MicroRNA-202 inhibits cell proliferation, migration and invasion of glioma by directly targeting metadherin

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Abstract. Glioma is the most common and aggressive type of primary malignant brain tumour. Increasing evidence has revealed that microRNAs play important roles in multiple biological processes related to glioma occurrence, development, diagnosis, treatment and prognosis. MicroRNA-202 (miR-202) has been studied in several types of human cancer, whereas the biological roles of miR-202 in glioma remain unknown. The present study, aimed to investigate the expression, clinical significance and biological roles of miR-202 in glioma, as well as its underlying molecular mechanism. We found that miR-202 was significantly down-regulated in glioma tissues and cell lines. Low miR-202 expression was associated with Karnofsky performance status (KPS) score and World Health Organization (WHO) grade of glioma patients. Functional assays revealed that ectopic expression of miR-202 inhibited cell proliferation, migration and invasion of glioma. In addition, metadherin (MTDH) was identified as a direct target gene of miR-202 in glioma through bioinformatic analysis, luciferase reporter assay, reverse transcription-quantitative polymerase chain reaction (RT-qPCR) and western blotting. Furthermore, MTDH expression was upregulated and negatively correlated with miR-202 expression in clinical glioma tissues. MTDH knockdown had similar roles to miR-202 overexpression in glioma cells. Rescue experiments revealed that upregulation of MTDH reversed the suppression of glioma cell growth and metastasis by miR-202. Moreover, miR-202 impaired the PI3K/Akt and Wnt/β-catenin pathways. These results highlight the tumour-suppressive effect of miR-202 in glioma, thereby suggesting that miR-202 may be a potential therapeutic target for the treatment of patients with this malignancy.

Introduction

Glioma is the most common and aggressive type of primary malignant brain tumour derived from glial cells and accounts for ~35-61% of all intracranial tumours (1). It can be classified into the following subtypes according to histology: astrocytomas, anaplastic astrocytomas, glioblastomas and other subtypes (1). The biological characteristics of glioma are high recurrence rates, uncontrollable invasiveness, strong angiogenesis and widespread hypoxia (2-5). Currently, therapeutic treatments for glioma include surgical excision, chemotherapy, radiation and biological therapies (6), among which surgery is the most preferred treatment. Radiation therapy and chemotherapy are considered effective supplementary treatment after surgery to prevent recurrence and metastasis (7). Despite the considerable progress in the treatment of predominant glioma, the average survival time of glioma patients is 9-12 months only (8,9). Therefore, understanding the molecular mechanisms of glioma tumourigenesis and progression are essential to the development of novel strategies for glioma therapy.

MicroRNAs (miRNAs) belong to a large group of evolutionarily conserved, short, endogenous and non-coding RNA molecules with ~19-22 nucleotides in length (10). miRNAs negatively modulate gene expression transcriptionally or post-transcriptionally by binding to the 3' untranslated regions (3'UTRs) of their target genes, thereby inducing their degradation or inhibiting their translation (11). Increasing evidence has demonstrated that miRNAs have been implicated in the regulation of various physiological and pathological processes including cell growth, the cell cycle, cell division, apoptosis, invasion, metastasis and angiogenesis (12-15). Over the past decade, aberrant expression of miRNAs has been implicated in a wide range of human types of cancer, such as miR-548b in glioma (16), miR-19b in gastric cancer (17), miR-181b in colorectal cancer (18) and miR-126 in hepatocellular carcinoma (19). An increasing number of studies have indicated that the dysregulation of miRNAs is closely associated with tumour occurrence and development (20,21). Specifically, downregulated miRNAs act as tumour suppressors in tumourigenesis by downregulating oncogenes, whereas other overexpressed miRNAs may function as tumour promoters via negative regulation of tumour suppressors (22,23). These findings demonstrated that miRNAs are potential therapeutic targets for cancer diagnosis, treatment and prognosis.
miR-202, located in 10q26, has been studied in several types of human cancers (22,24,25), however information concerning miR-202 in glioma is insufficient. The present study aimed to investigate miR-202 expression in glioma, to determine its correlation with clinicopathological parameters and identify the biological roles of miR-202 in glioma. The molecular mechanism underlying its tumour-suppressive effect was also elucidated. The results of the present study may contribute towards identifying a novel therapeutic target for the treatment of glioma.

Materials and methods

Tissue samples and cell lines. The present study was approved by the Ethics Committee of The First Affiliated Hospital of Henan University of Science and Technology (Henan, China). Written consent was also acquired from all glioma patients. Glioma and paired adjacent normal tissues were obtained from 43 glioma patients who underwent surgery at the Department of Neurosurgery of The First Affiliated Hospital of Henan University of Science and Technology. None of these patients were treated with neoadjuvant radiotherapy and adjuvant chemotherapy.

Five glioma cell lines (A172, U87, U251, U373 and LN229) and primary normal human astrocytes (NHAs) were purchased from the American Type Culture Collection (ATCC; Manassas, VA, USA). All cells were grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS) (both from Invitrogen, Carlsbad, CA, USA) in a humidified incubator at 37°C with 5% CO2.

Cell transfection. miR-202 mimics and miRNA negative control (miR-NC) were obtained from GenePharma (Shanghai, China). Small interfering RNA targeting metadherin (MTDH) (si-MTDH) and its negative control (si-NC) were synthesised by RiboBio (Guangzhou, China). MTDH overexpressed plasmid (pCDNA3.1-MTDH) and blank plasmid (pCDNA3.1) were purchased from the Chinese Academy of Sciences (Changchun, China). For functional assays, the cells were seeded into 6-well plates and transfected with miR-202 mimics, miR-NC, si-MTDH, si-NC, pCDNA3.1-MTDH or pCDNA3.1 using Lipofectamine 2000 reagent (Invitrogen) according to the manufacturer’s protocol.

Reverse transcription-quantitative polymerase chain reaction (RT-qPCR). Total RNA was extracted form tissues or cells using TRIzol reagent (Invitrogen). A NanoDrop® ND-1000 spectrophotometer was used to determine the purity and concentration of total RNA. TaqMan MicroRNA assay (Applied Biosystems, Foster City, CA, USA) was performed to detect miR-202 expression, with U6 used as the endogenous control. For mRNA expression, reverse transcription was performed using M-MLV Reverse Transcription system (Promega Corporation, Madison, WI, USA), followed by qPCR with SYBR Premix Ex Taq (Takara, Dalian, China). β-actin was used as an internal control for MTDH mRNA expression. The relative expression was analysed using the 2−ΔΔCt method (26). Primers are shown in Table I.

Cell Counting Kit-8 (CCK-8) assay. CCK-8 assay (Dojindo, Kumamoto, Japan) was performed to examine the cell proliferative capacity. Briefly, transfected cells were trypsinised, collected and re-seeded into 96-well plates at a density of 3,000 cells in 200 µl of medium in each well. Subsequently, the cells were incubated at 37°C with 5% CO2 for 24, 36, 48 and 72 h. At each time-point, a CCK-8 assay was performed according to the manufacturer’s instructions. CCK-8 reagent (10 µl) was added into each well and incubated at 37°C for another 4 h. The absorbance at 450 nm (OD450) was assessed using a microplate reader (Bio-Rad, Hercules, CA, USA).

Cell migration and invasion assays. Cell migration and invasion assays were used to determine the ability of glioma cell metastasis. Transfected cells were trypsinised, collected and re-suspended in FBS-free culture medium at 48 h post-transfection. For the migration assay, 1x105 cells were added into the upper chamber of a Transwell plate (BD Biosciences, Franklin Lakes, NJ, USA). The lower chamber was filled with 500 µl culture medium containing 20% FBS as a chemotactant. After incubation at 37°C with 5% CO2 for 48 h, the non-migrated cells were carefully removed with cotton swabs. The migrated cells were fixed, stained, washed and dried in air. Finally, migrated cells were photographed and counted in five random fields using an inverted microscope (Olympus Corporation, Tokyo, Japan). Cell invasion assays were conducted in a similar manner to the cell migration assays except that Transwell chambers were pre-coated with Matrigel (BD Biosciences, San Jose, CA, USA).

Bioinformatic analysis. Potential targets of miR-202 were analysed using publicly available algorithms: microRNA (www.microrna.org/microrna/home.do) and TargetScan (www.targetscan.org).

Western blotting. Total protein was isolated from tissues and cells using ice-cold RIPA lysis buffer (150 mm NaCl, 1% NP-40, 0.5% deoxycholate and 1% SDS). The concentration of total protein was detected using BCA assay kit (Beyotime Institute of Biotechnology, Haimen, China) according to the manufacturer's instructions. Equal amounts of proteins were resolved on 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and transferred to

Table I. RT-qPCR primers.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Sequences (5'→3')</th>
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<tbody>
<tr>
<td>miR-202</td>
<td>F CTCCTCAGGTGTCGCTGTC</td>
</tr>
<tr>
<td>R</td>
<td>GTGTCAGCTATCGGTGC</td>
</tr>
<tr>
<td>U6</td>
<td>F ATCTCCAGGGCTAAGCAG</td>
</tr>
<tr>
<td>R</td>
<td>GCCAGTGCTATCGGTGC</td>
</tr>
<tr>
<td>MTDH</td>
<td>F CTGAGCGAGAATGAGGA</td>
</tr>
<tr>
<td>R</td>
<td>CTGAGCGAGAATGAGGA</td>
</tr>
<tr>
<td>GAPDH</td>
<td>F ATAGCACAGCCTGGATAGCAACG</td>
</tr>
<tr>
<td>R</td>
<td>CACACAGTCAATTAGCCTTGTTG</td>
</tr>
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microRNA-202, miR-202; F, forward; R, reverse; MTDH, metadherin.
polyvinylidene fluoride membranes (Millipore, Billerica, MA, USA). The membranes were blocked with 5% skimmed milk in Tris-buffered saline containing 0.1% Tween-20 (TBST) at room temperature for 1 h, incubated with primary antibodies at 4°C overnight and washed in TBST three times. The primary antibodies used in the present study included mouse anti-human monoclonal MTDH (1:1,000 dilution; sc-517220), rabbit anti-human polyclonal AKT (sc-8312; 1:1,000 dilution), mouse anti-human monoclonal p-AKT (sc-514032; 1:1,000 dilution), β-catenin (sc-59737; 1:1,000 dilution), p-β-catenin (sc-57534; 1:1,000 dilution) and mouse anti-human monoclonal GAPDH (1:1,000 dilution; sc-137179) (all from Santa Cruz Biotechnology, Santa Cruz, CA, USA). Subsequently, the membranes were probed with goat anti-mouse horseradish peroxidase (HRP)-conjugated secondary antibody (1:4,000 dilution; Santa Cruz Biotechnology) for 1 h at room temperature. Finally, the protein bands were visualized using enhanced chemiluminescence (ECL; Pierce, Rockford, IL, USA). GAPDH was used as a loading control.

Luciferase reporter assay. Luciferase reporter plasmids, pGL3-MTDH-3'UTR wild-type (Wt) and pGL3-MTDH-3'UTR mutant (Mut), were synthesised and confirmed by GenePharma. HEK293T cells (Cell Bank of the Chinese Academy of Sciences, Shanghai, China) were seeded into 24-well plates at a density of 40-50% confluency. The cells were incubated at 37°C with 5% CO₂ overnight and transfected with a reporter plasmid, along with miR-20 mimics or miR-NC using Lipofectamine 2000. Following 48 h of incubation, the cells were harvested and the luciferase activity was determined using a Dual-Luciferase Reporter Assay System (Promega, Manheim, Germany). Renilla luciferase activity was used for normalization.

Statistical analysis. All data are expressed as the mean ± SD and analysed using Student’s t-tests or one-way ANOVA with SPSS 19.0 software (SPSS, Inc., Chicago, IL, USA). The correlation between miR-202 and MTDH mRNA expression was analysed using Spearman's correlation analysis. P<0.05 was considered to indicate statistically significant differences.

Results

miR-202 is downregulated in glioma tissue and cell lines. First, we assessed miR-202 expression in glioma and paired adjacent normal tissues using RT-qPCR. As shown in Fig. 1A, the expression of miR-202 in glioma tissues was lower than that in paired adjacent normal tissues (P<0.05). In addition, decreased miR-202 expression was observed in five glioma cell lines (A172, U87, U251, U373 and LN229) compared with primary NHA (Fig. 1B; P<0.05). These results revealed that miR-202 was downregulated in both glioma tissue and cell lines.

Correlation between the expression of miR-202 and the clinicopathological features in glioma patients. We then examined the correlation between the expression of miR-202 and the clinicopathological parameters of glioma patients. As shown in Table II, the expression levels of miR-202 were closely correlated with the KPS score (P=0.037) and WHO
grade (P=0.009). However, no significant correlations were found between the expression level of miR-202 and other clinicopathological factors, including sex, age or tumour size (all P>0.05).

miR-202 attenuates cell proliferation, migration and invasion of glioma. To examine the functions of miR-202 in glioma progression, miR-202 mimics were transiently transfected into U251 and U87 cells to increase expression (Fig. 2A; P<0.05). Firstly, we performed a CCK-8 assay to evaluate the effect of miR-202 on U251 and U87 cells. The results revealed that miR-202 overexpression inhibited the proliferative capacity of U251 and U87 cells (Fig. 2B; P<0.05). Cell migration and invasion assays were conducted to assess the role of miR-202 in metastasis. As shown in Fig. 2C, the resumption of miR-202 expression decreased the metastatic abilities in both U251 and U87 cells (P<0.05). Overall, these results revealed that miR-202 inhibited the cell growth and metastasis of glioma.

MTDH is a direct target of miR-202 in glioma. To better understand the molecular mechanism underlying the tumour-suppressive effect of miR-202 in glioma, the direct target genes of miR-202 were explored. Firstly, bioinformatic analysis was performed to predict the potential candidates of miR-202. Among various potential targets, MTDH attracted our attention since the 3'UTR of MTDH contains putative target sequences for miR-202 (Fig. 3A). Moreover, MTDH is highly expressed in glioma and involved in the tumourigenesis and progression of glioma (27-29). To confirm this hypothesis, a luciferase reporter assay was performed in HEK293T cells transfected with miR-202 mimics or miR-NC, along with luciferase reporter plasmids carrying WT and Mut sequences of the predicted binding sites. The results revealed that miR-202 markedly decreased the luciferase activities of pGL3-MTDH-3'UTR WT (Fig. 3B; P<0.05), but did not affect the activity of pGL3-MTDH-3'UTR Mut. Thus, miR-202 could directly target the 3'UTR of MTDH.

To further confirm the influence of miR-202 on the expression of MTDH, the mRNA and protein expression levels of MTDH in U251 and U87 cells with miR-202 overexpression were detected using RT-qPCR and western blotting, respectively. We found that miR-202 overexpression significantly suppressed endogenous MTDH mRNA (Fig. 3C; P<0.05) and protein (Fig. 3D; P<0.05) expression levels in U251 and U87 cells. Collectively, these results revealed that miR-202 negatively regulated the expression of MTDH by directly binding to the 3'UTR of MTDH.

Inverse correlation between miR-202 and MTDH in glioma tissues. To further investigate the association between miR-202 and MTDH, the expression of MTDH in glioma tissues was determined. The results revealed that MTDH mRNA was significantly increased in glioma tissues compared with that in paired adjacent normal tissues (Fig. 4A; P<0.05). Furthermore,
MTDH protein expression in glioma tissues and cell lines was assessed. As shown in Fig. 4B and C, MTDH protein expression was obviously upregulated in glioma tissues and cell lines compared with that in adjacent normal tissues and primary NHA, respectively. Spearman's correlation analysis indicated an inverse correlation between miR-202 and MTDH mRNA expression in glioma tissues (Fig. 4D; \( r=-0.5503; P=0.001 \)).

Inhibition of MTDH produces similar effects to miR-202 overexpression in glioma. MTDH was identified as a direct target of miR-202. Therefore, we hypothesised that miR-202 suppresses cell growth and metastasis in glioma via inhibition of MTDH expression. To confirm this hypothesis, endogenous MTDH expression was knocked down in U251 and U87 cells using si-MTDH (Fig. 5A; \( P<0.05 \)). CCK-8, and cell migration and invasion assays revealed that inhibition of MTDH prevented the proliferation (Fig. 5B; \( P<0.05 \)), migration and invasion (Fig. 5C; \( P<0.05 \)) of U251 and U87 cells. These results demonstrated that MTDH knockdown had similar effects to miR-202 overexpression in glioma and indicated that MTDH was a direct and functional target of miR-202.

Restoration of MTDH expression reverses miR-202 suppression of glioma cell growth and metastasis. To explore whether miR-202 targeting of MTDH is responsible for the inhibition of growth and metastasis in glioma, we utilised rescue experiments. U251 and U87 cells were transfected with pcDNA3.1-MTDH or pcDNA3.1. As shown in Fig. 6A, MTDH was successfully overexpressed in pcDNA3.1-transfected U251 and U87 cells (\( P<0.05 \)). CCK-8 and cell invasion assays revealed that the inhibition of proliferation (Fig. 6B; \( P<0.05 \)), migration and invasion (Fig. 6C; \( P<0.05 \)) of miR-202 in U251 and U87 cells was markedly reversed by MTDH overexpression. These results demonstrated that the tumour-suppressive effect of miR-202 in glioma cells was partially dependent on MTDH suppression.

miR-202 inhibits the activation of the PI3K/Akt and Wnt/β-catenin signalling pathways in glioma. It has been previously reported that MTDH contributes to the activation of the PI3K/Akt and Wnt/β-catenin pathways (30,31). Considering the regulatory effect of miR-202 on MTDH, we hypothesized that miR-202 re-expression may decrease the PI3K/Akt and
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Figure 4. Expression levels of MTDH in glioma tissues, and the correlation between MTDH mRNA and miR-202 expression in glioma tissues. (A) RT-qPCR analysis of MTDH mRNA expression in glioma and paired adjacent normal tissues. (B) MTDH protein expression was significantly upregulated in glioma tissues compared with normal tissues. (C) Glioma cell lines expressed a higher MTDH protein expression than NHA. (D) Reverse correlation between MTDH mRNA and miR-202 expression in glioma tissues as determined by Spearman's correlation analysis; *P<0.05. MTDH, metadherin; NHA, normal human astrocytes.

Figure 5. Inhibition of MTDH has similar effects to miR-202 overexpression in glioma cells. (A) MTDH protein expression in U251 and U87 cells transfected with si-MTDH or si-NC was detected using western blotting. (B) CCK-8 and (C) cell migration and invasion assays were performed in U251 and U87 cells transfected with si-MTDH or si-NC; *P<0.05. MTDH, metadherin.
Wnt/β-catenin pathways by negatively regulating MTDH. To confirm this assumption, western blot analysis was employed to detect AKT, p-AKT, β-catenin and p-β-catenin expression levels in glioma cells after transfection with miR-202 mimics or miR-NC. As expected, miR-202 overexpression decreased p-AKT and p-β-catenin expression levels in U251 and U87 cells (Fig. 7; P<0.05). These results revealed that miR-202 impaired the PI3K/Akt and Wnt/β-catenin pathways by regulating MTDH.

Discussion

In recent years, miRNAs have been reported to be aberrantly expressed in various types of human cancers, such as glioma (32-34). Dysregulated expression of miRNAs is often correlated with malignant biological behaviours of glioma, such as rapid growth, metastasis, apoptosis inhibition, radiation and chemotherapy resistance (10,35). Therefore, miRNAs may be used as diagnostic markers, and miRNA-based therapy may be a valuable strategy for cancer treatment. In the present study, miR-202 was identified as a tumour-suppressor miRNA for glioma and low expression of miR-202 was detected in
glioma tissues and cell lines. Low miR-202 expression was associated with the KPS score and WHO grade of glioma patients. In addition, the restoration of miR-202 expression suppressed cell proliferation, migration and invasion in glioma. MTDH was identified as a direct functional target of miR-202. The upregulation of miR-202 inhibited the activation of the PI3K/Akt and Wnt/β-catenin signalling pathways in glioma. Our results demonstrated that miR-202 was poorly expressed in glioma cells, and thus may be a potential therapeutic target for glioma patients.

A previous study reported that miR-202 is frequently dysregulated in multiple types of human tumours. In gastric cancer, miR-202 is downregulated in tumour tissues and negatively correlated with tumour size and age (36). In oesophageal squamous cell carcinoma, miR-202 is poorly expressed in tumour tissues and inversely correlated with the degree of cell differentiation and lymph node metastasis. In addition, miR-202 is decreased in the peripheral blood of oesophageal squamous cell carcinoma patients and significantly associated with the development, invasion and metastasis of oesophageal squamous cell carcinoma (37). Moreover, low expression levels of miR-202 are observed in multiple myeloma (24), colorectal cancer (22), hepatocellular carcinoma (25), lung (38) and cervical cancer (39). The high frequency of miR-202 downregulation in these types of human types of cancer suggests that miR-202 could be a diagnostic and prognostic marker for specific cancers.

Abberantly expressed miR-202 plays an important role in the initiation and progression of several types of tumours. Sun et al found that miR-202 overexpression suppresses cell growth in vitro and in vivo and enhances cell apoptosis in osteosarcoma (40). Another study revealed that the restoration of miR-202 expression suppresses cervical cancer cell growth and metastasis (39). Ma et al reported that ectopic expression of miR-202 inhibits cell proliferation, migration and invasion and induces cell apoptosis of oesophageal squamous cell carcinoma (37,41). Meanwhile, Jiang et al (38) demonstrated that the upregulation of miR-202 decreases cell proliferation and improves the G0/G1 cell cycle arrest and apoptosis in lung cancer. These findings revealed that miR-202 plays an important role in these types of cancers, and may be investigated as a potential therapeutic target for the treatment of specific cancers.

To investigate how miR-202 functions as a tumour suppressor in glioma, we explored the direct targets of miR-202. To date, few genes have been validated as direct targets of miR-202, including Gli1 in gastric cancer (36), BAFF in multiple myeloma (42), ARL5A in colorectal cancer (22), LPR6 in hepatocellular carcinoma (25), LAMA1 in esophageal squamous cell carcinoma (41) and CCND1 in lung cancer (38). In the present study, we screened potential candidates of miR-202 via bioinformatic analysis. MTDH was selected for further investigation since MTDH is highly expressed in glioma and involved in the tumourigenesis and progression of glioma (27-29). Luciferase reporter assay further confirmed that the 3’UTR of MTDH could be directly targeted by miR-202. In addition, endogenous MTDH expression on mRNA and protein levels was decreased in glioma cells with miR-202 overexpression. MTDH expression was increased in glioma tissues and negatively correlated with miR-202 expression. MTDH knockdown had similar effects to miR-202 overexpression in glioma. Rescue experiments revealed that upregulation of MTDH reversed miR-202 suppression of glioma cell growth and metastasis. These results suggested that miR-202 exerted its tumour-suppressive effect in glioma partly by negatively regulating MTDH. Identification of the miR-202 target in glioma is important for understanding its role in the initiation and progression of glioma.

MTDH, also known as astrocyte elevated gene-1 (AEG-1) and lysine-rich CEACAM1 co-isolated (LYRIC), was originally identified as a neuropathology-associated gene in primary human fetal astrocytes (43). MTDH is significantly overexpressed in numerous human types of cancer, and its expression level is correlated with the progression and poor prognosis of malignant tumours, such as breast (44) and cervical cancer (45), and hepatocellular carcinoma (46). A number of studies have ascertained the important roles of MTDH in cell proliferation, apoptosis regulation, angiogenesis, migration, invasion and metastasis of various human cancers by activating signal pathways, including the Ha-Ras and PI3K/Akt, nuclear factor-κB, ERK/mitogen-activated protein kinase and Wnt/β-catenin and aurora-A kinase signalling pathways (30,47-49). In glioma, MTDH is highly expressed in tumour tissues and cell lines. The expression levels of MTDH are correlated with the metastasis and histological grade of gliomas (27,28). Functional assays demonstrated that MTDH acts as an oncogene in glioma and thus, regulated tumour cell proliferation, apoptosis and metastasis (27,50,51). Therefore, targeting MTDH may prolong the survival time and improve the outcome of patients afflicted with this aggressive and invariably fatal disease. MTDH may be a useful therapeutic target for the therapy of glioma patients.

In conclusion, the present study demonstrated that miR-202 may be associated with carcinogenesis and progression of glioma by targeting MTDH. Future studies are warranted to explore whether the potential of miR-202 may be fully realised in glioma treatments.

References


