

The miR-200 family: multiple effects on gliomas

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Abstract: Gliomas are the most common type of primary brain tumors. MicroRNAs (miRNAs) are small noncoding RNAs that can epigenetically regulate target gene expression. The microRNA 200 family includes miR-200a, 200b, 200c, 141 and 429. Numerous studies have indicated that members of the miR-200 family play an important role in glioma development and metastasis. In this review, we summarize the data from various studies and highlight the effects of miR-200 on glioma metastasis, therapeutic response and prognosis.

Keywords: glioma, miR-200 family, metastasis, chemoresistance, radioresistance

Introduction

Gliomas are the most common type of primary brain tumors, accounting for almost 30% of central nervous system tumors and 80% of all malignant brain tumors.^{1,2} Based on the World Health Organization (WHO) classification, gliomas can be divided into four grades – WHO I, II, III and IV.³ Glioblastoma (GBM; WHO grade IV) is the most common and aggressive primary brain tumor in adults, accounting for ~46% of primary malignant brain tumors.⁴ Gliomas are characterized by their rapid growth and high degree of infiltration. Despite the difficulty in surgically removing gliomas,⁵ the current primary treatments include surgical resection, radiotherapy and chemotherapy. Unfortunately, despite the remarkable development in surgery and adjuvant therapy, the median survival rate for patients with gliomas has not considerably improved over the past few decades. Furthermore, clinical outcomes remain poor due to the adverse events that accompany these treatments and the increasing resistance to radiotherapy and chemotherapy.^{6–8} The underlying mechanisms of glioma pathogenesis are still largely unknown. Thus, improving our understanding of glioma molecular pathogenesis is necessary to develop more efficacious and precise treatment schemes.

MicroRNAs (miRNAs) are small noncoding RNAs that are 17–24 nucleotides in length. miRNAs regulate target gene expression through inhibiting translation or degrading target mRNAs.⁹ It has been reported that miRNAs regulate cell growth associated with the development and metastasis of cancers.¹⁰ Some miRNAs have been specifically implicated in glioma pathogenesis. For example, recent reviews have indicated that circulating miRNAs could be potential glioma biomarkers and reported that miRNAs are associated with drug resistance, which may have direct therapeutic implications.^{9,11,12}

The miRNA-200 family consists of miR-200a, 200b, 200c, 141 and 429. All these miRNAs are derived from two different gene clusters. miR-200a, miR-200b and miR-429 are derived from chromosome 1p33.36, and miR-200c and miR-141

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are derived from chromosome 12p13.3 (Table 1).¹³ These miRNAs are highly homologous, with only one nucleotide difference in their seed sequences (Table 1).¹³ Increasing evidence demonstrates that the microRNA-200 family is closely associated with glioma initiation, progression and metastasis.^{14,15} The goal of this review is to update the research field on the multiple roles of the miR-200 family in gliomas.

miR-200 expression in gliomas

Studies that have identified miRNAs that are aberrantly expressed in gliomas have provided important information regarding the roles of miRNAs in tumor biology. Studies that focused on the miRNA-200 family have offered new insight into glioma development and metastasis. Interestingly, while these studies have utilized different detection platforms and samples to identify differentially expressed miRNAs (Table 2), the majority found that miR-200a, 200b, 200c, 141 and 429 are downregulated in glioma tissues.^{15–22} More interestingly, miR-200a was consistently lower in grade IV (GBMs) gliomas compared to low-grade II and III (LGs) gliomas, suggesting that miR-200a is responsible for glioma histological grading.¹⁷ However, some members of the miR-200 family were upregulated in gliomas. For example, one study showed that miR-429 was upregulated in glioma compared to non-neoplastic brain tissues.²³ Another study demonstrated that miR-141-3p was upregulated in high-grade gliomas (grades III and IV) compared to that of non-cancerous brain tissues or even LG gliomas (grades I and II).²⁴ Intriguingly, although one study showed that miR-200b was upregulated in glioma compared to normal brain tissues, inhibiting miR-200b expression enhanced pathological grading of glioma; therefore, miR-200b was still thought to be a tumor suppressor gene.²⁵ Of note, the reduced expression of miRNAs in the miR-200 family in gliomas was associated with epigenetic regulation. One study reported that DNA methylation and histone modifications repressed miR-200a, 200b and 429 expression, which promoted glioblastoma progression.²⁶

The variation in miRNA expression data from these studies might reflect a context-dependent expression pattern that relies on histological type or glioma grade. Indeed, it was reported that dysregulation of miRNAs might be associated with tumor stage, grade and progression status.²⁷ Therefore, the underlying mechanism of miRNA control of glioma warrants additional research.

miR-200 and metastasis of gliomas

Metastasis involves multiple steps that promote tumor cells to migrate from the primary tumor site and colonize in distant organs or tissues.²⁸ Interestingly, extracranial metastasis is rare in malignant gliomas,²⁹ which has been reported in only ~0.5% of patients.³⁰ The low incidence of extracranial metastasis could be attributed to some intrinsic biological obstacles, such as lack of the lymphatic system, which is crucial for systemic dissemination, or the presence of dense dura around cerebral veins, which inhibits tumor cell migration.²⁹

One study indicated that miR-200a inhibits glioma cell growth, migration and invasion by targeting single-minded homolog 2-short form (SIM2-s).¹⁶ Similarly, many studies have demonstrated that miR-200b inhibits glioma cell proliferation and invasion. More specifically, miR-200b can target different genes, including cAMP responsive element-binding protein 1 (CREB1), zinc finger E-box binding homeobox 2 (ZEB2), prominin 1 (PROM1), extracellular signal-regulated kinase 5 (ERK5), CD133^{10,19,31–33} and lactate dehydrogenase A (LDHA), which is associated with glioma cell proliferation and invasion. Therefore, targeting LDHA by miR-200b is regarded as a promising therapeutic strategy in glioma.³⁴ Moreover, miR-200b was reported to be involved in blood-tumor barrier (BTB) permeability. For example, miR-200b overexpression was associated with reduced expression of RhoA and ROCKII and subsequently contributed to a decrease in BTB permeability.³⁵ Therefore, downregulation of miR-200b may initiate a signaling cascade that increases BTB permeability and facilitates glioma cell invasion.

Table 1 The miR-200 family and their seed sequences

miR-200	Chromosome Location	Seed sequence of mature miRNAs
miR-200a	chromosome 1p33.36	UAACACUGUCUGGUAACGAUGU
miR-200b	chromosome 1p33.36	UAA U ACUGCCUGGUAUUGAUGA
miR-200c	chromosome 12p13.31	UAA UACUGCCGGGUAUUGAUGGA
miR-141	chromosome 12p13.31	UAA C ACUGUCUGGUAUUGAUGG
miR-429	chromosome 1p33.36	UAA U ACUGUCUGGUAUUAACCGU

Note: Seed nucleotide differences are highlighted.

Abbreviation: miRNAs, microRNAs.

Table 2 Literature summary of studies focused on miRNA 200 family expression in gliomas

Study	Samples/controls	miR-200 expression	Conclusion
Su et al (2014) ¹⁶	Samples: human glioma Controls: normal brain tissue	Decreased expression of miR-200a in glioma samples compared to normal brain tissue	miR-200a acted as a tumor suppressor by targeting the SIM2-s gene in gliomas
Berthois et al (2014) ¹⁷	Samples: 24 primary GBMs Controls: 10 low grade brain tumors (LGs)	miR200a was downregulated in GBMs compared to LGs	miR200a was involved in glioma progression and therapeutic response
Liu et al (2014) ¹⁸	Samples: 73 glioma tissues Controls: 30 normal brain tissues	miR-200b was downregulated in glioma tissues	miR-200b, as a tumor suppressor by targeting the RAB family, was a potential biomarker for glioma prognosis
Li et al (2016) ¹⁹	Samples: 88 cases of glioma specimens Controls: 25 normal brain tissues	miR-200b levels were decreased in primary glioma tissues compared to normal brain tissues	miR-200b had suppressive effects on glioma cells via targeting ZEB2
Wang et al (2015) ²⁵	Samples: primary gliomas from 123 patients (including 38 astrocytoma, 53 glioblastoma, and 32 ependymoma) Controls: normal brain tissues	miR-200b was increased in glioma tissues compared with normal brain tissues. A decrease in miR-200b expression with increasing pathological grading of gliomas	miR-200b levels were associated with the histological grading of gliomas. miR-200b could become a useful independent prognostic factor for glioma
Qin et al (2017) ¹⁵	Samples: human glioma samples (including grade II, grade III, and grade IV glioma tissues) Controls: paratumor tissues	miR-200c was reduced in glioma tissues compared to paratumor tissues	miR-200c played an important role in regulating glioma by targeting moesin
Peng et al (2016) ²⁰	Samples: glioma tissues from 36 patients with primary glioma Controls: adjacent normal tissues	miR-141 was lower in glioma compared to adjacent non-cancerous tissues	miR-141 acted as a tumor suppressor by targeting TGF- β 2
Zhou et al (2017) ²⁴	Samples: 27 human glioma specimens Controls: 5 normal brain tissues	miR-141-3p was increased in glioma tissues	miR-141-3p promoted tumor growth by targeting p53 and increased resistance in glioma cells to temozolomide
Chen et al (2015) ²¹	Samples: 12 glioma tissues Controls: adjacent non-tumor tissues	miR-429 was lower in glioma tissues than in adjacent non-neoplastic tissues	miR-429 had an important function in glioma invasion through BMK1 suppression
Sun et al (2016) ²³	Samples: 92 gliomas (including 11 grade I, 37 grade II, 24 grade III, and 20 grade IV) Controls: non-neoplastic brain tissues	miR-429 was increased in glioma tissues compared to non-neoplastic brain tissues	miR-429 was upregulated in glioma tissues. Patients with high miR-429 level had lower 5-year survival rates

Abbreviations: miRNA, microRNA; GBMs, glioblastomas.

On the other hand, several studies have reported that miR-200c plays an important role in regulating glioma cell growth and invasion. For example, one study showed that miR-200c overexpression impaired glioma cell proliferation and invasion by targeting moesin.¹⁵ Another study found that miR-200c prevented the invasion and migration of glioblastoma by activating EGFR pathways that reversed the epithelial–mesenchymal transition in glioblastoma.³⁶ Intriguingly, due to the homology in seed sequences, miR-200c and miR-141 share the same target, ZEB1, which is known to inhibit glioma cell growth and migration.³⁷ However, recent studies obtained inconsistent results. For example, one study reported that miR-141, acting as a tumor suppressor, inhibited glioma cell proliferation, migration and invasion by targeting TGF- β 2,²⁰ while another study indicated that miR-141-3p promoted glioblastoma progression and temozolomide resistance by

targeting p53.²⁴ Similarly, another report suggested that miR-429 was a potential tumor-suppressive miRNA and inhibited glioblastoma proliferation by targeting SOX2,³⁸ while a contrasting study reported that miR-429 was upregulated in glioma tissues, suggesting that miR-429 contributes to glioma progression.²³ The exact reason for the discrepancies in these studies is still unclear, but it suggests that members of miR-200 family might play context-dependent roles. Hence, more studies are needed to clarify the functional roles of miR-200 family in gliomas.

Long non-coding RNAs (lncRNAs) might also interact with microRNAs in glioma.³⁹ One study reported that miR-200a was negatively regulated by the lncRNA ATB, which is involved in glioma malignancy.⁴⁰ lncRNA TCF7 can also bind to miR-200c and inhibit miR-200c expression, which can promote glioma cell proliferation, self-renewal and

migration.⁴¹ Conversely, increasing data indicate that miRNAs have the capacity to regulate lncRNAs. For example, lncRNA HOTAIR was found to be a downstream target of miR-141, which is involved in glioma cell proliferation, migration and invasion.⁴² One study also demonstrated that miR-429 directly targeted the lncRNA XIST, which promoted glioma tumorigenicity.⁴³ Therefore, a better understanding of the relationship between lncRNA and miRNA can help to develop potentially new therapeutic strategies for gliomas.

Effect of miR-200 on chemotherapeutic and radiotherapeutic responses and glioma prognosis

Given the difficulty in resecting whole glioma tumors, relapse frequently occurs following surgery. Therefore, treatment schemes for gliomas often include chemotherapy and/or radiotherapy after surgery. The first-line glioma drugs are temozolomide and bevacizumab. However, due to resistance to chemotherapeutic drugs and intolerance to radiotherapy, patients with glioma have poor prognoses. Increasing data indicate that the miR-200 family might contribute to some of the drug resistance in glioma treatment.

High levels of the DNA repair enzyme, O⁶-methylguanine methyltransferase (MGMT), are thought to be the main mechanism by which glioblastoma develops resistance to temozolomide.^{44,45} Interestingly, one study found that overexpression of miR-200a inhibits MGMT activity and promotes temozolomide sensitivity; however, overexpression of MGMT also inhibited miR-200a expression.¹⁷ The exact mechanism by which MGMT affects miR-200a remains unclear, but some reports speculate that apoptosis is involved.^{17,46} In addition, although several studies have reported that miR-141 functions as a tumor suppressor that represses glioma cell proliferation and invasion,²⁰ one study indicated that miR-141-3p promoted temozolomide resistance by inhibiting p53 expression in an orthotopic mouse model of human glioma, and that inhibition of miRNA-141-3p reduced glioma cell growth and prolonged survival rates in glioma-bearing mice.²⁴ Radiotherapy is an additional glioma treatment strategy. One study demonstrated that miR-200c increases glioma cell radiosensitivity by activating EGFR-associated signaling.³⁶

Apart from chemotherapy and radiotherapy, immunotherapy has recently emerged as an alternative glioma treatment.^{47–49} However, some glioma patients benefit from immunotherapy, but others do not.⁵⁰ For those who do not respond to immunotherapy alone, combinatorial treatment with miRNAs may be prove beneficial. Evidence suggested

that the miR-200 family could modulate the tumor immune response. For example, myeloid-derived suppressor cells (MDSCs) can produce reactive oxygen species and suppress tumor immune response and modulate the tumor environment.⁵¹ Furthermore, it was reported that miR-200c plays a significant role in the regulation of tumor-associated MDSCs.⁵² However, the exact relationship between the miR-200 family and glioma immunotherapy is still largely unknown. Therefore, future detailed studies are needed to improve the efficacy of immunotherapy.

Overall, the current data suggest that the miR-200 family could influence clinical outcomes and glioma prognosis through multiple mechanisms. Indeed, it has been clearly demonstrated that higher miR-200b expression correlates with better outcomes and a significantly higher 5-year survival rate in glioma patients and that reduced miR-200b expression might be associated with poor prognosis.^{18,22,25,53} In contrast, one study reported that high miR-429 expression correlates with poor prognosis in glioma patients,²³ while other studies indicated that miR-429 functions as either an oncogene or a tumor suppressor.^{54,55} The underlying mechanism for this discrepancy is unknown; therefore, more research is needed to clarify the roles of miR-429 in gliomas.

Interactions among different members of the miR-200 family in gliomas

It is well known that, similar to other miRNA families, each miRNA in the miR-200 family can regulate the expression of several mRNAs, and each mRNA can also be regulated by several miRNAs, forming a complex regulatory network (Table 3). Importantly, in gliomas, the target genes dysregulated by miR-200 are associated with many conserved signaling pathways involved in cell processes such as cell proliferation, apoptosis, invasion and drug resistance.^{20,24,36,37} Because miR-200 can target multiple downstream genes in glioma tissues, miR-200 might play both oncogenic and antioncogenic roles. For instance, TGF- β 2 regulates many cellular processes including proliferation, differentiation, adhesion and migration.⁵⁶ TGF- β 2 expression is upregulated in glioma,⁵⁷ and TGF- β 2 has been found to play an important role in glioma initiation and development.⁵⁸ In this context, miR-141 acts as a tumor suppressor by targeting TGF- β 2.²⁰ However, the tumor suppressor p53 is also a direct target of miR-141.²⁴ Therefore, miR-141 may also function as an oncogenic factor through negatively targeting p53 to promote tumor growth and inhibit cell apoptosis. Future research should focus on the specific biological context of miR-200 in gliomas.

Table 3 Target genes of the miR-200 family in glioma tissues

miRNA	miRNA targets (mRNA)	Reference
miR-200a	SIM2-s, TGF- β 2	16,40
miR-200b	RAB family, ZEB2, CREB1, CD133, LDHA, RhoA, ROCKII, PROM1, ERK5	10,18,19,31–35
miR-200c	Moesin, VEGF, HIF-1 α , MMP2, ZEB1	15,36,37
miR-141	ATF5, ZEB1, TGF- β 2, p53, HOTAIR, SKA2	14,20,24,37,42
miR-429	BMK1, SOX2	21,38

Abbreviation: miRNA, microRNA.

Conclusion

Numerous studies have shown that members of the miR-200 family, as epigenetic regulatory molecules, can regulate physiological and pathological processes through targeting multiple downstream genes, consequently affecting proliferation and invasion of glioma cells as well as the therapeutic response and prognosis of gliomas. Intriguingly, the contradictory roles of microRNAs, especially miR-141 and miR-429, may differentially impact glioma development and progression. In the future, more detailed studies are needed to delineate the underlying mechanisms by which miRNAs in the miR-200 family affect glioma cells to develop more efficient treatments.

Disclosure

The authors report no conflicts of interest in this work.

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