Between these independent studies, six lncRNAs were consistently altered in a similar pattern, with LOC100192378, H19, RP11-112J3.16, and LOC100127888 being upregulated, and HCG4 and FLJ39609 being downregulated in GSCs (167). The effects and mechanism of action of these lncRNAs on the biological properties of GSC remains unknown, although H19 has been reported to play an important role in the maintenance of adult hematopoietic stem cells (168).

THERAPEUTIC RESPONSE AND RESISTANCE

Differential expression of lncRNAs has been associated with therapeutic response in GBM patients. Through gene expression profiling of GBM cell lines treated with the EGFR inhibitor erlotinib (ERL), the lncRNA GAS5 was significantly increased after treatment in both ERL-resistant and ERL-sensitive glioma cell lines. Moreover, knockdown of GAS5 sensitized GBM cells to ERL treatment (169). GAS5 is reportedly upregulated in growth-arrested cells and sensitizes mammalian cells to apoptosis, by suppressing genes responsive to glucocorticoid (170). GAS5 may also sensitize mammalian cells to apoptosis through binding to the DNA-binding domain of the glucocorticoid receptor (GR) and competing with target genes of glucocorticoid response elements (GREs).

MECHANISMS OF ACTION OF LNCRNA IN GBM

Little is known about the regulation of lncRNA expression in GBM. c-Myc, a transcription factor, has been found to induce the expression of the lncRNA H19 in GBM cells (171). Additional transcription factors, c-Myc, NFKB, E2F6, TAF1, and SMAD, which are well-known regulators in GBM (172–175), have been found to possess several binding sites in the promoter region of the lncRNA, CRNDE, which may mediate these important signaling pathways. Similarly, the lncRNA, HOTAIRM1, is highly overexpressed in GBM, and its gene promoter sequence has been bound by NFKB, PU.1, and USF-1 (176).The lncRNA, GASS, functions as a decoy GRE by binding to the DNA-binding domain of the GR and competing with target genes of GREs. Thus, GASS acts to suppress GR-induced transcriptional activity and may

enhance ERL effects in GBM (132, 170). Through interaction with EZH2, lncRNA HOTAIR regulates cell cycle progression in glioma. Proteins with bromodomain and extraterminal (BET) domain are potential therapeutic targets in cancer and GBM, as treatment of GBM samples with a BET inhibitor decreases GBM growth and causes reduced HOTAIR expression. Interestingly, a protein with a BET domain has been found to directly bind the HOTAIR promoter (177). PNKY plays an important role in neuronal differentiation and chromatin-state maps of the PNKY/BRN2 locus in GSCs and shows widespread active chromatin marks at their promoters (178). PNKY can bind to PTBP1, which is upregulated in GBM, and plays a role as a driver gene in GBM tumor growth as well as in the V-SVZ neurogenic lineage (179). CRNDE, an oncogenic lncRNA, induces cell proliferation, migration, and invasion, and inhibits apoptosis in GBM cells and GSCs via the activation of multiple signaling pathways. It functions as a sponge by binding miRNAs, such as miR-384, resulting in the downregulation of piwi-like RNA-mediated gene silencing 4 (PIWIL4) and STAT3 protein in GBM cells (160). CRNDE also upregulates X-linked inhibitor of apoptosis (XIAP) and the evolutionarily conserved serine/threonine protein kinase, PAK7, by binding and inhibiting miR-186, which targets XIAP and PAK7 in GBM cells (159). The lncRNA, nuclear-enriched abundant transcript 1 (NEAT1), is essential for the formation of nuclear body paraspeckles (180) and is upregulated in GBM tissues. Inhibition of NEAT1 reduces cell proliferation, invasion, and migration. NEAT1 exerts its oncogenic effects through the direct binding of miR-449b-5p, leading to upregulation of the RTK MET (180).

Conclusion

MicroRNAs and long noncoding RNAs are frequently deregulated in cancer and GBM, where they regulate all aspects of malignancy, including tumor cell proliferation, survival, migration, and invasion, as well as cancer stem cells, angiogenesis, tumor immune responses, therapy resistance, and the microenvironment. Studying these noncoding RNAs could lead to a better understanding of GBM initiation and progression. MiRNAs and lncRNAs could also be clinically exploited for diagnostic, prognostic, and therapeutic purposes. However, more research is required, especially in the case of lncRNAs, for a better understanding and efficient clinical exploitation of this large and important class of regulatory molecules in cancer and GBM.

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