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Review

Roles of microRNAs during glioma tumorigenesis and progression

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Summary. Glioma is the most common and aggressive type of brain tumor. It has a poor prognosis and a high recurrence rate. Despite continued advances in surgery, chemotherapy and radiotherapy, the clinical outcomes remain dismal. MicroRNAs (miRNAs) play important roles in the initiation and progression of a multitude of tumors. Until now, the molecular mechanism that is responsible for glioma tumorigenesis and progression remains unclear. Increasing evidence has shown that miRNAs play an important role in glioma. In this review, we focus on the current advances in determining the role of miRNAs in regulating tumorigenesis and the progression of glioma. In addition, the relevant roles of miRNAs about the diagnosis and target therapy have been clarified.

Key words: Development, Glioma, Occurrence, miRNA, Diagnosis, Therapy

Introduction

The first microRNA (miRNA) was discovered more than 30 years ago in the nematode caenorhabditis elegans. miRNAs are small, non-coding RNAs that exert post-transcriptional regulation of gene expression and influence diverse biological activities (Lee et al., 1993; Wightman et al., 1993). All miRNA families undergo a series of biogenesis steps that convert the primary miRNA transcript into the active, ~22 nucleotide mature miRNA, The mature miRNA is loaded into the RNA induced silencing complex (RISC) where it directs the complex to target mRNAs, which leads to translational repression and target mRNA degradation. miRNAs play important roles in a wide variety of physiological and pathological processes including cancer. It was also reported that they regulate up to 60% of all mammalian genes. MiRNA play crucial roles in regulating cell behavior and modulating gene expression at the post-transcriptional level by binding to mRNA and suppressing translation. Studies have revealed that a single miRNA can regulate hundreds of targets (Lewis et al., 2005; Helwak et al., 2013). They also have been associated with glioma formation and growth. Gliomas are the most common and deadly malignant primary brain tumors. They are highly invasive and migrate into the normal brain parenchyma along vessels and white matter fiber-tracts. Despite multimodal treatment options including surgery, radiation and chemotherapy, patients with glioma have an overall poor outcome. According to the World Health Organization (WHO) classification of central nervous system tumors, brain gliomas are classified into grades I-IV, which partially indicates the degree of malignancy and prognosis. However, even gliomas of the same grade or histological type do not have identical prognosis. As described, miRNAs have diverse roles in regulating cancer cell function and pluripotency, the focus of this review will be circulating miRNA biomarkers for glioma and how they can be further studied to aid the successful treatment of this disease.

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Role of microRNAs in glioma

Hundreds of studies on miRNAs in gliomas indicated that various microRNAs(miRNAs) play important roles in glioma. Several of them, including miR-30, miR-105, miR-124, miR-130b, miR-140, miR-145, miR-181, miR-211, miR-302b, miR-342, miR-365, miR-373, miR-424, miR-485-5p, miR-489, miR-495, and miR-524 were down-regulated (Table 1), whereas several, such as miR-10b, miR-15a, miR-15b, miR-16, miR-17, miR-19a, miR-19b , miR-21, miR-23a, miR-25, miR-92b, miR-130b, miR-106b, miR-182, miR-193a-3p and miR-221/222, were upregulated in glioma tissue (Fig. 1, Table 2). These miRNAs are believed to collectively regulate one third of the genes in the genome. Different miRNA expression in gliomas have roles in the regulation of lots tumorigenic processes, including glioma cell proliferation, invasion, migration, progression, apoptosis and resistance to radiotherapy and chemotherapy (Fig. 2). The development of glioma is associated with a significant increase in the expression of pro-oncogenic miRNA and inhibition of miRNA with antitumor activities (Koshkin et al., 2014).

miRNA regulation in glioma

miRNAs as suppressors of glioma development

miR-124

miR-124 is down-regulated in glioma tissues, human glioma cell lines and GSCs (Silber et al., 2008; Lang et al., 2012; Wei et al., 2013). Three oncogenes, NRAS, PIM3 and SNAI2, are downstream targets of miR-124, which has been shown to regulate stem cell functions and is often up-regulated in glioma (Lang et al., 2012; Xia et al., 2012). Stable overexpression of miR-124 and knockdown of SNAI2 have inhibited the tumorigenicity and invasion of glioma cells in vivo (Xia et al., 2012). These findings suggest that miRNAs play an important role in CD133 positive cells from gliomas. Originally,

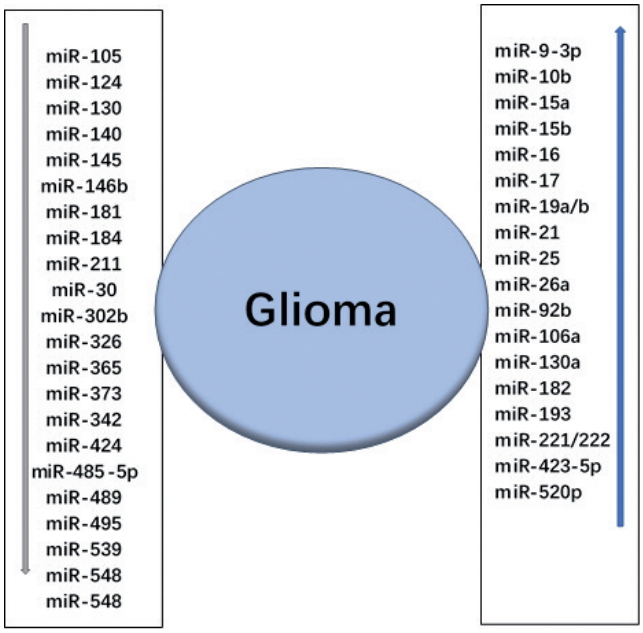

Fig. 1. miRNAs consistently deregulated in glioma. The most common overexpressed miRNAs in glioma are shown with an “up” arrow and downregulated - with a “down” arrow.

Table 1. miRNAs as suppressors of glioma development.

miRNA	Down-regulation	Target	Function	Reference
miR-105	Down	targeting SUZ12	inhibits human glioma cell malignancy	Zhang et al., 2017
miR-124	Down	R-RAS, N_RAS	Suppresses migration and invasion	Cai et al., 2017
miR-130b	Down	CYLD TAP63	Inhibits proliferation, invasion, and apoptosis	Su et al., 2010; Xiao et al., 2017
miR-140	Down	JAG1	Inhibits growth and invasion	Yang et al., 2017
miR-145	Down	Sox9 adducin3 ABCG2	Inhibits migration and invasion	Zhao et al., 2017
miR-181 cluster	Down	Bcl-2, cyclin B1	inhibits glioma cell proliferation enhances radiosensitivity and chemosensitivity	Ciafre et al., 2005; Shi et al., 2010; Liu et al., 2017
miR-211	Down	PTEN, p27, and p57	associated with poor prognosis	Zhang et al., 2017
miR-302b	Down	Cyclin D1, MMP2 and MMP9	correlates with tumorigenesis and unfavorable prognosis	Lv et al., 2017
miR-326	Down	NOB1 Notch	tumor suppressor	Chen et al., 2015
miR-365	Down	PIK3R3	Inhibits proliferation migration and invasion	Zhu et al., 2107
miR-342	Down	targeting PAK4	inhibits progression	Liu et al., 2017
miR-373	Down	TGFBR-2	Inhibits migration and invasion	Wei et al., 2016
miR-424	Down	CPG island	Tumor suppressor	Gao et al., 2017
miR-485-5p	Down	down-regulating TPD52L2	inhibits glioma cell proliferation and invasion	Yu et al., 2017
miR-489	Down	targeting SPIN1-mediated PI3K/AKT pathway	inhibits proliferation, cell cycle progression and induces apoptosis of glioma cells	Liu et al., 2017
miR-495	Down	CDK6	Inhibits proliferation and invasion	Chen et al., 2013
miR-539	Down	targeting DIXDC1	inhibits glioma cell proliferation and invasion	Quan et al., 2017

miR-124 was found to promote neuronal differentiation by targeting PTBP1, which encodes a global repressor of alternative pre-mRNA splicing, and triggering brain-specific alternative pre-mRNA splicing (Makeyev et al., 2007).

miR-130

TAp63 has been identified as a tumor suppressor that represses metastasis. In a study that involved both mouse and human tumor cell lines, Dicer and miR-130b were shown to be targets of TAp63. Binding of TAp63 to the Dicer promoter led to transcriptional activation. In addition to regulating Dicer, it was found that TAp63 targets miR-130b, which leads to its upregulation and decrease in invasion. Inactivation of TAp63 leads to increased metastasis and invasion. Dicer and miR-130b were shown to be targets of TAp63 (Su et al., 2010). Xiao et al. also reported that miR-130b inhibits proliferation, invasion, and apoptosis by directly

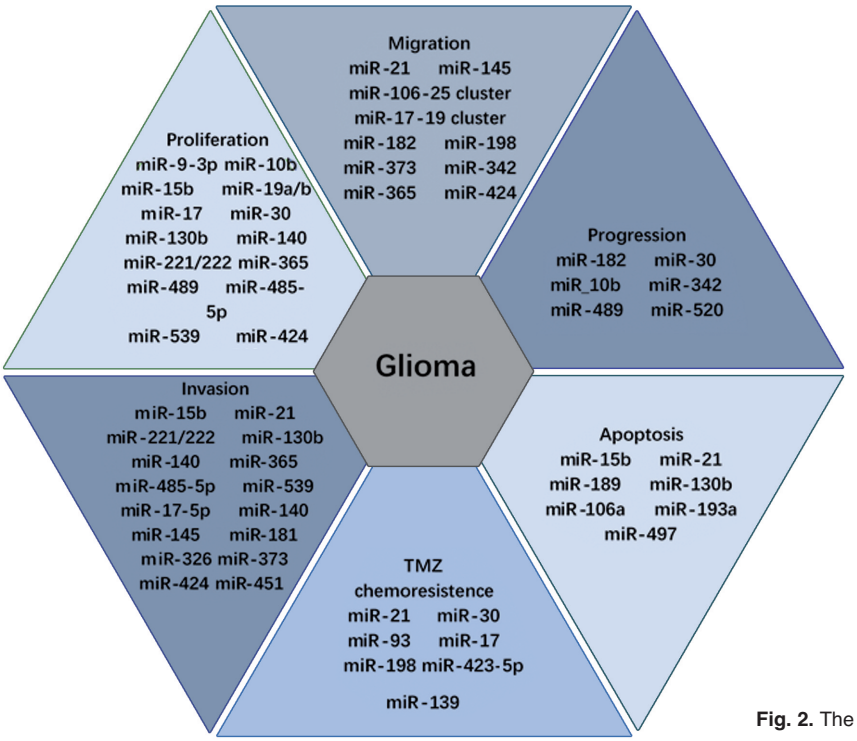

Fig. 2. The roles of miRNAs in glioma.

Table 2. miRNAs promoting tumorigenesis and development of glioma.

miRNA	Down-regulation	Target	Function	Reference
miR-9-3p	up	E2F	inhibits glioblastoma cell proliferation and cell cycle progression	Xiupeng et al., 2017
miR-10b	up	BCL2L11/Bim, CDKN1A/p21, CDKN2A/p16	proliferation and cell cycle progression and apoptosis	Charlotte et al., 2014
miR-15b	Up	CCNE1, NRP-2 , MMP-3	Suppresses the growth and invasion, inhibits proliferation and induces appotosis	Sun et al., 2014
miR-21	Up	PI3k/Akt	Invasion and migration apoptosis	Li et al., 2014
miR-17-19 cluster	Up	Cyclin D1, MDM2, PTEN RhoB	Migration TMZ chenmoresistance	Brian et al., 2013; Chen et al., 2016; Li et al., 2017a,b
miR-106-25 cluster	up	NEFL, CDKN1C. IL-8, PI3k/Akt, integrin-β8	proliferation and cell cycle progression and apoptosis	Fang et al., 2011; Murphy et al., 2013; Fabbri et al., 2015; Jiang et al., 2015
miR-182	up	LRRC4	Promote proliferation and cell cycle progression and apoptosis	Kouri et al., 2015
miR-198	Up	MGMT	Enhances TMZ sensitivity	Nie et al., 2017
miR-221/222	up	PTEN, p27, and p57, TIMP2	Invasion and proliferation	Zhang et al., 2012, 2015
miR-423-5p	Up		TMZ chenmoresistance	Li et al., 2017a,b
miR-520b	Up	targeting MBD2	inhibits the development of glioma	Cui et al., 2017

targeting cylindromatosis (CYLD) (Xiao et al., 2017).

miR-184

This inhibits cell proliferation and invasion, and specifically targets TNFAIP2 in Glioma. (Cheng et al., 2015). There are other reports that miR-184 inhibits the malignant biological behavior of human glioma by targeting FIH-1 (Yuan et al., 2014), and that mRNA-184 promotes proliferation ability of glioma cells by regulating FOXO3 (Cui et al., 2014).

miR-326

This functions as a tumor suppressor in glioma by targeting the Nin one binding protein (NOB1) (Zhou et al., 2013). Interestingly, miR-326 suppressed Notch and was suppressed by Notch. miR-326 was downregulated in gliomas by decreased expression of its host gene. miR-326 also partially mediated the toxic effects of Notch knockdown (Kefas et al., 2009).

miR-365

PIK3R3 overexpression in miR-365 expressing cells could rescue proliferation, migration and invasion inhibition of miR-365. In addition, miR-365 was able to inhibit the phosphorylation of AKT and mTOR in vitro and in vivo, which are key participants in the AKT/mTOR pathway. This suggests that miR-365 functioned as a tumor suppressor in glioma by targeting PIK3R3. In turn, this suggests that miR-365 has potential as a therapeutic target for glioma (Zhu et al., 2017).

miR-424

This functions as a tumor suppressor in glioma cells and is down-regulated by DNA methylation (Jin et al., 2017). miR-424 has been found to be dysregulated in many different types of human cancers. Its expression was significantly decreased in glioma tumor tissues in comparison to normal brain tissues, In vitro cellular function assays further indicated that miR-424 inhibited cell invasion and migration, and promoted cell apoptosis (Gao et al., 2017).

others

miR-105 inhibits human glioma cell progression by targeting SOX9 (Liu et al., 2016). miR-145 inhibits the proliferation, migration and invasion of glioma by targeting Sox9, ABCG2 and adducin 3 in human glioma cells (Lu et al., 2015; Rani et al., 2013). miRNA microarrays revealed that miR-181a, miR-181b and miR-181c were downregulated miRNAs in glioma cells and tumors (Ciafre et al., 2005). They inhibit glioma cell proliferation by targeting cyclin B1 (Wang et al., 2014). Wei et al. reported that miR-373 inhibits glioma cell invasion and migration by targeting TGFBR-2 (Wei et al., 2016).

There are another four miRNAs that were found to inhibit proliferation, cell cycle progression and induce apoptosis of glioma cells. They are miR-485-5p, miR-489, miR-495, and miR-539. miR-485-5p can down-regulate TPD52L2 (Yu et al., 2017), miR-489 targeted SPIN1-mediated PI3K/AKT pathway (Liu et al., 2017a,b), miR-539 targeted DIXDC1 (Quan et al., 2017). and miR-495 can regulate CDK6 expression and is involved in glioma cell growth inhibition (Chen et al., 2013; Nie et al., 2015,).

miRNAs promoting tumorigenesis and the development of glioma

miR-10b

The result of locked nucleic acid real-time PCR indicated that miR-10b regulation status differed for high-grade and low-grade tumors. It was up-regulated in high grade and significantly down-regulated in low-grade gliomas (Visani et al., 2013), and did not exist in normal brain tissue. miR-10b was implicated in the regulation of glioma proliferation and apoptosis. There was some evidence to suggest that miR-10b promoted glioma invasion (Sasayama et al., 2009).

miR-21

This was highly expressed in all cancer cells that were evaluated, including hepatocellular carcinoma, ovarian cancer, lung cancer and glioma. In contrast, low levels were observed in normal brain tissue. It was reported that miR-21 is commonly up-regulated in glioma and promotes migration and invasion by targeting MMP inhibitors RECK and TIMP3 (Gabriely et al., 2008).

miR-182

Dysregulation of the transforming growth factor β (TGF-β)/smad pathway in high-grade glioma is known to contribute to tumor progression. MiR-182 has been shown to be a target of TGF-β, which, once activated, downregulates the expression of NF-ϰB inhibitors. It was upregulated in glioma cell lines and primary glioma specimens in comparison to normal brain (Jiang et al., 2010). miR-182 also promotes proliferation and cell cycle progression and apoptosis by targeting LRRC4 (Kouri et al., 2015).

miR-17-92 cluster

Developmentally regulated microRNA clusters often show altered regulation in glial tumorigenesis and neural development. One example is the miR-17-92 cluster, a group of six co-transcribed miRNAs on chromosome 13, which includes miR-17a, miR-18a, miR-19a, miR-19b,

miR-20a, and miR-92a. This cluster is a typical case that is known as oncogenes in diverse tumor subtypes. The miR-17-92 cluster was also implicated in the regulation of glioblastoma neurosphere (presumably stem cells) differentiation, apoptosis and proliferation. It was shown that expression of several members of miR-17-92 was significantly higher in primary astrocytic tumors than in normal brain and significantly increased with tumor grade (Petrocca et al., 2008). Inhibition of miR-17-92 induced apoptosis and decreased cell proliferation in glioblastoma neurospheres. miR-17-92 inhibition was also associated with increased mRNA and/or protein expression of CDKN1A, E2F1, PTEN and CTGF. The CTGF gene was shown to be a direct target of miR-17-92 in glioblastoma neurospheres by luciferase reporter assays. Therefore, the study proposed that miR-17-92 and its target CTGF mediate the effects of differentiation-promoting treatment of glioblastoma cells.

miR-106b-25 cluster

There is another cluster as a paralog of the miR-17-92 cluster, the miR-106b-25 cluster, which includes three miRNAs (miR-106b, miR-93 and miR-25). As observed during normal development of mice, enhanced expression of the miR-106b-25 cluster plays an auxiliary role in glioma progression and results in greater proliferation ability and anti-apoptotic effects of tumors with upregulated expression levels of the miR-17-92 cluster (Zhang et al., 2013). There is reason to believe that the miR-106b-25 cluster plays an indispensable role in the malignant process of gliomas by promoting cell cycle progression, enhancing cell proliferation, inhibiting cell apoptosis and inducing blood vessel formation. In the present study, all members of the miR-106b-25 cluster and four miRNAs in the miR-17-92 cluster were included in the aberrantly expressed miRNAs.

miR-221/222

Some reports have revealed miR-221/222 in glioma malignancy. The genes for miR-221 and miR-222 occupy adjacent sites on the X chromosome. Their expression appears to be co-regulated and they have almost the same target (Gillies et al., 2007). They were upregulated in gliomas and cell lines. The ability of miRNA-221/222 to negatively regulate the pro-apoptotic gene PUMA is responsible for its anti-apoptotic effect (Zhang et al., 2009a,b). miR-221 upregulation was confirmed in a subsequent study, which also found that miR-221 levels are higher in higher-grade tumors (Zhang et al., 2010). Dysregulation of the transforming growth factor β (TGF-β)/smad pathway in high-grade glioma is known to contribute to tumor progression. MiR-182 has been shown to be a target of TGF-β, which, once activated, downregulates the expression of NF-κB inhibitors, and was upregulated in glioma cell lines and primary glioma specimens in comparison to the normal brain (Jiang et al., 2010).

miR-423-5p

Li et al. reported that miR-423-5p expression was increased in gliomas and was a potential tumor promoter by targeting ING-4. The overexpression of miR-423-5p resulted in upregulation of important signaling molecules, such as p-AKT and p-ERK1/2. In clinical samples, miR-423-5p was dysregulated. A corresponding alteration in ING-4 expression was observed (P=0.0207). Furthermore, the overexpression of miR-423-5p strengthened glioma cell proliferation, angiogenesis and invasion (Li et al., 2017a,b).

miR-520b

This has been reported to play critical roles in tumor progression in many types of cancers. Cui et al. found that miR-520b could inhibit growth and progression in glioma by targeting methyl-CpG-binding domain 2 (MBD2). (Liu et al., 2016a,b; Cui et al., 2017).

Others

miR-15a, miR-16, and miR-23a are nonspecific miRNAs that are expressed in many tissues. The expression of miR-15a and miR-16, which are expressed primarily in lymphocytes and monocytes, was higher in glioma than in normal brain tissue. miR-15b suppresses the glioma cells growth and invasion, inhibits proliferation and induces apoptosis by targeting CCNE1, NRP-2 and MMP-3 (Sun et al., 2014).

MiRNA as biomarkers for glioma

The information that biomarkers provide about cancer can be used as important prognosis factors and a response to therapy, as well as to improve diagnosis and to aid earlier detection. It can also be used to distinguish tumor grades and subtypes. The extensive alterations in miRNA expression in diseases provide great potential for clinical diagnostics based on miRNA signatures. miRNAs are more stable than mRNAs. They could be detected by using a range of readily accessible high-throughput techniques, including quantitative, real-time, polymerase, chain reactions (qRT-PCR) and ELISA. The role of miRNA in glioma development and progression, and their specificity, makes it an important candidate biomarker that could provide important characteristic information of a tumor and improve treatment and prognosis. miRNA signatures have been identified in both glioma tissue and the circulation of glioma patients. Although the identification of miRNA biomarkers for cancer continues to increase, there are no clinically utilized miRNA biomarkers for glioma. The expression of specific miRNAs can differ between the sample types that are used in studies. Although miR-15b did not appear to be significantly downregulated in a study using plasma samples, a significant increase in miR-15b levels in CSF samples was detected. Charlotte et al. has also

identified miR-15b-5p as an miRNA with altered expression in serum and CSF samples. A number of environmental factors including diet, infection, and stress on epigenetic mechanisms including miRNA expression shows that different lifestyles can affect the expression of miRNA. In turn, this could affect their detection and use as biomarkers. The methods of isolating and measuring miRNA expression that a study employs can also affect the identification of miRNA biomarkers and cause differences between studies.

The biologically relevant targets of each miRNA may vary from one tissue to another, whereas many genes contain putative binding sites for multiple miRNAs. Today, there are more than one hundred ongoing trials that incorporate miRNAs as biomarkers (Nana-Sinkam and Croce, 2013). Even so, miRNAs still could represent important diagnostic, prognostic or predictive target molecules in the treatment of tumors. Shi et al. demonstrated that the down-regulation of miR-124 in tumor tissue promoted glioma development, angiogenesis, and chemoresistance. This suggests that miR-124 may be a useful diagnostic marker and therapeutic target in glioma (Shi et al., 2014), and that low miR-105 expression is a novel, poor prognostic predictor for human glioma (Guan et al., 2015). Qiu et al. demonstrated that interactions of miR-323/miR-326/miR-329 and miR-130a/miR-155/miR-210 are prognostic indicators of the clinical outcome of glioblastoma patients (Qiu et al., 2013).

miRNA markers that were found to have these characteristics included miR-222 for gender, miR-137 as a race-dependent marker, and miR-140 as a marker for survival .Also, it was shown that the overexpression of miR-21 and miR-145 causes the cancer cells to be resistant to sunitinib and temozolomide .Down-regulation of miR-326 may have potential value for predicting clinical outcomes in glioma patients with high pathological grades. This suggests that miR-326 is an important candidate tumor suppressor, and that its down-regulated expression may contribute to glioma progression. Zhao et al. indicate that miR-524 mediates the EGFR/EGFRvIII stimulating effect, and that miR-524 may serve as a potential therapeutic agent and classical-specific biomarker for the development of glioma. The main appeal of miRNA biomarkers is the tissue and cell specificity of their expression, which can be illustrated by miR-10b.

Although multiple miRNA biomarkers have been identified in glioma, especially in GBM, the functions of most miRNAs remain unknown because of the lack of candidate target genes under the specific biological conditions.

miRNAs for the diagnosis and targeted therapy of GBM

miRNAs for the diagnosis of glioma

As mentioned earlier, the use of miRNAs to diagnosis glioma was not easy. However, the miRNA expression in disease still provides great potential for clinical diagnostics based on miRNA signatures. Furthermore, miRNAs are more stable than mRNAs and can be recovered from formalin-fixed paraffin sections (FFPE) and other sources with low overall RNA quality (Scott, 2015). Therefore, recent and ongoing studies have focused on circulating cell components, CSF and blood in the diagnosis and evaluation of brain tumors. Roth et al. reported that, in comparison to normal controls, the plasma levels of miR-21, miR-128 and miR-342-3p were shown to be significantly altered in GBM patients. Qu et al. reported that miR-21 levels, particularly when combined with other miRs such as miR-15b, have a much better diagnostic performance (Qu et al., 2015). Roth et al. reported that miR-128 and miR-342-3p from a total of 1158 miRNA that were tested in glioblastoma patient peripheral blood compared to normal control blood and miR-128 and miR-342-3p correlated positively with glioma histopathological grade. The expression of miR-128 is contradictory, ranging from robust to poor. In the blood of glioblastoma patients, miR-128 overexpression has been identified, in comparison with controls, whereas miR-128 was downregulated in GBM tissue when compared to normal human brain (Godlewski et al., 2008; Zhang et al., 2009; Roth et al., 2011). Interestingly, reduced miR-342-3p expression in glioblastoma patient sera versus control sera was observed in both Yang et al. and Roth et al. study. This suggests that this miRNA may, indeed, be a suitable biomarker for glioblastoma diagnosis. Recently, it has been shown that miR-454-3p in plasma of glioma patients is significantly higher than in plasma from normal controls and lower in LGGs than in HGGs. Its expression also correlated with the overall outcomes of glioma patients (Shao et al., 2015). Also, miR-29 shows high diagnostic potential, enabling differentiation between patients of stage I-II with stage III-IV (Yu and Li, 2016) Furthermore, the miR-454-3p expression in the post-operative plasmas is markedly downregulated in comparison to the pre-operative plasmas, and a correlation of worsening prognosis of glioma was observed with increasing miR-454-3p expression (Shao et al., 2015). Also, a huge increase in miR-210 expression was found in GBM patients' serum samples compared to controls. This was associated with the tumor grade and the patient's poor outcome (Yu and Li, 2016).

MiRNA and chemo-sensitive

Chemotherapy is the treatment of cancer by a single or multiple cytotoxic drug that works mainly by inhibiting the proliferation of actively dividing cells. These drugs include alkylating agents, platinum agents, nitrogen mustards, antimetabolites, anthracyclins, alkaloids or taxanes (Malhotra and Perry, 2003). miRNA studies have proved that abnormal miRNA expression may affect chemo-sensitivity. They also have verified several miRNAs that are associated with TMZ resistance: miR-21, miR-20a, miR-30b/c,miR-423-5p,

miR-198, miR-95, miR-10a, miR-181d, miR-139 and miR-520b (Shi et al., 2010; Ujifuku et al., 2010; Tumilson et al., 2014; Cui et al., 2017; Li et al., 2017a-c; Nie et al., 2017). It has also been shown that the overexpression of miR-21 and miR-145 make the cancer cells resistant to sunitinib and temozolomide (Costa et al., 2013). The overexpression of miR-198 and miR-181d enhances TMZ sensitivity by targeting MGMT. As well as affecting TMZ, miR-21, miR-30b and miR-30c have been identified as regulators of TNF-related apoptosis-inducing ligand (TRAIL). Therefore, these three miRNAs could affect the sensitivity of glioma cells to treatment with the TRAIL ligand, since their upregulation was shown in TRAIL-resistant glioma cell lines (Quintavalle et al., 2013). Li et al. reported that miR-423-5p expression was increased in gliomas and a potential tumor promoter by targeting ING-4 in glioma cells resistant to temozolomide. (Li et al., 2017a-c) Cui et al. reported that miR-520b rendered glioma cells more sensitive to TMZ treatment and promoted TMZ-induced apoptosis in glioma cells by suppressing its target gene, MBD2. Using computational and TCGA analysis, Li et al. discovered that miR-139 was decreased in glioblastoma in comparison to human brain tissue and inhibits Mcl-1 expression and potentiates TMZ-induced apoptosis in glioma (Li et al., 2013).

Therapeutic implications and future perspectives

miRNsA play a critical role in mediating intercellular communication. Some miRNA-based therapies will become an important component of targeted therapies for a variety of diseases in the future. Despite the most advanced treatment with combinations of surgery, radiotherapy and chemotherapy, glioblastoma multiforme, the most malignant and most common glioma, is associated with an average life expectancy of only 14 months. As mentioned above, miR-10b is overexpressed in the majority of gliomas, but not in normal brain. Inhibition of this miRNA decreases glioma cell proliferation, but does not affect normal cell viability in vitro or in vivo (Gabriely et al., 2011). This is one of the major limitations of miRNA candidates for therapeutic applications in general and brain tumors , specific, effective, delivery systems. On a positive note, Yaghi et al utilized lipid nanoparticles as a strategy to prevent degradation of miR-124 and effectively deliver it to murine glioma models (Yaghi et al., 2017). This approach has led to an increase in median overall survival, an effect that appeared to be due in part to a reversal of tumor-induced immunosuppression.

Ernst et al. proposed that miR-17-92 and its target CTGF mediate the effects of differentiation-promoting treatment of glioblastoma cells. The accumulating evidence suggests that a subset of cells initiate and maintain the growth of gliomas and are responsible for their resistance to therapy. miR-181a overexpression sensitizes glioma cells to radiation treatment concurrently with the down-regulation of Bcl-2 (Chen et al., 2010). Also, miR-181b and miR-181c were significantly down-regulated in patients who responded to radiation therapy and temozolomide in comparison to patients with progressive disease (Slaby et al., 2010). In addition, MiR-26a enhances the radio-sensitivity of glioblastoma multiform cells by targeting ataxia-telangiectasia mutated. MiR-146b-5p overexpression attenuates stemness and radio-resistance of glioma stem cells by targeting the HuR/lincRNA-p21/β-catenin pathway. The microRNA-153/Nrf-2/GPx1 pathway regulates radio-sensitivity and stemness of glioma stem cells by means of reactive oxygen species (Yang et al., 2015). Therefore, the expression levels of miR-181b and miR-181c, miR-26a, miR-146b-5p, miR-153 could serve as predictive markers of response to radiation therapy and temozolomide in glioma patients. Moreover, the study of miRNAs is helpful in the identification of novel biomarkers in disease diagnosis and monitoring. Increasing development of miRNAs as biomarkers and clarification as possible therapeutic targets are likely to cause them to assume a substantial role in molecular neuro-oncology in the future.

Conclusions

It is thought that miRNAs regulate the expression of one third of the human genome. miRNAs up- or down-regulate tumor cell proliferation, death, migration, invasion, angiogenesis and other activities by affecting the expressions of numerous target mRNAs. The expression of several miRNAs is emerging as regulators in the control of glioma cell self-renewal and differentiation. The expression of some miRNAs correlates with patient prognosis. In this review, we have focused on the biological activity of miRNAs in glioma. We have described evidence that specific miRNAs regulate glioma cell proliferation, invasion, migration, and chemresistance. As shown in Table1, miRNAs have diverse inhibiting and stimulating effects on the proliferation and differentiation of glioma, and identify the target molecules. We also summarize the roles of miRNAs in glioma therapy. miRNAs could be used in the future as direct pharmacological targets to treat glioma. Nonetheless, the broad and profound involvement of miRNAs in the regulation of gene expression presents an opportunity for a better understanding of the mechanisms of glioma initiation and progression and, perhaps, for the use of miRNAs as future agents or targets for glioma therapy.

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