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Review

Systematic Review of MicroRNAs and its Therapeutic Potential in Glioma

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MicroRNAs (miRNAs) are short noncoding RNAs. The discovery of miRNA has provided a novel tool to the research of tumor pathogenesis, and a new strategy to the diagnosis and prognosis of human cancers. Currently, numerous studies have indicated that the deregulation of miRNAs in glioma is closely related to glioma pathogenesis and progress. miRNAs function as key regulators of glioma through negative control of the target gene expression, by targeting the 3′-untranslated region of its messenger RNA which regulate the cell proliferation, apoptosis and prognosis of glioma. Moreover, radiation and chemotherapy resistance in glioma therapy is also caused by deregulation of miRNAs. It has been suggested that miRNAs act as tumor suppressors or oncogenes in glioma. Not only can miRNAs be used as biomarkers of glioma diagnosis and therapy, but also as novel targets of glioma gene therapy.

Key words: Glioma, microRNAs, molecular therapy

INTRODUCTION

Glioma is the most frequent and malignant brain tumor, accounting for 78% of intracranial primary tumors.[1] It originates from neural mesenchymal cells (i.e., glial cells, ependyma, and choroid plexus epithelial cells) and neural parenchymal cells (neurons); it can be classified as astrocytoma, glioblastoma, medulloblastoma (MB), ependymoma, and oligodendroglioma according to its origin.[2] Glioma is classified into five grades (I–IV) according to the World Health Organization (WHO), and each grade includes a variety of pathological subtypes.[3] Due to its invasive nature, rich blood supply and infiltrating growth, traditional treatments such as surgical techniques and radiotherapy, still obtain a poor prognosis.[4-8]

Although there are a series of comprehensive treatment measures for glioma, the mortality of malignant glioma remains high; median survival since diagnosis is < 14 months.[9,10] Astrocytoma is divided into low-grade glioma (WHO I–II) and high-grade glioma (WHO III–IV).[11] The average survival of the low-grade glioma reaches 6–10 years, but for high-grade glioma, the average survival has been reported to reach only 12–15 months to 30–36 months.[12,13] The situation of glioblastoma multiforme (GBM) is extremely serious, and the prognosis is prominently poor. Due to its highly invasive nature, surgery is often not effective, and because of its resistance to radiation and chemotherapy, GBM has a high relapse rate and is difficult to cure.[14-16] At present, treatment of GMB includes radiotherapy after surgical resection, followed by temozolomide (TMZ) as adjunctive therapy, then synchronous chemotherapy, again followed by TMZ cycles of chemotherapy.[17,18] Because of GBM's high radiation and chemotherapy resistance, the 2-year survival rate is only 30% and 5-year survival rate is 9.8%.[19]

Today, the application of MicroRNAs (miRNAs) treatment for glioma has attracted researchers' attention. Theoretically, miRNA can prevent the occurrence of glioma at the molecular level, and greatly improve survival. For example, a knock down study of miR-21 in glioblastoma cell lines led to decreased cell growth, reduced invasiveness, enhanced cell apoptosis, and suppressed tumorgenicity. The research showed that after decreasing the expression of miR-21, the tumor cell activity clearly decreased, and could partially inhibit U373 malignant gliomas (MG) cells tolerance to VM-26.[20-22] This experiment also suggested that miR-21 down regulation could increase chemotherapy sensitivity of cancer cells, which provides a novel tool to develop a new antitumor therapies.

Although the research of miRNAs in gliomas is still at the initial stage, with the establishment and improvement of the specific miRNA expression profiles of glioma, researchers will be able to provide a new direction for the diagnosis and treatment of human glioma. In this review, we summarize the current finding of miRNAs, which are deregulated in glioma, and discuss the molecular diagnostic and therapeutic potential of miRNAs in glioma.

Introduction of microRNAs

With the further development of the Human Genome Project, scientists have elucidated more of the function of the noncoding sequences which account for 99% of the human genome, the most striking of which is miRNA function. miRNA is a class of

single-stranded small RNA, approximately 19–25 nucleotides, and is produced by a former transcript stem-loop structure.[23] Although they do not have an open reading frame and even encode proteins, they play a vital role in variety of important physiological and pathological processes in organisms.[16] They can bind to the 3'-untranslated region (UTR) of their target messenger RNA (mRNA) via imperfect complementary base-pairing, acting as important regulators of diverse biological processes at the posttranscriptional level.[24] This induces mRNA cleavage that could result in silencing of specific genes, which regulates the ontogenesis, cell apoptosis, proliferation, differentiation, and any other processes that play a vital role in many diseases, especially in cancer.[25] There are numerous studies that demonstrate that miRNA could function as oncogenes or as tumor suppressors in glioma.[24,26-28] The discovery of miRNA has provided a novel tool to research tumor pathogenesis, and a new strategy for the diagnosis and prognosis of human cancers.

Lin-4 and let-7 are the first two miRNAs that have been discovered in nematode *Caenorhabditis elegans*.[29,30] Using experiments and bioinformatics, researchers have found hundreds of miRNAs in the organism. Presumably, about one-third of human encoding genes are negative regulated by miRNAs,[31,32] leading to increased study in areas such as molecular biology, genetics, and clinical medicine.

Biogenesis of microRNA

In order to understand the context of miRNA in gliomas pathology, we highlight the essential steps of the biogenesis of miRNA [Figure 1]. miRNA is a stem-loop structure encoded by an endogenous gene. Biogenesis starts with the transcription of the genome by RNA polymerase II/III, producing a primary transcript called pri-miRNA, which shows one or more stem-loop

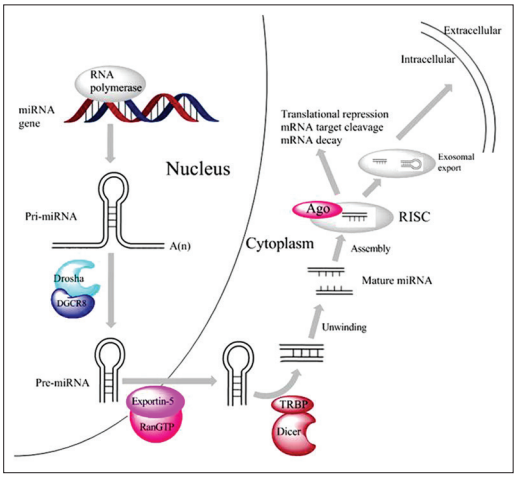

Figure 1. Biogenesis of microRNAs (miRNAs). The miRNA gene is transcribed by RNA polymerase II/III. The transcript is called Pri-miRNA, which is cleaved by Drosha-DGCR8 complex and forms pre-miRNA. This is transported to cytoplasm from nucleus by the exportin-5 and RanGTP cofactor. Pre-miRNA is processed by the transactivating response RNA binding protein-Dicer complex into a miRNA duplex, which is unwound to form mature miRNA. The guide stand binds to Ago to form RNA-induced silencing complex (RISC). RISC complementary pairs with the target messenger RNA (mRNA) 3'-untranslated region, leading to mRNA cleavage and translation repression. The passenger stand is degraded, and the surplus miRNAs are exported to extracellular matrix by exosomes

structures by intramolecular base-pairing.[33] The transcript is then cleaved into an approximately 60–110 length sequence called pre-miRNA by the complex of Drosha/DGCR8. It is transported into cytoplasm with the assistance of the exportin-5/Ran-GTP cofactor.[34] In the cytoplasm, the stem-loop structure is cleaved into an approximately 19–25 nucleotide double-stranded miRNA by the transactivating response RNA binding protein-Dicer complex. Subsequently, one strand participates in forming the RNA-induced silencing complex which complementary pairs with the 3'-UTR of the target mRNA, leading to translation repression,[35,36] and has been implicated in numerous pathological processes.[37]

Relationship between microRNAs and tumo

At least one-third of coding genes are regulated by miRNAs.[38,39] Research has shown that miRNA expression profiles are different between tumor tissue and normal tissue. miRNA expressed in different kinds of tumor tissue is inordinately up or down-regulated.[40] In other words, one specific miRNA up-regulated in certain types of cancer maybe decreased in others.[41] The deregulation of miRNA influences the cell signal pathways significantly, resulting in out of control cell proliferation and differentiation.[42]

In recent years, a large body of literature has reported that miRNAs are of significance to tumor biology.[43-45] miRNAs are involved in tumorigenicity, especially, in malignancy.[46] Calin *et al.*[47] first reported in 2002 that miRNAs were involved in tumorigenicity. Since then, hundreds of miRNAs have been associated with tumorigenicity. Due to radiotherapy and chemotherapy resistance, the treatment of glioma has remained a huge challenge, so finding prognostic factors is the key.[48] For example, researchers showed that the down regulation of two miRNAs miR-181a and miR-181c resulted in TMZ chemotherapy resistance and in the poor prognosis of glioma.[49]

MicroRNA deregulation has become a new characteristic of malignant tumor, so some specific miRNAs are potentially novel biomarkers of cancer diagnosis and prognosis.[50-52] More than 50% of miRNA genes are located in the fragile site of chromosomes, and in the process of tumorigenesis. Genetic alterations such as deletion, amplification, and translocation often occur in these regions.[53,54] For specific cancers, miRNAs expression profiles can easily be identified for their distinctive characteristics, and could be used as biomarkers for tumor classification.[55,56] Quantitative detection of miRNAs levels in plasma of tumor patients can be used in human cancer diagnosis,[57] and blood screening of miRNAs could predict tumor metastasis.[58] For example, down regulation of miR-221 or methylation of miR-9-1 have been shown to be biomarkers of colorectal tumor metastasis.[59,60] Therefore, miRNA expression profiles can not only be used as tumor diagnostic biomarker, but also can be used for prognosis.[61]

Studies in chronic B cell lymphoma,[62] ovarian carcinoma,[63] glioma,[64] lung cancer,[65,66] liver cancer,[67] and colon cancer[68,69] have demonstrated that miRNA expression profile is different between tumor tissue and normal tissue. Thus, the deregulation of miRNA in tumor tissues may contribute to tumorigenicity and progression. Research of miRNAs deregulation in tumor may reveal tumorigenesis mechanisms, novel diagnostic and prognostic biomarkers, and new targets of gene therapy

MicroRNAs in glioma

Deregulation of miRNAs can affect the proliferation, apoptosis, invasion, migration, and drug resistance of glioma cells. miR-21 was the first miRNA investigated in glioma. In 2005, Chan *et al.*[70] demonstrated that miR-21 was distinctly up-regulated in glioma. Overexpression of miR-21 suppressed apoptotic gene expression and induced tumor progression. Similarly, other studies indicated that various other miRNAs were deregulated in glioma.[49,71] Ciafrè *et al.*[72] have quantitatively analyzed hundreds of miRNA expression through microarray, and found that there are 13 kinds of miRNAs deregulated in glioma: 9 were up-regulated such as miR-21, miR-9-2, miR-10b, miR-25, miR-123, miR-125b-1, miR-125b-2, miR-221, miR-130a, while miR-128-1, miR-181a, miR-181b, miR-181c were down-regulated.

Recently, a large number of miRNAs were detected in mammalian brain tissue and involved in regulating the development of brain tissue, neuronal differentiation and higher neural function (such as learning, memory, *etc.*). In addition, mirRNAs are correlated with diseases such as neurodegenerative disease, psychosis and brain tumor.[73] Research showed that there were a group of cells in glioma, called glioma stem cells (GSCs), which can proliferate and unlimitedly self-renew, and have multi-directional differentiation potential, compared with normal tumor cells. The GSCs are more active in proliferation and tumorigenicity, and may play a vital role in the occurrence, development and relapse of glioma because their biological characteristics are similar with neural stem cells.[74] With further investigation of miRNA biological function, researchers found that there were complicated regulatory networks between miRNA and its target genes, and miRNA impact tumorigenesis through deregulating vital molecules in signaling pathways such as transforming growth factor beta (TGF-β), Wnt, Notch and the epidermal growth factor receptor (EGFR) pathways.

There are many signaling pathway involved in cancer stem cells, for example, receptor tyrosine kinase (RTK)-Akt, Notch, bone morphogenetic proteins/TGF-β, Hedgehog-Gli, Wnt-b-catenin, signal transducer and activator of transcription 3 (STAT3), and glycogen synthase kinase-3-e. They interact and supplement each other, resulting in deregulation of the G1/S phase checkpoint, eventually causing disordered cell cycle regulation, aberrant proliferation and tumorigenesis.

The RTK-Akt signaling pathway plays a crucial role in cancer stem cells, research showed that miR-7 could block cell cycle progress by suppressing insulin receptor substrate-2 in ATK pathway. miR-7 can also suppress EGFR expression, and by blocking the RTK-Akt signaling pathway can reduce invasiveness and viability of glioma cells.[75] GSCs are more dependent on the ATK pathway than glioma cells. Therefore, suppressing the AKT pathway could inhibit the growth of GSCs.[76,74] The Notch signaling pathway is important to maintain stem cell self-renewal and inhibit cell differentiation.[77] A study showed that miR-326 could induce apoptosis of glioma cells and GSCs through the Notch signaling pathway.[78] Another study demonstrated that miR-107 could inhibit proliferation and invasiveness of GSCs by suppressing Notch levels.[79] Li *et al.*[80] first found that premiR-34a is down-regulated in glioma, indicating that miR-34a could suppress the expression of Notch-1, Notch-2, cyclin-dependent protein kinases-6 (CDK6) and c-Met in glioma simultaneously, and that low Notch levels could inhibit the formation of tumor spheres.[81] In addition, aberrant expression of Notch is associated with GSCs radiotherapy resistance.[82] TGF-β could induce angiogenesis and promote invasiveness as a key molecule of TGF-β signaling pathway and oncogene,[83] and it has been investigated that it also promotes tumor progression and invasiveness in high-grade gliomas.[84] miR-34a is a novel regulator of TGF-β signaling pathway in GBM, miR-34a regulates the TGF-β signaling pathway through a Smad4 transcriptional network, and its direct target is Smad4.[85] TGF-β pathway has been deemed as an oncogenic factor in GBM:[86] mediated by Id1 and Id3, TGF-β signaling pathway could enhance self-renewal of tumor-derived spheroids *in vitro*.[87] Recently, research demonstrated that overexpression of miR-146a suppressed TGF-β1 mediated U87 proliferation and migration, and miR-146a could suppress the Smad4 level, miR-146a was deemed as a novel regulator of TGF-β signaling pathways in GBM.[88] Hedgehog-Gli signaling pathways also play a vital role in adult stem cells self-renewal, including neural stem cells.[89] Research has indicated that the Hedgehog-Gli signaling pathway was involved in tumorigenicity and self-renewal of the GSCs. Therefore, blocking Hedgehog-Gli signaling pathway could inhibit the growth of GSCs and promote apoptosis.[90-93] Notch pathway also affects Gli transcript in mammalian skin cells; Notchl knockdown could induce GliZ to be unregulated and lead to basal cell carcinoma.[93] Gu *et al.*[94] have found 17 kinds of miRNAs deregulated in GBMs through microarray analysis which targets the Hedgehog-Gli pathway; they indicated that miR-144 was up-regulated in GBMs with a high Gli1 level, while miR-125b-1 was down-regulated. In MBs, miR-125b has been reported as a suppressor of Hedgehog-Gli pathway, the authors also demonstrated that miR-125b, miR-326 and miR-324-5p were regulators of Hedgehog-Gli signaling pathway as well, which means that these miRNAs are involved in the tumorigenic potential of Hedgehog-Gli pathway.[95] Moreover, STAT3 signaling pathway also played a crucial role in the maintenance of GSCs proliferation; knockdown STAT3 can inhibit the growth of GSCs, and thus STAT3 act as oncogene in GSCs.[96,97] Research demonstrated that miR-124 could inhibit STAT3 signaling to enhance T cell-mediated immune clearance of glioma, and miR-124 was identified to modulate the STAT3 signaling pathway, which is a key pathway mediating immune suppression in tumor microenvironment.[98] miR-21 modulates hTERT expression by STAT3 in GBM, the author indicated that STAT3 was a crucial mediator between miR-21 and hTERT.[99]

In other words, miRNAs have played a vital role in the following aspects of the mechanism of occurrence and development of glioma. First, they can regulate the tumor suppressor gene expression. For instance, miR-21 could inhibit apoptosis related gene expression,[100] and miR-221 and miR-222 could decrease the level of anti-oncogene p27.[101] Second, they could act on signaling pathways involved in glioma occurrence and development. For example, miR-7 could suppress tumorigenicity through blocking the AKT pathway.[75] miR-7 was down-regulated in glioma, and the glioma cell lines in which miR-7 is up-regulated have lower viability and invasiveness.[102] Third, miRNA could induce differentiation of GSCs, and overexpression of miR-124 and miR-137 could induce GSCs differentiation to form glioma cells. There are 6 kinds of miRNA up-regulated in CD133 negative cell lines (miR-16, miR-107, miR-185, miR-425, miR-451, and miR-486), while they are down-regulated in CD133 positive cell lines.[103]

MICRORNAS DEREGULATED IN GLIOMA

MicroRNAs uegulated in glioma

Many literatures have indicated that the common deregulation of miRNAs in glioma is over expression. We summarize three kinds of miRNAs in detail, which have been investigated incisively and comprehensively, and they are miR-21, miR-93 and miR-221/222. Although both expression profile and function of a series of miRNAs have been intensively investigated, the target and mechanism of vast majority miRNAs remain unknown, and need further investigation [Table 1].

miR-21

miR-21 was the first miRNA which was investigated in glioma in 2005. Research showed that miR-21 was over expressed in glioma compared with normal brain tissue,[70] and the investigator also indicated that knockdown miR-21 in glioma cell lines could activate caspase involved in apoptosis, suggesting that miR-21 function as an oncogene in tumorigenicity. The up regulation of miR-21 was extreme in grade IV astrocytomas,[21] and functional studies indicated that miR-21 knockdown in GBM cells could reduce invasiveness, enhance apoptosis, decrease cell growth, and suppress tumorigenicity.[20,21,70]

Research demonstrated that insulin-like growth factor-binding protein-3 (IGFBP3) was a novel target of miR-21 in GBM and suggested that miR-21 down regulates the expression of IGFBP3, which acts as a tumor suppressor in human GBM.[105] miR-21 has played a vital role in apoptosis and proliferation of GBM GSCs. Shang *et al.*[106] have found that miR-21 down regulation affects apoptosis and proliferation of GSCs, partly by directly down regulating FASLG, which revealed that FASLG is also a novel target of miR-21. Han *et al.*[107] demonstrated that miR-21 was regulated by β-catenin/STAT3 pathway that could induce cell proliferation and invasion via STAT3 factor in glioma cells by targeting RECK. Papagiannakopoulos *et al.*[22] reported that miR-21 was involved in three tumor suppressive pathways, namely p53, TGF-β, and mitochondrial apoptotic pathways, by targeting heterogeneous nuclear ribonucleoprotein K, TAp63, and programmed cell death 4, which are key factors in cell cycle regulations and apoptosis. In addition, a study showed that knockdown miR-21 contributed to the radio-sensitization of glioma cell lines through inhibiting phosphoinositide 3-kinase/ATK pathway and enhanced irradiation-induced autophagy, suggesting that miR-21 played an important role in radio-resistance of malignant glioma.[108]

Drug resistance is considered a multifactorial phenomenon in cancer, and leads to poor prognosis. Ren *et al.*[109] demonstrated that knockdown of miR-21 contributed to sensitizing human GBM cells U251 (PTEN-mutant) and LN229 (PTEN-wild type) to the anticancer drug taxol, suggested that PTEN maybe another target of miR-21 in glioma. Qian *et al.*[110] also reported that miR-21 was involved in TMZ resistance and concomitant treatment with miR-21 inhibitor and TMZ gained the best antitumor effect in LN229 cells. miR-21 level is also involved in poor prognosis of glioma patients. Numerous papers indicated that miR-21 level in high-grade (III–IV) gliomas was higher than in low-grade (I–II) gliomas,[21,70,105-107] Hermansen *et al.*[111] showed that miR-21 was located in both tumor cells and tumor blood vessels and its presence in the tumor cell compartment is an unfavorable prognostic in gliomas. Furthermore, co-inhibition of miR-10b and miR-21 exerts a synergistic inhibition on the proliferation and invasion of human glioma cells.[112]

The investigation of the mechanism of miR-21 up-regulated in gliomas is helpful to understanding the pathogenesis of gliomas. DNA demethylation is considered a mechanism for the transcriptional activation of miR-21 in ovarian tumor cells.[113] Global hypomethylation is common in human cancer. DNA demethylation can activate oncogenes in GBM and other human cancers.[114] However, the exact epigenetic role of miR-21 in gliomas needs further investigation.

miR-93

Numerous studies have found that miR-93 is over expressed in GBM.[115-117] miR-93 is a member of miR-106b-25 cluster, which is a paralog of the miR-17-92 cluster, both of which possess carcinogenic activities.[118-121] Dong *et al.*[122] have illustrated the functional properties of miR-93, and they found that miR-93 could promote tumor formation and angiogenesis by targeting integrin-β8 which is associated with apoptosis in GBM. The authors also indicated that miR-93 could induce angiogenesis and promote tumor growth via a series of *in vivo* and *in vitro* experiments. They confirmed this with a co-culture with a U87 cell line which was transfected with exogenous miR-93, enhanced the proliferation, migration, and tube formation of endothelial cells. Moreover, the up regulation of miR-93 increased blood vessel formation prominently in mice, which have GBM xenograft tumors, which suggested that miR-93 is an angiogenic inducer indeed and propose a novel therapy for human GBM.[123]

miR-221/222

miR-221 and miR-222 are located on chromosome Xp11.3, belong to the same cluster, and have the same target specificity.[124] These two miRNAs are often overexpressed in high-grade astrocytomas (WHO grade III and IV) and primary GBM.[72,125,126] Research indicated that they played a vital role in cell cycle progression.[127,128] miR-221/222 could also suppress the expression of p27kip1 (cyclin-dependent kinase inhibitor 1B),[127] which is a negative cell cycle regulator and often down-regulated in high-grade astrocytomas.[129] p27kip1 is an CDK inhibitor; it binds to CDK with a cyclin and leads to cell cycle arrest in G1 phase. Research showed that p27kip1 was a direct target of miR-221/222.[127] According to bioinformatics analysis, CDK4 may serve as an activator of miR-221, and the expression of p27kip1 will be enhanced when CDK4 was suppressed,[130] inhibiting the transcription of miR-221 can achieve the same goal.[127] According to an analysis of miRNA expression profile during cell cycle progression of GBM cells, the author found that miR-221/222 was overexpressed during G1/S phase; they also indicated that CDKN1C/p57 was also a target of miR-221/222 besides p27kip1.[56] Zhang *et al.*[131] found 16 kinds of miR-221/22 target which can interact with ATK by bioinformatics analysis, suggested that miR-221/22 may also regulate the AKT pathway in glioma. In addition, the study also indicated that up-regulation of miR-221/222 can enhance proliferation and invasiveness of glioma cell *in vitro*, and can induce glioma growth in a subcutaneous xenograft mouse model.

Other microRNAs up-regulated in glioma

There are many other miRNAs, which are substantially upregulated in glioma cell lines and tissue compared with normal tissue [Table 1]. Similar to miR-21, miR-93 and miR-221/222, their

Table 1: Up-regulated miRNAs and their function in glioma

miRNAs	Targets	Function (down regulation)	Grade	References
Hsa-mir-21	IGFBP3	Invasiveness ↓	Grade III-IV	20-22,70,104-114
	FASLG	Apoptosis ↑		
	RECK	Cell growth ↓		
	HNRPK	Tumorigenicity ↓		
	TAp63			
	PDCD4			
	PTEN			
Hsa-mir-93	Integrin-β8	Proliferation ↓	Grade III-IV	115-123
		Angiogenesis ↓		
		Migration ↓		
Hsa-mir-221/222	p27kip1	Proliferation ↓	Grade III-IV	124-131
	CDKN1C/p57	Angiogenesis↓		
	AKT			
Has-mir-10b	HOXD10	Invasiveness ↓		72,117,139-141
Hsa-mir-15b	CCNE1	Proliferation ↓		100,115,116,141-143
Has-mir-17	POLD2	Viability ↓	Grade III-IV	116,117,135,141,142,144
	TGF-β-RII	Proliferation ↓		
	CTGF	Apoptosis ↑		
	CAMTA1			
Hsa-mir-18a	Smad4	Viability ↓		141,145
	CTGF	Apoptosis ↑		
		Proliferation ↓		
Hsa-mir-23b	VHL	Growth ↓	Grade III-IV	136
		Apoptosis ↓		
		Invasiveness ↓		
Hsa-mir-33a	PDE8A	GIC self-renewal ↓	GBM	146
	UVRAG	Subcutaneous tumor		
		Growth ↓		
Has-mir-92b	NLK	Proliferation ↓		137
		Cell cycle progression ↓		
		Cell survival ↓		
		Invasiveness ↓		
Hsa-mir-146a	Notch-1	Viability ↓	GBM	88,138
		Apoptosis ↑		
		Chemosensitivity ↑		
Has-mir-155		Viability ↓		116,117,142,145,147
		Apoptosis ↑		
		Chemosensitivity ↑		
Has-mir-182				116,117,148
Has-mir-183				116,142,148
Has-mir-210		Growth ↑		141,142,144,147
		Angiogenesis ↑		
		Invasiveness ↑		
		Apoptosis ↑		

Contd...

Table 1: Contd...

miRNAs	Targets	Function (down regulation)	Grade	References
Hsa-mir-335	Daam 1	Apoptosis ↑	Grade III-IV	141,149
		Invasiveness ↓		
		In vivo tumor volume ↓		
Hsa-mir-372	PHLPP2	Proliferation ↓	Grade III-IV	132,133
		Invasiveness ↓		
		Induced G1/S arrest		
		Apoptosis ↑		
Has-mir-381	LRRC4	Proliferation ↓		150
Has-mir-454-3p		Potential noninvasive biomarker	Grade III-IV	134

miRNAs: MicroRNAs; IGFBP3: Insulin-like growth factor-binding protein-3; GBM: Glioblastoma multiforme; HNRPK: Heterogeneous nuclear ribonucleoprotein K; VHL: Von Hippel-Lindau; NLK: Nemo-like kinase; TGF-β: Transforming growth factor beta; CTGF: Connective tissue growth factor

down regulation also induced cell growth, invasiveness, migration, and proliferation of glioma by binding to their target. Moreover, they may serve as a potential noninvasive biomarker for the diagnosis and prognosis of glioma. miR-372 was confirmed up-regulated in glioma cell lines and tissues, decreasing the miR-372 level would prominently reduce cell proliferation, invasiveness, and enhance apoptosis by targeting PHLPP2.[132,133] Guo *et al.*[134] indicated that miR-454-3p would act as a potential prognostic indicator in human glioma. miR-17 expression significantly predicts poor prognosis in human glioma,[135] and down regulation of miR-23b causes growth inhibition, suppresses invasion of glioma *in vitro*, and induces apoptosis by targeting von Hippel–Lindau.[136] Wang *et al.*[137] indicated that miR-92b is also up-regulated in glioma, and down regulation leads to proliferation and invasion inhibition by targeting nemo-like kinase. In addition, down regulation of miR-146a could block TGF-β signaling pathways in GBM.[138] There are also many other miRNAs reported up-regulated in glioma such as miR-10b, miR-15b, miR-18a, miR-33a, miR-155, miR-182, miR-183, miR-210, miR-335, and miR-381 [Table 1]; these miRNAs reported in at least one research study, act as oncogenes in glioma, and can be used as therapeutic target of glioma therapy.

MicroRNAs down-regulated in glioma

In addition, in this paper, we review 22 kinds of miRNAs, which were confirmed as down-regulated in glioma [Table 2], and may act as tumor suppressors in glioma by regulating the expression of their target. Here, we summarized four kinds of miRNAs, miR-128, miR-7, miR-218, and miR-181, which have been reported by multiple publications.

miR-128

microR-128 is considered a brain specific miRNA,[151] and several studies have reported that miR-128 is down-regulated in GBM, but it has less decreased levels in low-grade glioma.[152] It can suppress tumor growth via several direct targets in gliomas. Bmi-1 is the first target of miR-128 which could promote stem cell self-renewal, and was confirmed as oncogene,[153] Bmi-1 was also considered as the first neural stem cell self-renewal factor which is regulated by miR-218. The authors indicated that miR-128 overexpression not only reduced glioma cell proliferation *in vitro* significantly, but also suppressed glioma xenograft growth *in vivo*.

Another direct target of miR-128 is E2F3a.[152] A study indicated that miR-128 could inhibit glioma cells proliferation by targeting transcription factor E2F3a; the authors showed that the levels of E2F3a were negatively correlated to the levels of miR-128 whether in gliomas and normal brain tissues. Furthermore, the levels of E2F3a in T98G cells were reduced by over expression of miR-128.

Moreover, research showed that miR-128 could repress glioma-initiating neural stem cells growth by enhancing neuronal differentiation, via targeting oncogenic RTKs such as EGFR and platelet-derived growth facto receptor-α (PDGFRα). The author indicated that decreased expression of miR-128 correlates with aggressive human glioma subtypes, and they confirmed miR-128 is a tumor suppressor *in vivo*.[154] Peruzzi *et al.*[155] illustrated that miR-128 was confirmed as an important suppressor of polycomb repressor complex (PRC), which is oncogenic in GBM, miR-128 inhibited PRC activity by directly targeting its key component SUZ12 of PRC2. The authors also indicated that the absence of miR-128 is an early event in glioma genesis. Another study revealed EphB1 and EphB2 are novel miR-128 targets in glioma;[156] miR-128 could promote cell-cell adhesion in U87 cells by targeting EphB1 and EphB2, and the authors indicated that miR-128 significantly inhibited cell migration through down regulating of EphB2 in glioma. WEE1 and Msi1 have also confirmed as the direct targets of miR-128 involved in proliferation of glioma.[141] Shi *et al.*[157] identified that p70S6K1 was a novel direct target of miR-128; overexpression of miR-128 suppressed p70S6K1 and its downstream signaling molecules such as hypoxia-inducible factor-1 (HIF-1) and vascular endothelial growth factor expression, which were involved in angiogenesis in glioma. Thus, miR-128 can be regarded as a tumor suppressor of glioma. Recently, a study showed that the SNAI1/miR-128/SP1 axis played a vital role in glioma progression, and SP1 was confirmed as another target of miR-128,[158] suggested that this axis is a potential candidate molecular target for clinical diagnosis and treatment.

miR-7

miR-7 is also down-regulated in glioma targeting critical cancer signaling pathway. Disruption of the EGFR and ATK signaling pathways are the most common genetic alterations in GBM.[159,160] Kefas *et al.*[75] indicated that miR-7 could deregulate these two vital signaling pathways in GBM. miR-7 decreased the expression of EGFR prominently in GBM, and it also blocked the ATK signaling pathway by targeting its upstream regulators ISR1 and ISR2, the authors also demonstrated that the viability and invasiveness of GBM cells were prominently decreased through transfected miR-7.

In line with this study, Liu *et al.*[161] reported that miR-7 suppressed the PI3K/ATK and Raf/MEK/ERK pathways

Table 2: Down-regulated miRNAs and their function in glioma

miRNAs	Targets	Function (up regulation)	Grade	References
Hsa-mir-128	Bmi-1	Proliferation ↓	Grade III-IV	151-159
	E2F3a	Glioma xenograft growth ↓		
	EGFR	giNSC growth ↓		
	PDGFRα	Migration ↓		
	SUZ12	Angiogenesis ↓		
	EphB1	Cell-cell adhesion ↑		
	EphB2			
	WEE1			
	Msi1			
	p70S6K1			
	SP1			
Hsa-mir-7	ISR1	Viability ↓	Grade III-IV	75,159-165
	ISR2	Migration ↓		
	EGFR	Invasiveness ↓		
	PI3K	Proliferation ↓		
	Raf-1	Radiosensitivity ↓		
	FAK			
	IGF-1R			
Hsa-mir-218	IKK-β	Apoptosis ↑	Grade III-IV	166-171
	ECOP	Invasiveness ↓		
	LEF1	Tumorigenicity ↓		
	Bmi1	Migration ↓		
		Chemoresistance ↓		
		Angiogenesis ↓		
Has-mir-181a/b/c	Bcl-2	Radiosensitivity ↑	Grade III-IV	72,125,172-176
	Cyclin B1	Chemosensitivity ↓		
		Invasiveness ↓		
		Proliferation ↓		
Has-mir-34a	SIRT1	Viability ↓		183-185
	c-Met	Proliferation ↓		
	Notch-1/2	Apoptosis ↑		
	PDGFRα	Invasiveness ↓		
	Msi1	*In vivo* tumor volume ↓		
		Differentiation ↑		
Has-mir-149	Rap1B	Proliferation ↓		142,186
	Wnt-pathway	Migration ↓		
Hsa-mir-326	Notch-1/2	Proliferation ↓		171,172
	PKM2	Apoptosis ↑		
		Viability ↓		
		Invasiveness ↓		
Hsa-mir-124	SNAI2	Proliferation ↓		100,116,141,146,186
	R-Ras	Migration ↓		
	N-Ras	Invasiveness ↓		
		Stemness ↓		

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Table 2: Contd...

miRNAs	Targets	Function (up regulation)	Grade	References
		Angiogenesis ↓		
		Chemosensitivity ↑		
Hsa-mir-100	ATM	Radiosensitivity ↑		187
Hsa-mir-101	EZH2 Msi1	Angiogenesis ↓		188,189
		Migration ↓		
		Viability ↓		
		Proliferation ↓		
Hsa-mir-16	NF-kB1	Glioma cell growth ↓		190
	BCL2	Invasiveness ↓		
Hsa-mir-136	AEG-1	TMZ resistance ↓		191,192
	E2F1			
Has-mir-137	RTVP-1	Proliferation ↓	GBM	100,117,141,188,193,194
	c-KIT	Apoptosis ↓	GSCs	
	YBX1	Migration ↓		
	AKT2	GSC stemness ↑		
	CDC42			
	CDK6			
	TGF β2			
Has-mir-152	KLF4	Proliferation ↓	GBM	195
		Migration ↓		
		Invasiveness ↓		
		Inducing apoptosis ↑		
Has-mir-214	UBC9	Proliferation ↓	Grade III-IV	179
		Migration ↓		
		Invasiveness ↓		
		Tumor angiogenesis ↓		
Has-mir-31			Grade III-IV	196
Has-mir-142-3p	TGFBR1/2	Glioma growth ↓		197
		Glioma-infiltrating macrophages ↓		
Has-mir-205		Survival rate ↑	Grade III-IV	198
Has-mir-297	DGK-α	Invasiveness ↓	GBM	182
		Apoptosis ↑		
		Tumorigenicity ↓		
Has-miR-326	SMO	Tumorigenicity ↓	Grade III-IV	177,178
		Stemness ↓		
		Migration ↓		
		Invasiveness ↓		
		Proliferation ↓		
		Apoptosis ↑		
		Differentiation ↑		
Has-mir-622	ATF2	Proliferation ↓		180
		Invasiveness ↓		
		Migration ↓		
Has-mir-708		Proliferation ↓	GBM	134

Contd...

Table 2: Contd...

miRNAs	Targets	Function (up regulation)	Grade	References
		Invasiveness ↓		
		Apoptosis ↑		

miRNAs: MicroRNAs; EGFR: Epidermal growth factor receptor; PDGFRα: Platelet-derived growth facto receptor-α; FAK: Focal adhesion kinase; LEF1: Lymphoid enhancer-binding factor 1; Bcl-2: B cell lymphoma/leukemia-2; CDK6: Cyclin-dependent protein kinases-6; TGF β2: Transforming growth factor beta; TGFBR1/2: Transforming growth factor; beta receptor1/2; GSCs: Glioma stem cells; GBM: Glioblastoma multiforme; IGF-1R: Insulin-like growth 1 receptor; ECOP: EGFR-coamplified and overexpressed protein; UBC9: Ubiquitin-conjugating enzyme 9; DGK-α: Diacylglycerol kinase alpha; ATF2: Activating transcription factor 2

simultaneously through targeting the two transcription factors PI3K and Raf-1, which are both located in downstream of EGFR. Moreover, transfection with miR-7 could induce GBM cell apoptosis, inhibit proliferation, suppress migration *in vitro,* and reduce tumorigenicity *in vivo*.

Another miR-7 target identified in GBM is focal adhesion kinase (FAK). Wu *et al.*[162] illustrated that miR-7 directly suppressed GBM cell invasion via targeting FAK; they indicated that overexpression of miR-7 decreased the invasion and migration of U87 and U251 cells, and the level of endogenous miR-7 and FAK showed negative correlation. The authors also reported that miR-7 repressed the expression of invasion factors p-ERK1/2, matrix metalloproteinase 2 (MMP-2) and MMP-9 in GBM.[162] Recently, a study showed that miR-7 could inhibit glucose metabolism and cellular growth in gliomas by directly targeting IGF 1 receptor.[163] Interestingly, miR-7-5p was also regulated in GBM microvasculature and suppressed vascular endothelial cell proliferation through targeting RAF1, confirmed as oncogene.[164] Babae *et al.*[165] reported that GBM angiogenesis and growth was suppressed by transfecting with miR-7, transfection of miR-7 in endothelial cells reduced cell viability, tube formation, sprouting and migration, similar to anti-angiogenic drug sunitinib. All of these studies confirm that miR-7 is down-regulated in gliomas. A functional analysis indicated that miR-7 is a tumor suppressor of gliomas suggesting that miR-7 is a novel molecular drug for glioma treatment.

miR-218

MicroR-218 was confirmed down-regulated in tumor tissue, and numerous evidence indicated that miR-218 acts as a tumor suppressor in human glioma.[166-171] The research reported that the level of miR-218 was prominently down-regulated in glioma cell lines and over expression of miR-218 could enhance apoptosis and inhibit invasion of glioma cells. The author also indicated that this was mediated by inactivating the nuclear factor kappa β (NF-kβ)/MMP-9 pathway via down-regulating IKK-β, which is the upstream regulator of NF-kβ, and it has proven a bona fide target of miR-218.[166] Moreover, NF-kβ is a vital member of NF-kβ pathway and the level of numerous NF-kβ-regulated genes were elevated.[167] In addition, EGFR-coamplified and overexpressed protein (ECOP) was confirmed as a key regulator of NF-kβ signal,[168] and research demonstrated that transfection with miR-218 could induce apoptosis in glioma cells and inhibit tumorigenicity by targeting ECOP, and not only inhibit NF-kβ activity but also suppress the expression of its downstream target genes such as B cell lymphoma (BcL)-xL, MYC, and CCND1.[167]

In addition, oncogenic transcription factor lymphoid enhancer-binding factor 1 (LEF1) was another target of miR-218. Liu *et al.*[169] showed that miR-218 was down-regulated in glioma tissues, and its level was especially low in GBM, and miR-218 could reverse high invasiveness of GBM cells by targeting the oncogenic transcription factor LEF1 and blocking the invasive axis, miR-218-LEF1-MMPs. The MMP family is downstream effectors of the Wnt/LEF1 pathway.

Our previous study has found that miR-218 could inhibit glioma invasiveness, migration, proliferation, and cancer stem-like cell self-renewal by targeting the polycomb group gene Bmi1.[170] Recent research indicated that GBM, especially the mesenchymal GBM, is a highly malignant tumor which frequently exhibits regions of severe hypoxia and necrosis, and tumor hypoxia that has been associated with chemoresistance. MiR-218 up-regulated in mice harboring intracranial tumors could reduce tumor burden observably, and also increase survival when treated with the chemotherapeutic agent TMZ. Furthermore, down-regulated miR-218 increases the expression of multiple components of RTK signaling pathway, which enhances the activation of HIF, HIF2α in particular, suggesting that an miR-218-RTK-HIF2α signal axis could promote GBM cell survival and tumor angiogenesis.[171]

miR-181 cluster

The miR-181 family, including miR-181a, miR-181b and miR-181c, was reported down-regulated in human gliomas,[72,125] suggesting that these miRNAs may act as tumor suppressors in gliomas. Research demonstrated that the level of miR-181a was inversely related to the tumor grade, but down-regulated miR-181b was only detected in grade II–IV astrocytomas,[172] and the level of miR-181c in gliomas seems to be similar to normal brain tissue.[125] Numerous studies revealed that GBM transected with miR-181a and miR-181b, could inhibit cell growth and invasion, induce apoptosis and lose the ability of anchorage-independent growth.[125,172]

The radiation and chemotherapy resistance are two knotty problems in glioma treatment and contribute to the poor prognosis of gliomas. Chen *et al.*[173] illustrated that transiently overexpression of miR-181a could notably elevate the sensitivity of malignant glioma U87 MG cells to radiation treatment concurrent with the down regulation of protein Bcl-2/leukemia-2, which suggested that Bcl-2 could act as a target of miR-181a in gliomas. TMZ resistance is also a troublesome problem in glioma therapy. Research showed that up regulation of miR-181 family could enhance the chemo-sensitivity of TMZ in glioblastoma cells by targeting Rap1B-mediated cytoskeleton remodeling, and overexpression of these miRNAs could suppress invasive proliferation of glioblastoma cells.[174] Gong *et al.*[175] also demonstrated that aplysin could enhance TMZ sensitivity in glioma cells by increasing miR-181 level, which exhibit antitumor activity via inducing apoptosis and cell cycle arrest. Recently, a study indicated that miR-181 could inhibit glioma cell proliferation by targeting cyclin B1, which is a positive cell - cycle regulator, the authors illustrated that transfection with miR-181 could inhibit cell proliferation in U251 and SHG-44 cells.[176]

Other microRNAs down-regulated in glioma

Furthermore, targets and functions of novel miRNAs such as miR-326, miR-214, miR-31, miR-142-3p, miR-205, miR-297, miR-326, miR-622, and miR-708, are reported in at least in one study [Table 2]. There are two studies reported that miR-326 was down-regulated in human glioma, and overexpression of miR-326 could act as a suppressor of Hedgehog signaling pathway, and reduce cell proliferation, viability and invasiveness in glioma by targeting SMO.[177,178] miR-214 has been reported down-regulated in gliomas, and it played a vital role in tumor cell proliferation, migration, invasion, and tumor angiogenesis by targeting ubiquitin-conjugating enzyme 9.[179] Zhang *et al.*[180] found that miR-622 is significantly down-regulated in glioma tissues and cell lines; overexpression of miR-622 could suppress proliferation, invasion, and migration by directly targeting activating transcription factor 2. A study also showed that miR-203 down regulation was associated with unfavorable prognosis in human glioma.[181] miR-297 could inhibit invasiveness and tumorigenicity of GBM by targeting diacylglycerol kinase alpha,[182] and miR-708 would also act as tumor suppressor in human glioblastoma cells.[134] All of these studies have indicated that these miRNAs could act as tumor suppressors of glioma.

MicroRNAs with disputed levels of expression in glioma

In addition to the series of miRNAs up or down-regulated in glioma, which have been confirmed by multiple studies mentioned above, there are still miRNAs with unclear levels and obscure function in glioma. Here, we will discuss two kinds of these disputed miRNAs in detail.

miR-184

miR-184 is known to play a key role in neurological development and apoptosis, but whether the level of miR-184 is up or down-regulated in glioma remains disputed. MiR-184 was reported to be down-regulated by Emdad *et al.*[199] who demonstrated that the level of miR-184 was decreased in malignant glioma compared with normal brain tissue. SND1 is known to be over-expressed in human glioma tissue, and its level exhibited a negative correlation with miR-184. Transfecting with miR-184 or knockdown of SND1 could inhibit invasiveness of glioma cells and suppress colony formation, reduce anchorage-independent growth in soft agar, and significantly improved survival of tumor-bearing mice. Finally, the authors indicated that miR-184 acted as a tumor suppressor in glioma by targeting SND1. In keeping with this study, Malzkorn *et al.*[144] also indicated that up regulation of miR-184 in A172 and T98G glioma cells significantly decreased ($P < 0.05$) cell viability and proliferation. miR-184 also reduced invasiveness in matrigel assays of T98G cells. Remarkably, overexpression of miR-184 could increase apoptotic activity in A172 cells, but decrease apoptotic activity in T98G cells. In addition, another two research studies showed that miR-184 could inhibit neuroblastoma cell survival by targeting the serine/threonine kinase AKT2, which is a major downstream effector of the PI3K pathway.[200,201]

Nevertheless, contradictory to these studies, Foley *et al.*[202] indicated that up regulation of miR-184 could enhance the malignant biological behavior of human glioma cell line A172 by targeting FIH-1. They showed that miR-184 was significantly up-regulated in human glioma by HIF-1α. They verified that down regulation of miR-184 could inhibit cell viability and increase the HEB cell apoptotic rate by targeting FIH-1, which was confirmed as a negative regulator of HIF-1α. In line with this study, there is also a study which showed that overexpression of miR-184 could promote the cell proliferation capacity of glioma cell U87 and T98G by regulated FOXO3.[203] Moreover, miR-184 level was significantly high in hepatocellular carcinoma (HCC), where it acted as an oncogenic regulator in HCC,[204,205] and it played the same role in squamous cell carcinoma of tongue.[206] Whether the level of miR-184 is up- or down-regulated in human glioma needs further investigation, and how miR-184 participates in the regulatory network in glioma needs in-depth research.

miR-145

MicroR-145 is another miRNA which has been confirmed disputed level in glioma.[27,207-209] There are two studies which indicated that miR-145 was down-regulated in glioma.[27,207] Lee *et al.*[27] showed that overexpression of miR-145 could decrease proliferation and invasion in glioma. They also found when inserting miR-145 expression cassette into herpes simplex virus tk-expressing adenoviral vector, and transfected that recombinant vector into mice, the survival of the mice was improved. In line with these studies, another research study indicated that up regulating miR-145 could increase the sensibility of radiotherapy and chemotherapy by targeting Oct4 and Sox 2.[216] To strengthen this observation, Rani *et al.*[207] demonstrated that miR-145 could act as a tumor suppressor by targeting Sox 9 in human glioma cells. On the contrary, Koo *et al.*[209] indicated that miR-145 was up-regulated in highly invasive GBM cell lines, and decrease miR-145 expression could inhibit invasiveness of GBM cell. Therefore, whether miR-145 is down- or up-regulated in glioma also needs further investigation, and to illuminate the mechanism of how miR-145 works in glioma could be significant in the treatment of gliomas.

THERAPEUTIC POTENTIAL OF MICRORNAS IN GLIOMA

The study demonstrated that the expression profile of miRNAs is prominently different between glioma tissue and normal brain tissue, which suggests a novel biomarker for diagnosis and therapy of glioma. Moreover, the specific deregulation of miRNAs in tumor cell lines compared with normal cells indicates that these specific miRNAs can act as candidates of tumor diagnostic biomarkers and in human glioma. Through analyzing the miRNA expression profile in colon cancer, liver cancer, pancreatic cancer, and stomach cancer specimens, researchers found these tumor miRNA expression profiles are markers of tumor grade.[210]

Recent studies have shown that miRNAs have significant value for diagnosis, prognosis and therapy. For instance, up regulation of miR-21 is closely related to the high level of Ki-67 and metastasis of liver cancer.[211] In pancreatic adenocarcinoma, patients with high level of miR-196-a-2 whose median survival was only 14.3 months, had far higher levels than patients with low miR-196-a-2 level whose median survival was up to 26.5 months,[212] suggesting that miR-196-a-2 can predict survival rate. MiR-15b overexpression is closely involved in tumorigenicity and poor prognosis of melanoma,[213] low levels of miR-26 is associated with shorter overall survival in liver cancer patients.[214] There are numerous studies showing that miRNAs expression profile not only plays a crucial role in diagnosis, but also can estimate the prognosis.[61] Nevertheless, it is certain that miRNA can be a molecular target for therapy.[33,43-45,215,216] Wong *et al.*[217] have reported that

concomitant treatment with miR-21 inhibitor and TMZ results in a significant higher apoptotic rate than TMZ treatment alone, and thus transfection with anti-miR-21 oligonucleotide could decrease TMZ-resistance in GBM. Griveau *et al.*[218] indicated that locked nucleic acid-lipid nanocapsule complexes (LNA–LNCs) could sensitize human glioblastoma cells to radiation-induced cell death by silencing miR-21, and showed newly developed LNCs represented an interesting tool to convey LNAs within GBM cells to silence well-defined miRNA pathways. This will trigger beneficial synergistic effects to overcome radio-resistance.

Molecular therapy is developing rapidly in oncotherapy because of its lower toxicity and adaptability to personalization.[219] This kind of therapy still needs detailed study of the mechanism of action. miRNAs could block the biological signaling pathway by inhibiting the expression of its key molecular targets, which participate in vital metabolism regulation in organism. The molecular therapy of glioma is divided into molecular diagnosis and therapy.[220] A number of miRNAs play a crucial role in new strategies for tumor molecular therapy. Nevertheless, delivery of miRNAs to the central nervous system is a big challenge due to a multitude factors such as the blood-brain barrier, blood components and the reticular endothelial tissue uptake (reticuloendothelial system), the extracellular matrix, and intracellular obstacles. In spite of these problems, many improved cellular delivery strategies are developing rapidly. For instance, delivering oligonucleotides directionally via lipid capsule,[221,222] the recombinant adeno-associated virus can penetrate the blood-brain barrier when transferring endogenous miRNAs.[222] The method to transfer miRNAs which serve as tumor suppressors in glioma still needs further investigation. Success will relieve the suffering of the patients and improve poor prognosis.

In conclusion, glioma is the most frequent and malignant brain tumor, and recently, researchers found that miRNAs play a crucial role in glioma pathogenesis. However, whether the occurrence and development of cancers have caused the deregulation of miRNAs or the aberration of miRNA gives rise to tumor and deterioration still needs further investigation. miRNA is a negative regulator, which could decrease gene levels at the posttranscriptional level and function as a tumor suppressors or oncogenes in human glioma. In this paper, we reviewed 43 kinds of miRNAs deregulated in glioma, which could regulate the key molecules participating in the occurrence and development of glioma, are involved in glioma cell proliferation, invasiveness, migration, apoptosis, and prognosis, and affect the radiation and chemotherapy resistance of glioma. miRNAs could be a new biomarker in pathology, which suggests a novel strategy for diagnosis and therapy of glioma.

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