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REVIEW ARTICLE

Recent advances of the regulation roles of MicroRNA in glioblastoma

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Abstract
Glioblastoma (GBM) is one of the most malignant neural tumors, and patients with GBM often die soon after the onset. The pathogenesis of GBM is very complicated, and there is no effective treatment for GBM. The current research results show that a variety of microRNA (miRNA) are involved in the regulation of GBM occurrence and development through specific signal pathways. Meanwhile, as a non-invasive biological indicator, there is an important clinical value of miRNA in the diagnosis and prognosis of GBM. The research of targeted miRNA treatment for GBM is still in the cell and animal model stage, although the basic research shows a good result, there is still a certain distance to the clinical application.

Keywords Glioblastoma · MicroRNA · Area under curve · Prognostic model · Temozolomide

Introduction

Glioblastoma (GBM) is not only one of the most common neurological malignancies but also the most malignant glioma (WHO Class, IV) [1]. GBM shows such characteristics as rapid growth, early metastasis, and short disease course, and over 70% of GBM patients die at about 6 months after the onset of symptoms, with the 5-year survival less than 10% [2]. GBM originates primarily from astrocytes and oligodendrocytes, and the related mechanisms underlying its pathogenesis is very complicated. Currently, there are no particularly useful treatment options in clinical practice, and recurrence may occur even if surgery has been performed due to the invasion and metastasis of the tumor in the early stage. MicroRNAs (miRNAs) are non-coding RNAs that contain 22 nucleotide sequences and do not possess the function of translating proteins. They mainly regulate the expression of genes by directly binding to the target functional genes, thereby exerting the corresponding biological functions [3, 4]. In recent years, studies on the expression of miRNA in GBM and its related functional mechanisms show that multiple miRNAs have been involved in the regulation

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of the entire process of development and progression of GBM. miRNAs have important clinical values as markers for diagnostic evaluations and targets of new molecular biological therapies [5, 6]. We herein reviewed the research progress on the functional roles of the specific miRNAs in GBM and the related clinical applications. We have identified the miRNAs to be reported in this paper based on recent references. We believe that these miRNAs we choose can represent current research hotspots and frontiers.

Involvement of miRNAs in the pathogenesis of GBM

Similar to other malignancies, GBM has a very sophisticated mechanism of pathogenesis, and the various regulatory factors in different stages involving GBM are different to a certain degree. As an essential player in the mechanisms underlying molecular regulation, miRNAs are involved in the pathogenesis and progression of GBM with their specific functional role.

Involvement of specific miRNAs in the regulation of proliferation of GBM

For the related studies, the study by Xu et al. based on the cell line models (T98G and LN229 cells) showed that miR-92b could interact with C-terminal of heat shock protein 70/miR-92b/chromosome 10-deleted phosphatase tensin protein to regulate the expression of the phosphatidylinositol 3-kinase/protein kinase B signaling pathway [7]. The increased signal expression of phosphatidylinositol 3-kinase/protein kinase B can promote the proliferation of GBM cells, and decreased miR-92b expression can weaken the growth of GBM cells. Yang et al. also found that elevated miR-196a-5p expression was noted in both GBM tumor tissues and U87 cell lines, while miR-196a-5p could targeted inhibit the expression of the zinc finger protein domain 11 [8]. Animal experiments have shown that enhanced expressions of zinc finger protein domain 11 can inhibit the growth of the GBM cells and promote the apoptosis of tumor cells. Therefore, miR-196a-5p promotes GBM mainly by inhibiting ZMYND11. In a study on the mechanisms underlying the pathogenesis of GBM, Liu et al. found that miR-153 could regulate glutamine metabolism in GBM tumor cells, and that the expression of miR-153 in GBM tumor tissues was decreased significantly and glutamine synthesis was significantly increased (a marker of proliferation and metabolism of tumor cells) as compared with matched paracancerous tissues [9]. Mechanistic studies have shown that miR-153 can target glutamine kinase directly to inhibit the synthesis of glutamine and that the decreased miR-153 expression leads to increased glutamine synthesis in GBM. The study by Wu et al. also showed that increased expressions of miR-18a was present in GBM, that miR-18a mainly promoted the onset of GBM by targeting the regulation of the expression of the chromodomain homolog protein 7 directly, and that the chromosome homolog protein 7 could be involved in the regulation of the cell cycle of GBM [10]. Zhou et al. found in a study that the expression of miR-141-3p was increased in GBM tissues and that the increase of miR-141-3p was positively correlated with p53 expression [11]. The studies based on mouse models have shown that miR-141-3p can promote the proliferation of the GBM tumor cells and contribute to the enhanced tolerance of GBM to temozolomide (TMZ), which is mainly achieved by targeting the regulation of the expression of p53 gene directly. The above results also indicated that miRNA play critical regulatory roles in promoting GBM proliferation.

Involvement of specific miRNA in the regulation of GBM invasion

GBM is of extremely high malignancy, and invasion and distal metastasis can occur at an early stage. For example, Li et al. found that GBM cell lines (U87 and A172 cells) from GBM patients had significantly increased expressions of miR-30b-5p, and that degree of elevation in miR-30b-5p was associated with worse clinical prognosis [12]. Mechanistic studies have shown that miR-30b-5p is positively correlated with the expression of proline-rich transmembrane protein 2, and decreased expression of miR-30b-5p can reduce proline-rich transmembrane protein 2, thereby reducing the proliferation and invasion of U87 and A172 cells. This indicates that miR-30b-5p promotes the development of GBM mainly by targeting the regulation of the expression of proline-rich transmembrane protein 2. Lee et al. found based on the cell model (LN229, T98G and U87 cells) that miR-296-5p could promote the invasion and metastasis of GBM cells, which is mainly achieved through the direct regulation(inhibition) of the expression of the NGF receptor and caspase-8 expression by miR-296-5p, while decreased expression of the NGF receptor and caspase-8 expression can contribute to weakened invasion of GBM cells [13]. Wang et al. also explored the role of miR-217 in the pathogenesis and regulatory effects of GBM [14]. The results showed that increased miR-217 expressions and decreased expression of Tyr-3/Trp-5 monooxygenase-activating protein were seen in GBM tissues and cell lines and that decreasing miR-217 expression or increasing Tyr-3/Trp-5 monooxygenase activator protein gamma expression in vitro could inhibit the proliferation, migration, invasion and mitosis of U87 cells. The functional studies have shown that miR-217 can directly engage in a targeted binding to the 3′-non-translated region of Tyr-3/Trp-5-monooxygenase activator protein γ so as to inhibit

its expressions, indicating that miR-217 is involved in the regulation of invasion of GBM.

MiRNAs for diagnosis and prognosis of GBM

GBM is extremely malignant; patients have early metastases at the time of admission, and the prognosis is poor. The accurate diagnosis and GBM prognosis assessment can help take targeted clinical treatment measures and improve the long-term prognosis and quality of life of patients. In addition, invasive biopsy, non-invasive imaging, and serological tests as the gold standards for diagnosis are also of high value in both diagnosis and prognosis. With the progress in molecular biological detection technologies, detection of specific miRNAs in GBM become more convenient and provides vital support for miRNAs for improving the diagnosis and prognosis of GBM. A wide array of research data has also shown that the excellent application values of miRNAs in this area.

Specific miRNAs for improving the diagnosis of GBM

Due to the changes in the expression in specific miRNAs in GBM, scholars have also studied the clinical values of miRNAs for GBM diagnosis. For example, the study by Toraih et al. based on the clinical specimens of primary pleomorphic GBM patients ($n = 43$) showed that the expressions of miR-16, miR-17, miR-21, miR-221 and miR-375 were elevated in the GBM tissues, while the expression of miR-34a was decreased; specifically, the AUCs of miR-34, miR-17, miR-221 and miR-21 for the diagnosis of GBM from high to low were 0.927, 0.900, 0.845 and 0. 836, respectively The diagnostic sensitivity and specificity were both high [15]. Meanwhile, the investigators found that the level of miR-221 and the methylation degree of methylguanine-DNA transferase (reflecting the degree of DNA injury tolerated by the tumor cells) was significantly correlated with each other ($p < 0.001$). In contrast, the expression levels of miR-17, miR-221, and miR-326 were negatively correlated with the proportion of patients with clinical relapses ($p < 0.001$), indicative of the critical diagnostic evaluation values of these miRNA markers [15]. Besides, Akers et al. studied the expressions of miRNAs in the cerebrospinal fluid specimens in GBM patients, and the results showed that nine miRNAs were abnormally expressed [16]. Meanwhile, they established the scoring model containing multiple abnormal miRNAs, and the results showed that the joint score and the GBM tumor volume were significantly positively correlated ($p = 0.\ 008$) [16]. The sensitivity and specificity of the joint score for the diagnosis of GBM were 67% and 80%, respectively, demonstrating the diagnostic values of the joint scoring based on the cerebrospinal fluid measurement results for GBM.

Clinical values of single miRNA indicators for the prognosis of GBM patients

Since GBM is a neurological tumor with a high degree of malignancy (a WHO grade IV), non-invasive biological indicators show significant values in the accurate prognosis assessment of GBM. A plethora of data has also been accumulated in the clinical studies on specific miRNAs for the prognosis of GBM patients. For example, Xiong et al. investigated the value of miR-141 for the prognosis of human GBM, and the results showed that the GBM cell lines and human GBM specimens had significantly low expressions of miR-141 and that enhancing miR-141 expression could suppress the proliferation of GBM LN229 and U89 cell lines [17]. Patients with decreased miR-141 GBM had a higher tumor stage, worse clinical prognosis and shorter survival, and Cox analysis showed that low miR-141 expressions represented the independent risk factor for poor prognosis [17]. The study by Cheng et al. also showed that miR-144-3p could be used as the prognostic indicator for GBM patients, that the expression of miR-144-3p in the tumor tissues of patients with GBM was significantly lower than in the matched adjacent tissues, and that the serum miR-144-3p was negatively correlated with the stage of tumors and recurrence [18]. The Cox analysis showed that a low level of miR-144-3p was an independent predictor of poor prognosis, and the functional study has shown that miR-144-3p primarily inhibits the invasion and metastasis of GBM cells by targeting the regulation of the expressions of FZD7 [18]. Chen et al. studied the values of serum miR-203 levels for the clinical prognosis of patients with GBM. Compared with the low-grade glioma and healthy control, the level of serum miR-203 was significantly low in GBM patients, a low level of miR- 203 was positively correlated with a greater tumor size and a lower Kappes score, the overall survival and progression-free survival of patients with a low level of miR-203 were shorter, and a low level of miR-203 was also an independent risk factor for the poor prognosis [19]. The study by Malekpour Afshar et al. showed that the expression of miR-93 in the cancer tissues of GBM patients was lower than in the normal brain tissue and that the low expression level of miR-93 was correlated with a high tumor stage ($p = 0.02$); the multivariate analysis showed that a low expression level of miR-93 serves as an independent risk factor for poor prognosis (HR = 4.3, 95% CI 0.8–17.2, $p = 0.02$) [20].

Prognostic values of multi-miRNA combined scoring model

The multi-miRNA combined scoring model, including miRNA, helps improve the accuracy of the assessment of single indicators and has also garnered the attention of researchers. An example is that Yuan et al. established the prognostic scoring model incorporating three miRNAs (miR-222, miR-302d, and miR-646) based on the miRNA microarray screening results of GBM patient's cohort with a large sample size ($n = 563$): prognosis score = (0. 112 × expression level of miR-222) + (− 3.671 × miR-302d) ± (− 2.971 × miR-646) ± (0.023 × age). The validation results showed that the AUC of the 5-year survival of the GBM patients in model prediction could reach 0. 854 (95% CI 0.744–0.964), exhibiting high prognostic values, and provided certain references for methods judging the clinical prognosis of GBM [21]. In addition, the study by Hermansen et al. based on a GBM patients cohort ($n = 40$) showed that multiple serum miRNA markers could be used for the clinical prognosis of the GBM patients and that the accuracy of miR-107, miR-548x, miR-3125 and miR-331 -3p for the short-term and long-term prognosis could reach 78% [22]. The investigators established the prognostic scoring model (miRNA-sum scoring) incorporating miR-107 and miR-331. After age adjustment, the prognosis of patients with low miRNA-sum scores was worse (HR = 0.66; 95% CI 0. 45–0.97; $p = 0.033$) [22]. Subsequently, the data analysis of the Kyoto Gene and Genome Encyclopedia showed that the miRNAs incorporated into scoring mainly targeted regulated the functional genes involved in the regulation of cell cycle and proliferation of GBM.

miRNAs for the clinical treatment of GBM

Although the clinically ongoing search is done for safer and more effective methods for the treatment of GBM, the progress of recent related research is limited. Since specific miRNAs play a crucial regulatory role in the development and progression of GBM, methods based on targeted miRNA regulation may also provide an important reference for the development of new drugs. Due to a variety of factors (drug synthesis and indefinite safety and efficacy), therapeutic methods based on targeted miRNA currently remain at the level of cellular and animal models, and there are many problems to resolve to realize clinical applications.

Targeted treatment of GBM by specific miRNAs

With the in-depth study on the regulation of specific miRNAs in GBM, some scholars also target miRNAs for the treatment of GBM. As regards the related studies, such as Zhi et al. found that the expression of miR-520d-5p in the tumor tissue of the humanized xenograft tumor was decreased significantly while enhancing the expression of miR-520d-5p could inhibit the proliferation of human GBM cells and induce the resetting of the cancer cell cycle [23]. Mechanistic studies have shown that miR-520d-5p primarily directly targeted the pituitary tumor transforming gene 1 activation to suppress the tumor of glioma cells. Studies have shown that miR-520d-5p may be a potential therapeutic asset for GBM. Dong et al. also found that the expression of miR-429 in the GBM tissue was decreased significantly as compared with the normal adjacent tissue ($p < 0.01$), and an increased expression of miR-429 could inhibit the proliferation of GBM cells and induce tumor cells, induce the accelerated apoptosis of tumor cells and weaken the invasion of tumors [24]. The function of miR-429 is mainly achieved by decreasing SOX2 protein expression. Based on the cell model (A172 cell line), Shin et al. found that the addition of miR-29b could enhance the apoptosis of tumor cells, and weaken the expression of proteins associated with tumor cell proliferation and metastasis, such as type 1 collagen α2, type 3 collagen α1, type 4 collagen α1, elastin, matrix metalloproteinase 24 and the acidic secretory proteins by enriched cysteine, thereby exerting the anti-GBM potency [25]. In addition, similar studies have shown that miR-194-5p, miR-518b and miR-543, etc., also possess certain cancer-suppressive effects. The regulatory sites of these miRNAs are predominantly associated with such critical functions as GBM proliferation, invasion, and apoptosis [26].

Values of specific miRNAs as an auxiliary option for conventional chemotherapeutic drugs for the treatment of GBM

As the first-line clinical drug for the treatment of GBM, TMZ displays good efficacy and safety profiles [27]. However, the resistance of GBM to TMZ is also an important issue that baffles clinicians, and the relevant mechanisms have yet been elucidated fully, which also affects the long-term efficacy of the drug. Studies have shown that regulation of specific miRNAs can, to a certain degree, improve the resistance of GBM to TMZ and strengthen the efficacy of chemotherapy. Based on cell-level studies (U87 cells), Sharif et al. found that the addition of miR-124 (through mesenchymal stem cells) to the cell line could decrease the expression activity of the target gene cyclin-dependent kinase 6, thereby enhancing the sensitivity of the GBM cell line to TMZ treatment and weakening invasiveness of GBM cells [28]. The study by Cheng et al. showed that miR-132 expression in GBM patients could induce the tolerance of GBM to TMZ and enhance the proliferation of the GBM cells. Mechanistic studies have shown that the function of miR-132 is mainly realized through the targeted regulation of the

expression of the tumor suppressor candidate gene 3 [29]. Zhang et al. also found that miR-625 could inhibit the proliferation of GBM cancer cells and strengthen the sensitivity of tumors to chemotherapy [30]. The function of miR-625 is mainly realized through the directly targeted regulation of the expression of protein kinase 2, and an increase in the expression of protein kinase 2 could enhance the apoptosis of the tumor cells.

Values of specific miRNAs in improving the efficacy of other drugs

Curcumin is a drug for the treatment of GBM. The study by Li et al. [32] showed that increasing the expression of miR-378 can enhance the inhibitory effects of curcumin on tumor cells (U87 cells) [31]. The mechanistic study showed that miR-378 realizes this function mainly by affecting p-p38 gene expression. In addition, miR-326 could also increase the sensitivity of the GBM cells to treatment with curcumin. This function of miR-326 is mainly achieved through the regulation of the hedgehog protein/GLI1 signaling pathway [32, 33]. Through an animal model, Li et al. found that miR-378 could affect the GBM response to radiotherapy, thus improving the efficacy of radiotherapy [31]. The U87 cells with enhanced expressions of miR-378 were inoculated into an animal model, which then received 12 Gy of irradiation. As a result, the tumor growth and survival of the inoculated animals were significantly longer than in the control group (mice inoculated with U87 cells without enhanced miR-378 expression, $p = 0.04$), which also provides references for improving the effects of clinical radiotherapy to a certain extent [31]. The tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a brand-new antitumor drug entering clinical trials (phases II and III) recently. Although there are no studies on GBM patients, it has also shown specific effects on GBM in the basic trials [34]. In a study, Wang et al. [37] found that miR-133a expressed in the GBM patients could directly inhibit the activation of the death receptor 5 and the nuclear factor kappa B signaling pathway from enhancing the tolerance of GBM to TRAIL [35]. In vitro experiments have confirmed that it could reduce miR-133a and significantly improve the therapeutic effects of TRAIL. Based on genomic analysis, Zhang et al. also found that miR-7 might be used as a potential marker of TRAIL to induce GBM cell apoptosis. Based on the inoculated animal model, we found that enhancing miR-7 could promote TRAIL-induced apoptosis of GBM. Signal pathway analysis revealed that miR-7 mainly plays such a role by targeted regulating the X-linked apoptosis to inhibit protein genes (involved in the regulation of apoptosis) and might serve as a target for improving TRAIL for the treatment of GBM or other malignancies [36]. Erythropoietin (EPO) has been widely used for the treatment of chronic renal failure, tumors and chemotherapy-induced anemia. In contrast, recent studies have shown that EPO can enhance the invasion ability of malignant tumors [37]. Meanwhile, EPO can also pass the blood–brain barrier and show similar effects on malignancies of the nervous system (such as GBM). The study by Alural et al. also showed that EPO could reduce the expression of miR-451 in the U87 cells. At the same time, the main targeted regulatory genes of miR-451 are matrix metalloproteinase 2 and matrix metalloproteinase 9 (both important proteins involved in the invasion of GBM), providing important references for improving the treatment of EPO and decreasing the oncogenic effects of EPO [38]. The details of some recently reported related miRNAs are listed in Table 1.

Isocitrate dehydrogenases (IDH) gene mutation and miRNAs

2016 World Health Organization Classification of Tumors of the Central Nervous System (2016 WHO CNS) represented a major change in the classification of brain tumors. Gliomas with IDH gene mutations (IDHMT) were found to be less aggressive than their wildtype (IDHWT) counterparts. We searched related literatures regarding the IDH gene mutation and certain miRNA's interactions or impact. However, very few studies focused on this topic. Grassian et al. created a panel of isogenic epithelial cell lines with either wild-type IDH1/2 or clinically relevant IDH1/2 mutations [39]. Differences were noted in the ability of IDH mutations to cause robust 2-HG accumulation. IDH1/2 mutants that produce high levels of 2-HG cause an epithelial-mesenchymal transition (EMT)-like phenotype, characterized by changes in EMT-related gene expression and cellular morphology. 2-HG is sufficient to recapitulate aspects of this phenotype in the absence of an IDH mutation [39]. In the cells types examined, mutant IDH-induced EMT is dependent on up-regulation of the transcription factor ZEB1 and down-regulation of the miR-200 family of microRNAs [39]. Furthermore, sustained knockdown of IDH1 in IDH1 R132H mutant cells is sufficient to reverse many characteristics of EMT, demonstrating that continued expression of mutant IDH is required to maintain this phenotype. These results suggest mutant IDH proteins can reversibly deregulate discrete signaling pathways that contribute to tumorigenesis [39].

Conclusion

Specific miRNAs play critical regulatory roles in GBM and exert important effects on proliferation, migration, invasion, and drug resistance of GBM. Recent studies have explored

Table 1 Some recent descovered miRNA expression profiles in glioblastoma

Entry	miRNA	Location	Roles	Disregulation pattern	Predicted targeted genes
1	miR-21		miR-21 is considered to be a typical 'onco-miR', which acts by inhibiting the expression of phosphatases, which limit the activity of signalling pathways such as AKT and MAPK. As most of the targets of miR-21 are tumor suppressors, miR-21 is associated with a wide variety of cancers	Up-regulated	ANP32A, BTG2, Bcl2, P12/CDK2AP1, HNRPK, IL-12p35, JAG1, MEF2C, hMSH2, PDCD4, PTEN, RECK, RhoB, SMARCA4, TGFBRII, SPRY1, SPRY2, TP63, Tropomyosin
2	miR-10b	2q31.1	miR-10b may be a mediator between obesity and cancer in post-menopausal women, regulating several known cancer-relevant genes. MiR-10b expression may have diagnostic and therapeutic implications for the incidence and prognosis of certain cancers	Up-regulated	SRSF1, PIEZO1, MAPRE1, CDKN2A, TP-53 and TRA2B
3	miR-15b	3q25.33	mRNA binding involved in posttranscriptional gene silencing	Up-regulated	IFT80, SMC4, B3GAT3P1, MIR15B, MIR16-2, RF00254, ENSG00000248710, TRIM59-IFT80-001
5	miR-92b	1q22	miR-92b could be activated by Mef2 and subsequently downregulates Mef2 through binding to its 3′UTR, forming a negative regulatory circuit that fine-tunes the level of Mef2. Deletion of miR-92b caused abnormally high Mef2 expression, leading to muscle defects and lethality	Up-regulated	ENSG00000231064, MUC1, LOC105371450, MIR92B, lnc-THBS3-2, GBAP1, CLK2, MSTO2P, MSTO1, UBAP2L, GON4L, PYGO2, KHDC4, THBS3, ENSG00000271267
6	miR-93	7q22.1	miR-93 expression in glioma tissues and cells was increased significantly than that in normal brain tissues and cells. Furthermore, miR-93 promoted glioma cell migration and invasion. RBL2 was recognized as a direct target of miR-93 in glioma cells, and overexpression of RBL2 could reverse the stimulative effect of miR-93 in glioma cell	Up-regulated	RBL2, MIR25, MIR93, MIR106B, piR-36984, piR-47148, AZGP1, MCM7
7	miR-210	11p15.5	mRNA binding involved in posttranscriptional gene silencing	Up-regulated	MIR210, MIR210HG, HRAS, TMEM80, LRRC56, PHRF1, RNH1, ENSG00000270105, lnc-PHRF1-1
8	miR-155	21q21.3	mRNA binding involved in posttranscriptional gene silencing	Up-regulated	MIR155, lnc-MRPL39-2, MRPL39, lnc-JAM2-1, MIR155HG, EU375836
9	miR-106b	7q22.1	miRNAs belonging to the miR-106b~25 cluster have emerged as key oncogenic drivers as well as potential biomarkers and plausible therapeutic targets in different tumor types	Up-regulated	MIR25, MIR93, MIR106B, piR-36984, piR-47148, AZGP1, MCM7
10	miR-25	7q22.1	miRNAs belonging to the miR-106b~25 cluster have emerged as key oncogenic drivers as well as potential biomarkers and plausible therapeutic targets in different tumor types	Up-regulated	MIR25, MIR93, MIR106B, piR-36984, piR-47148, AZGP1, MCM7
11	miR-132	17p13.3	miR-132 played important roles in regulating bupivacaine -induced neurotoxicity through IGF1R and may act as a promising molecular target for the treatment of human neurotoxicity induced by bupivacaine	Down-regulated	MIR212, MIR132, lnc-HIC1-3, RTN4RL1, TSR1, PITPNA, SGSM2, SLC43A2, SMG6, RF00017-2214
16	miR-149	2q37.3	miR-149 is generally recognized as a tumour suppressor with reduction in distinct cancers, while it is also reported that miR-149 could function as an oncogene	Down-regulated	LOC100130449, MIR149, HDLB, PGPC1
17	miR-137	1p21.3	VKORC1 is a direct target of miR-137 and the miR-137 rs2660304 polymorphism is associated with warfarin maintenance dose in patients with atrial fibrillation	Down-regulated	VKORC1, MIR2682, MK631887, MIR137, ENSG00000259946, MIR137HG, MK631885, lnc-SNX7-10

Table 1 (continued)

Entry	miRNA	Location	Roles	Disregulation pattern	Predicted targeted genes
18	miR-203A	14q32.33	miR-203a-3p promotes cancer cell proliferation, colony formation and migration and invasion by targeting PDE4D	Down-regulated	PDE4D, MIR203A, MIR203B, lnc-KIF26A-1
19	miR-329	14q32.31	It serves a tumor suppressive role in colorectal cancer by directly targeting transforming growth factor beta-1	Down-regulated	TGF-β1, MIR377, MIR154, MIR496, MIR134, MIR323B, MIR485, MIR487A, MIR329-1, MIR329-2, MIR323A, MIR758, ENSG00000222185, ENSG00000222095

the clinical values of specific miRNAs (either used alone or in combination) for the diagnosis and prognosis of GBM. They have attempted to use the specific miRNAs to treat GBM or improve the efficacy of other chemotherapeutics. A large amount of research data has been accumulated therein. However, there are still many issues to overcome in the GBM clinical applications of targeted miRNA therapy, and the efficacy and safety profiles also merit further studies. With the development of the molecular biology and techniques of drug synthesis, it is believed that GBM diagnosis and treatment methods based on specific miRNAs will usher in further development.

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Compliance with ethical standards

Conflict of interest All authors declared no conflict of interest. All authors agreed and approved the final manuscript for publication.

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