

MicroRNAs in human glioblastoma: from bench to bedside

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1. ABSTRACT

Glioblastoma (GBM) is the most common and malignant adult primary brain tumor and one of the most lethal types of all cancers. Currently, despite interventional therapy (e.g. multimodal treatments with surgery, radiotherapy and chemotherapy), the overall prognosis for GBM patients remains poor. Thus, it is necessary to understand the molecular pathogenesis of GBM, which provides new insight into modern therapy. As a novel molecule, microRNA (miRNA) contributes to the pathogenesis of various types of tumor, including GBM. So far, miRNA has been shown to function in regulating protein-coding gene expression. This allows miRNAs to have direct function in regulation of various cellular events, including cell proliferation, apoptosis, and differentiation. Great progress has been made in identifying novel tumor-related miRNAs and their potential target genes. In this review, we focus on the most current research in miRNAs and their role in GBM regulation. In addition, we summarize some miRNAs found as biomarkers in GBM and their role in treatment.

2. INTRODUCTION

Glioblastoma (GBM) is the most common and aggressive type of glioma (1). It has many features, including a short post-diagnosis lifespan, high recurrence rate, and high mortality rate (2). In addition,

GBM characterized by high levels of cellular and molecular heterogeneity has a high level of resistance towards chemo- and radiotherapy (3, 4). Even with the most current therapeutic regimen, including maximal and safe surgical resection followed by adjuvant chemotherapy and radiotherapy, the prognosis of GBM has barely increased, with a median survival of only 12–15 months (2). Thus, it is necessary to explore the changes at the molecular level in GBM, which may provide novel strategies for treatment.

miRNAs belong to the family of non-coding RNAs, which are about 22 nucleotides in size and mostly suppress gene expression at the post-transcriptional level (5). Via negatively modulating the translation process and targeting mRNA stability (6), miRNAs affect thousands of endogenous mRNA targets, which act in concert to regulate various cell events, including proliferation, development, differentiation, and apoptosis (7, 8). For example, miRNA is a key factor required to coordinate precisely the gene regulatory networks in nervous system development. Although some miRNAs are in charge of neuron differentiation (9), others are involved in neuron maturation (10). Misexpression of some brain-specific miRNAs has been found to contribute towards neurodevelopmental disorders (11). miRNAs have also been suggested to regulate cancer pathophysiology, including development,

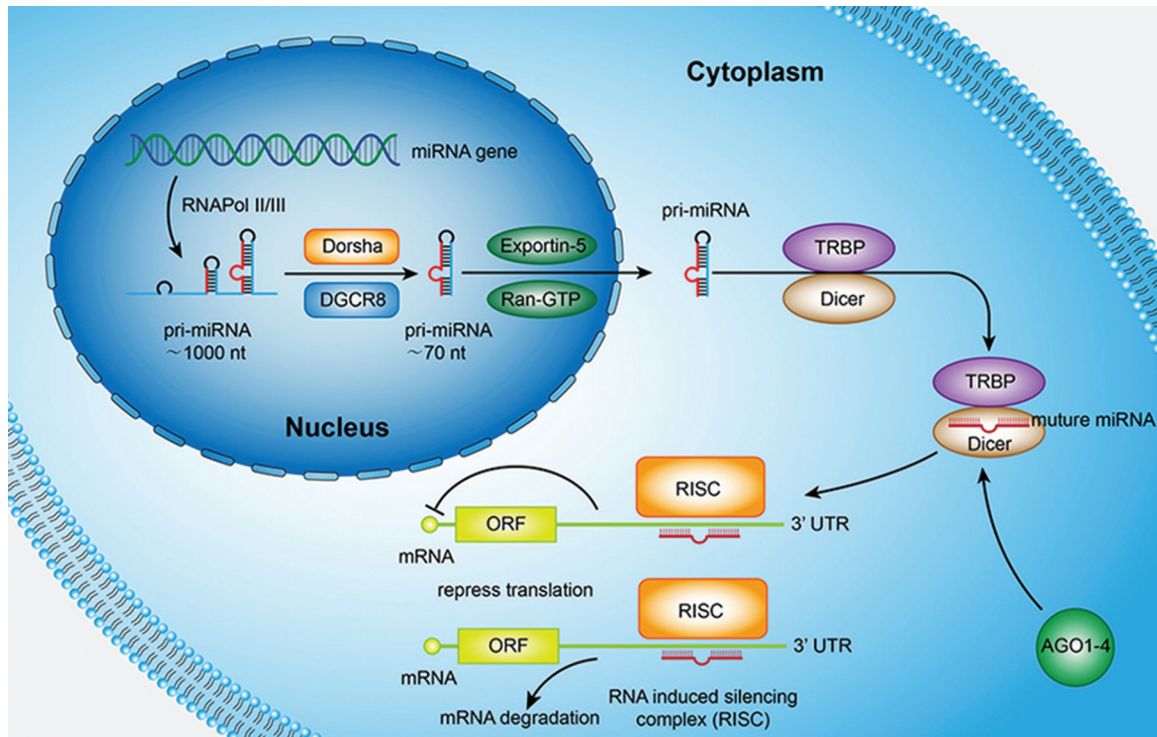


Figure 1. miRNA biogenesis in GBM. miRNAs are transcribed by RNA polymerase II/III to form primary miRNAs (pri-miRNA). These pri-miRNA transcripts are cleaved by the Drosha/DGCR8 complex to yield pre-miRNA, which is transported out of the nucleus and processed through modifications by RNase III, Dicer/TRBP and Ago2 to generate miRNA duplex. The miRNA duplex is unwound into a mature single-stranded miRNA, and assembled into the RNA-induced silencing complex (RISC). The RISC searches for its complementary mRNA via the inside miRNA and eventually degrades the corresponding mRNA

progression, recurrence, metastasis and resistance to treatment (12). Furthermore, miRNA can also function as a tumor suppressor gene, oncogene, or both, depending on the cell context (12), and is closely correlated with cancer profiling and treatment resistance (13, 14). Similarly, in the central nervous system, the relationship between glioma pathobiology and miRNA seems to be close (15-17).

In this paper, we review some of the most recent findings on miRNAs and their function in GBM formation and progression, decipher specific miRNA candidates, presenting the significance of exploring new mechanisms, and that could be used for prognostic purposes, and discuss miRNA-based therapeutic approaches for GBM.

3. BIOGENESIS OF miRNAs IN GBM

In order to understand the context of miRNA in GBM pathology, we first introduce the physiological features of miRNA and its working

mechanisms (Figure 1). miRNAs are small RNA molecules that consist of 20–22 nucleotides (18). Biogenesis of miRNA begins with transcription by RNA polymerase II or RNA polymerase III, producing primary miRNA (pri-miRNA) (19, 20). The pri-miRNA contains various numbers of hairpin structures with flanking single-stranded upstream and downstream regions (Figure 1). The hairpin structure of the pri-miRNA is then cleaved by the complex comprising of Drosha and its interacting partner, DiGeorge syndrome critical region gene 8 (DGCR8), to yield a ~70-nucleotide precursor miRNA (pre-miRNA), which subsequently is actively transported out of the nucleus (19, 21). In the cytoplasm, pre-miRNA is processed through a series of modifications by RNase III endonuclease, Dicer/TRBP (the double-stranded RNA binding factor) and Ago 2 (Argonut protein 2) to generate a ~22-nucleotide miRNA duplex (20). The miRNA duplex is unwound into a mature single-stranded miRNA (one of the strands) by a helicase, and only the functional

strand is assembled into the RNA-induced silencing complex (RISC) (7, 22) (Figure 1). The RISC searches for its complementary mRNA via the inside miRNA and eventually degrades the corresponding mRNA (7), which positively or negatively regulates an array of cellular processes, for example, proliferation, death, metastasis, invasion, and angiogenesis (23-25).

4. IDENTIFICATION OF SPECIFIC miRNAS IN NETWORK FOR GBM PATHOGENESIS

GBM development is closely linked to abnormal epigenetic regulation in genes that are initially in charge of cell physiological processes, including growth, proliferation and apoptosis, and recently, three core signaling pathways (receptor tyrosine kinase (RTK)/RAS/phosphatidylinositol 3-kinase (PI3K), p53 and retinoblastoma protein (RB) signaling pathways) were identified to be responsible for malignant process of the tumor, by The Cancer Genome Atlas (TCGA) (26). Some studies have indicated that, through their ability to regulate a large number of genes, miRNAs have generated interest in explaining the control of diverse oncogenic signaling pathways to regulate multiple critical functions in GBM (27, 28). Thus, identification of the targets of miRNAs and elucidation of the complex miRNA–mRNA network could greatly help us to understand role of miRNAs during GBM pathogenesis.

4.1. EGFR/PTEN/PI3K/AKT signaling pathways

The epidermal growth factor receptor (EGFR)/AKT/PI3K signaling pathways have been shown to contribute to human GBM pathogenesis (26). Stimulation of the EGFR leads to activation of its downstream effectors that initiate tumor growth, survival, angiogenesis and progression (29). Although this activation pathway is held in check by the phosphatase and tensin homolog (PTEN) protein, PTEN mutations are frequent in GBM, which makes the PI3K/AKT pathway constitutively active (30, 31). Recently, involvement of miRNAs in these core signaling pathways for regulation of GBM cell events has also been demonstrated by mechanistic studies. For example, among important components of the EGFR signaling pathway are mRNA targets of miRNA miR-21, which is upregulated in GBM (32). An *in vitro* study found decreased expression of EGFR and activated AKT independent of PTEN status in GBM cell lines U251 (mutant PTEN) and

LN229 (wild-type PTEN) treated by miR-21-specific antisense oligonucleotide, although previous research has found that downregulation of miR-21 could lead to higher PTEN expression (33, 34).

Another miRNA involved in the EGFR signaling is miR-34a. Yin *et al.* reported that miR-34a can target Yin Yang (YY)1, which is a transcription factor stimulating the expression of EGFR, and forced expression of miR-34a in GBM cells markedly downregulates EGFR expression mediated by YY1, decreases cell migration, profoundly decreases expression of key cell cycle regulatory proteins including cyclin-A1, -B1, -D1 and -D3, and increases expression of cyclin kinase inhibitor proteins (p21 and p27). These data suggest that miR-34a acting as a tumor suppressor inhibits GBM cell growth by moderating the expression of EGFR and cell-cycle proteins (35).

Modulation of EGFR expression using miRNA in glioma cells has also been described by Lu *et al.* (36). Previous studies demonstrated ADAM (a disintegrin and metalloprotease) 17 as a primary upstream component for multiple EGFR pro-ligands and found that ADAM17 overexpression can contribute to glioma progression (37-39). In that study, the authors showed that miR-145 was a tumor suppressive miRNA and its overexpression in glioma cells reduced EGFR and ADAM17 protein expression, however, mRNA expression of EGFR and ADAM17 was unaltered. These data revealed that miR-145 targets ADAM17 and EGFR by post-transcriptional repression. Furthermore, miR-145 also significantly decreased p-extracellular signal-regulated kinase expression, which is a downstream protein involved in EGFR signaling. Taken together, miR-145 exerts anti-glioma effects through the ADAM17/EGFR/ERK signaling pathways (36).

In addition, Tian *et al.* have shown that miR-451, which has a repressive role and is downregulated in glioma, inhibits the calcium binding protein 39 gene (CAB39) expression via its 3'-untranslated region. Moreover, transfection with miR-451 mimics activated phosphorylated-AKT in U251, LN229, A172 and U87 cells, and overexpression of miR-451 markedly downregulates liver kinase B (LKB) 1, AMPK, p-AMPK and PI3K; all of which are factors upstream of the AKT pathway, and as well as CAB39, are downregulated in glioma xenografts. Additionally, CAB39 is an element of the trimeric LKB1–STRAD (STe20-Related ADaptor)–MO25 (Mouse protein 25) complex and functions to

stabilize the binding of STRAD to LKB1 and mediates LKB1 translocation (40-42). It has been concluded that miR-451 suppression of glioma *in vivo* and *in vitro* might be through direct targeting of CAB39 and indirect inhibition of the PI3K/AKT pathway (43).

Finally, a recent study has demonstrated that miR-7 could directly inhibit EGFR expression and antagonize downstream protein kinases such as ERK, AKT and signal transducer and activator of transcription (STAT)3 in glioma (44). However, miR-7 also represses the AKT pathway via targeting upstream regulators including insulin receptor substrate (IRS)-1 and IRS-2 independent of EGFR inhibition (45). In addition, enhancing miR-7 levels *in vitro* could significantly decrease glioma cell proliferation and invasiveness (44, 45).

4.2. p53 signaling pathway

p53 signaling is associated with several cellular programs, including cell-cycle arrest, response of cells to DNA damage, senescence, apoptosis, and differentiation (46, 47). When cells are under genotoxic and cytotoxic stress, p53 executes functions as a transcription factor to regulate expression of downstream effector genes including miRNA to determine cell fate (48-50). p53 mutations have been linked to clonal expansion of glioma cells (51), and the frequency rate is ~30% of all gliomas irrespective of tumor grade (52).

Previous studies have shown that miR-34a that is also involved in EGFR signaling is transcriptionally regulated by p53 and functions downstream of the p53 pathway as a tumor suppressor (35, 53, 54). Li *et al.* have reported that miR-34a expression is markedly reduced in GBM tissues compared with normal brain, and in mutant p53 glioma as compared to wild-type p53 glioma (55). Their experiment assaying the effect of p53 on miR-34a activity has shown that wild-type p53 but not mutant p53 downregulates normalized miR-34a luciferase activity, which indicates that mutant p53 does regulate miR-34a transcription. The role of miR-34a in glioma has been demonstrated *in vivo* and *in vitro*, and that this miRNA could inhibit GBM growth by targeting multiple oncogenes including c-MET and Notch (55).

Another miRNA found as a transcriptional target of p53 is miR-107, which is also downregulated in glioma tissues and cell lines; particularly in the p53-mutant glioma cells. The differences in miR-107 expression between wild-type and mutant p53 gliomas may be explained by the theory that, in

wild-type p53 cells, more p53 protein binds to the promoter region of miR-107, which leads to increased miR-107 expression. Similarly, p53-induced miR-107 acts as a tumor suppressor to inhibit glioma cell growth and downregulates expression of oncogenes CDK6 and Notch-2 (48).

The p53 signaling pathway may also be regulated by miRNAs (56). For example, miR-21 also targets p53, transforming growth factor- β and mitochondrial apoptotic networks, and these pathways are de-repressed in response to miR-21 knockdown, which leads to inhibition of GBM cell growth (57).

Moreover, transcription factor E2F1, which is present in many tumors, may modulate p53 expression (58), and this factor is found to be a direct functional target of antitumor miR-106a. Yang *et al.* have reported that low expression of miR-106a in glioma tissues is significantly correlated with high levels of E2F1 protein and high-grade glioma, and miR-106a can increase p53 expression via inhibition of E2F1 (59). However, the effect of miR-106a on proliferation of glioma cells is independent of p53.

4.3. RB signaling pathway

RB is a tumor-suppressor gene that inhibits entry of cells through G1 into the S-phase of the cell cycle (46). When phosphorylated by cyclin D, cyclin-dependent kinase (CDK)4 and CDK6, RB is inactive, resulting in disallowing progression through the cell cycle (51).

Wang *et al.* have found downregulation of miR-195 in glioma cell lines and human primary glioma tissues when compared to miR-195 expression in normal human astrocytes and normal brain tissues (59). This study has also demonstrated that miR-195 can inhibit glioma cell proliferation by directly targeting cyclin D1 and cyclin E1. Cyclin D1, cyclin E1 and phosphorylated RB (pRB) are known to orchestrate cell cycle progression, and functional interaction between cyclin D1, cyclin E1 and pRB plays a vital role in cancer cell growth and tumorigenesis (60, 61). Forced overexpression of miR-195 downregulates pRB and dramatically reduces the proliferation of glioma cells. Conversely, inhibition of miR-195 promotes cell proliferation, increases the percentage of S phase cells, and upregulates the phosphorylation of RB (59).

More than three target prediction databases indicate that all members of the RB family, including

RB1, RBL1 and RBL2, are targets of miR-106b (<http://mirecords.biolead.org/>). However, Zhang *et al.* have reported that RBL2 is the only member that is directly regulated by miR-106b, which is expressed at higher levels in glioma cells (63). They have also demonstrated that miR-106b may exert an oncogenic effect by promoting cell-cycle progression through the negative regulation of the downstream targets of miR-106b, especially RBL2 and p21, which participate in cell regulation (62).

Another miRNA involved in the RB signaling pathway is miR-495. Chen *et al.* have reported that overexpression of miR-495 can downregulate CDK6 expression and inhibit RB phosphorylation to suppress proliferation of GBM cells, while CDK6 is significantly expressed in GBM specimens and miR-495 is downregulated in glioma tissues (63).

Finally, Qiu *et al.* have identified a tumor-suppressive miRNA, miR-138, which is downregulated in both GBM clinical specimens and cell lines (65). miR-138 can exert a potent antitumor effect by inhibiting oncogene enhancer of zeste homolog (EZH) 2, as well as CDK6, E2F2 and E2F3. Moreover, a signal loop, EZH2-CDK4/6-pRB-E2F1, mediated by EZH2 is probably involved in GBM carcinogenesis, and this loop can be blocked by miR-138 (64).

5. miRNAs AS POTENTIAL PROGNOSTIC BIOMARKERS AND THERAPEUTIC TARGETS IN GBM

The extensive biological heterogeneity of GBM has great significance for the general prognosis of the malignancy, resulting in varied median survival that ranges from 1 week to several years after diagnosis (65, 66). Unfortunately, there is no thorough understanding yet of the prognostic factors affecting survival, which indicates the difficulties in the choice of therapeutic strategies using current clinicopathological determinants. With the development of genome-wide screening, investigation into the roles and expression patterns of miRNAs in GBM has provided significant insights into these molecules, and detecting differences in miRNA in GBM might help to overcome some of those limitations.

Recent progress has suggested that miRNAs are attractive candidates as prognostic biomarkers in glioma and several studies have shown an association between miRNA expression levels and prognosis of the malignancy. For instance,

increased expression of each of miR-9 (67), miR-17 (68), miR-182 (69), miR-224 (70), miR-335 (71), miR-372 (72) and miR-650 (73) has been demonstrated to predict poor prognosis in glioma patients, while miR-203 (74), miR-375 (75) and miR-328 (76) downregulation correlate with worse survival. In addition, Guan *et al.* have found that the combination of high miR-196a and miR-196b expression is associated with shorter overall survival in GBM (77). However, a later study has found that upregulation of miR-195a and miR-196b could indicate better prognosis of GBM patients, which contradicts the results of Guan *et al.* in terms of miR-196b (78). This may have been due to the difference in sampling and statistical analysis, which indicates that future improved evaluation will require standardization of methods and normalization.

Bioinformatics strategies have also been applied to establishing prognosis-related miRNAs. Wei *et al.*, using multivariate Cox analysis, found a specific five-miRNA signature (miR-181d, miR-518b, miR-524-5p, miR-566, and miR-1227) in GBM that was an independent prognostic biomarker after adjusting for other clinicopathological and genetic factors, such as extent of resection, temozolomide chemotherapy, preoperative Karnofsky performance status score, isocitrate dehydrogenase 1 mutation, and O-6-methylguanine DNA methyltransferase (MGMT) promoter methylation status (79). Srinivasan *et al.* set up a study that mined expression data based on 305 miRNAs from 222 GBM patients in the TCGA data set and identified a 10-miRNA signature that independently predicted survival (hsa-miR-20a, hsa-miR-106a, hsa-miR-17-5p, hsa-miR-31, hsa-miR-222, hsa-miR-148a, hsa-miR-221, hsa-miR-146b, hsa-miR-200b, and hsa-miR-193a) (80). Notably, none of the identified miRNAs overlapped in the two studies. More remarkably, a more recent study by Li *et al.*, also analyzed data in TCGA and reported some other novel prognostic miRNA signatures in five molecular subtypes of primary GBM (classical, neural, mesenchymal, proneural-G-CIMP and proneural-non G-CIMP). And they found patients with high-risk scores (which were calculated based on the expression of respective miRNA signature) had poor overall survival compared with patients with low-risk scores. The prognostic miRNA signature for the Mesenchymal subtype (four risky miRNAs: miR-373, miR-296, miR-191, miR-602; one protective miRNA: miR-223) was further validated in an independent cohort containing 41 samples, which obtained the same results (81). All of these indicated that prognosis stratification in GBM based on miRNAs

Table 1. Select miRNAs and their functional role, targets, and expression in GBM

miR	Functions	Targets	Expression pattern	Reference
miR-7	Migration(-), Invasion(-), Proliferation(-)	EGFR, IRS1/2	Down	(44, 45)
miR-21	Growth(+), Proliferation(+), Apoptosis(-)	PTEN, HNRPK, TAp63	Up	(33, 57)
miR-34a	Growth(-), Proliferation(-), Invasion(-), Migration(-)	c-Met, Notch1/2, YY1/EGFR pathway	Down	(35, 55)
miR-106a	Apoptosis(+), Proliferation(-), glucose uptake(-)	E2F1/p53, SLC2A3	Down	(90, 91)
miR-106b	Growth(+)	RBL2, p21	Up	(62)
miR-107	Proliferation(-), Growth(-), apoptosis(+)	CDK6, Notch-2, SALL4	Down	(48, 92)
miR-138	Proliferation(-), cell cycle arrest(+)	EZH2, CDK6, E2F2, E2F3	Down	(64)
miR-145	Invasion(-), Migration(-), Proliferation(-)	ADAM17/EGFR/ERK pathway	Down	(36)
miR-195	Proliferation(-)	Cyclin D1, Cyclin E1	Down	(59)
miR-451	Cell growth(-), Proliferation(-), apoptosis(+)	CAB39, PI3K/AKT pathway	Down	(43)
miR-495	Proliferation(-), Growth(-)	CDK6, pRB	Down	(63)
(+) = increased, (-) = decreased				

expression profiles could provide new approaches in the evaluation of the clinical outcomes and selection of the gene therapy targets.

As the results of years of effort begin to show the effects of miRNAs in GBM, researchers have revealed that miRNAs are not only putative biological markers for prognosis, but also one of the potentially effective therapeutic targets. Given that the loss of tumor-suppressive miRNAs and upregulation of oncogenic miRNAs are associated with various stages of GBM development, forced expression of silenced miRNAs and suppression of overexpressed miRNAs may present a promising therapeutic strategy. Recent advances in targeting miRNAs *in vitro* have promoted the evaluation of miRNAs in GBM treatment. In one study, miRNA-23a was shown to be upregulated in glioma, and inhibiting this miRNA by anti-miRNA-23a oligonucleotide significantly suppressed glioma cell growth (82). Given the oncogenic activity of miRNA-30a-5p in glioma, Jia *et al.* knocked down miRNA-30a-5p with antisense oligonucleotide in LN229 and SNB19 GBM cells and found that tumor cell growth and invasion were inhibited and apoptosis was induced (83). Moreover, co-inhibition of miRNA10b and miRNA-21, which are both significantly elevated in GBM, was found to exert synergistic inhibition on the proliferation and invasion of U87 GBM cells, and combination of these miRNA inhibitors could be an effective therapeutic strategy for controlling tumor growth (84).

In addition, miRNA-based therapy might be able to increase the efficacy of conventional chemotherapy and radiotherapy (85), for example, suppression of miRNA-21 in U251 and LN229 GBM cells resulted in sensitization of tumor cells to taxol (34). Dysregulation of miRNAs is associated with GBM treatment resistance (Table 2), therefore, combination of miRNA-targeted therapy with conventional therapies has the potential to create a synergistic effect against chemo- or radio-resistant GBM (86).

Progress has also been made in the investigation of delivery of miRNAs or antagomirs to target sites. A wide range of delivery systems based on chemical modification, liposomes, polymers, hydrogels and nanoparticles has been investigated in miRNA delivery (87). Recently, a miRNA-21 inhibitor (antisense oligonucleotides) was successfully delivered by poly (amidoamine) (PAMAM) dendrimer nanoparticles to glioma cells, as well as 5-fluorouracil and miR-21 inhibitor simultaneously loaded in the PAMAM dendrimer (88). Similarly, polyurethane-short branch polyethylenimine (PU-PEI) as a vehicle to deliver miR-145 into glioma cells was tested effectively in CD133-positive GBM cells (89). Furthermore, *in vivo* studies have shown positive results, taking advantage of cholesterol-conjugated antisense oligonucleotides and PAMAM-carried tumor-suppressive miRNA oligonucleotides against xenografted glioma in animal models (85).

Table 2. Summary of miRNAs related to sensitivity to radiotherapy or chemotherapy in GBM

miRNA	Up-/Down-regulation	Effective on sensitivity	Reference
miR-7	Down	Down (Radiotherapy)	(93)
miR-21	Down	Up (Radiotherapy & Chemotherapy)	(34, 88, 94, 95)
miR-100	Up	Up(Radiotherapy)	(96)
miR-125b-2	Down	Up (Chemotherapy)	(97)
miR-145	Up	Up (Radiotherapy & Chemotherapy)	(89)
miR-181a	Up	Up(Radiotherapy)	(98)
miR-195	Down	Up (Chemotherapy)	(99)
miR-328	Down	Up (Chemotherapy)	(100)
miR-451	Up	Up (Chemotherapy)	(101)
miR-455-3p	Down	Up (Chemotherapy)	(99)

However, significant challenges remain in the application of miRNA regulation to patient therapy, and no trials have been performed with glioma, which suggests that significant progress remains to be made. The use of miRNA-targeted therapeutic modalities presents the potential risk of affecting RNA species other than the intended miRNA target, which calls for safety demonstrations in future development of miRNA-based therapeutics.

6. CONCLUSION AND FUTURE DIRECTIONS

As the miRNA field evolves, new findings over the past few years have demonstrated that deregulation of miRNA expression is an integral process in GBM pathogenesis. miRNAs cover almost all aspects of GBM, including initiation and progression, as well as therapy and prognosis.

These fascinating small regulators of protein synthesis have great potential for new therapeutic approaches and improved understanding of GBM. Despite the remarkable recent progress, the connection between GBM and miRNAs remains incompletely understood and many questions remain regarding the possible therapeutic application of miRNAs, such as how do miRNAs affect gene expression, and how is their dysregulation a crucial part of tumor formation, maintenance, and

metastasis? What are all the target genes of specific GBM-related miRNAs and can they be used to guide current therapies or in the development of novel therapies? Larger and in-depth studies are needed to understand more fully the mechanism of miRNAs involved in GBM, and to demonstrate the advantages of miRNAs for molecular classification, new strategies for formulation of miRNA-based drugs, and to aid with tailoring drugs with higher specificity.

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Abbreviations: GBM, Glioblastoma; miRNA, microRNA; DGCR8, DiGeorge syndrome critical region gene 8; pri-miRNA, primary miRNA; pre-miRNA, precursor miRNA; RISC, RNA-induced silencing complex; RTK, receptor tyrosine kinase; TCGA, The Cancer Genome Atlas; RB, retinoblastoma protein; EGFR, epidermal growth factor receptor; PTEN, phosphatase and tensin homolog; ADAM, a disintegrin and metalloprotease; CAB39, calcium binding protein 39 gene; LKB, liver kinase B; STAT, signal transducer and activator of transcription; CD, cyclin-dependent kinase; Prb, phosphorylated RB; PU-PEI, polyethylenimine

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