MicroRNA-302a targets GAB2 to suppress cell proliferation, migration and invasion of glioma

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Abstract. Glioma is the most frequent and aggressive primary tumor of the brain in humans. Over the last few decades, significant progress has been made in early detection and multi-mode treatments, but the prognosis of gliomas is still extremely poor. MicroRNAs are endogenously expressed non-coding, single strand and short RNA molecules. Increasing number of studies demonstrated that microRNAs are dysregulated in a variety of human cancers, and play significant roles in tumorigenesis and tumor development, including glioma. In the present study, we for the first time found that microRNA-302a (miR-302a) was significantly downregulated in both glioma tissues and cell lines. In glioma patients, low miR-302a expression was correlated with KPS score and WHO grade. Restoration of miR-302a expression inhibited cell proliferation, migration and invasion of glioma in vitro. In addition, GAB2 was identified as a direct target of miR-302a. In clinical glioma tissues, GAB2 was upregulated and inversely correlated with miR-302a expression. GAB2 overexpression had similar biological roles with miR-302a overexpression in glioma cells, further confirming that GAB2 was a functional downstream target of miR-302a. Moreover, rescue experiments showed that upregulation of GAB2 effectively reversed the inhibition effects of miR-302a on glioma cells proliferation, migration and invasion. These findings suggested that miR-302a is an important tumor suppressor of glioma progression by directly targeting GAB2, thus providing new insight into the molecular mechanisms underlying glioma occurrence, development and evolution of glioma.

Introduction

Glioma is the most frequent and aggressive primary tumor of the brain in humans, and accounts for approximately 80% of primary malignant brain tumors (1,2). In view of their likely cellular origins, glioma could be classified into four groups, including astrocytomas, oligodendrogliomas, ependymomas and mixed tumors (3). Currently, the standard treatments of glioma include surgery resection followed by radiotherapy and chemotherapy (4). Despite significant progress made in early detection and multi-mode treatments over the last few decades, the prognosis of gliomas is still extremely poor (5). The average 5-year survival rate of glioma is only 4-5% and mean survival time following diagnosis is 12-15 months (6,7). The main cause of poor prognosis is that glioma is characterized by rapid growth, high invasiveness and suppression of cell apoptosis (8,9). Besides, poorly understanding the etiology and progression of glioma hampers the development of treatments and surveillance strategies (10). Therefore, fully understanding the molecular mechanisms underlying occurrence, development and evolution of glioma is urgently needed to investigate novel and effective therapeutic treatments.

microRNAs (miRNAs) are endogenously expressed non-coding, single strand and short RNA molecules that are approximately 18-25 nucleotide in length (11). miRNAs have been reported to participate in the regulation of human physiological and pathological processes, such as cell proliferation, cycle, apoptosis, differentiation, metabolism, migration, invasion and metastasis (12-14). miRNAs exert their regulatory functions through interacting with complementary sites that have the 3'-untranslated regions (3'UTRs) of target mRNAs, resulting in translation repression or mRNA degradation, and thus decreasing the protein expression of their target genes (15,16). An increasing number of studies demonstrated that miRNAs are dysregulated in a variety of human cancers, and play significant roles in tumorigenesis and tumor development (17-19). These miRNAs may have similar features to oncogenes or tumor suppressor genes mainly depending on the characteristic and roles of their target genes (20). Downregulated miRNAs in cancer may act as tumor suppressors and suppress carcinogenesis and progression by negatively regulating oncogenes. Conversely, upregulated miRNAs in
cancer may function as oncogenes through directly targeting tumor suppressors (21-24). Therefore, miRNAs may serve as novel therapeutic targets for antitumor therapeutic agents.

Although miR-302a has been reported to be frequently dysregulated in various human cancers, there is no information available concerning miR-302a in glioma. In the present study, we observed that miR-302a expression was downregulated in glioma tissues and cell lines. Moreover, reduced miR-302a expression was significantly correlated with KPS score and WHO grade of glioma patients. In addition, we provide evidence that miR-302a may act as a tumor suppressor in glioma by inhibiting cell proliferation, migration and invasion. Furthermore, we demonstrated that miR-302a exerted its tumor suppressive functions through directly targeting GAB2. These findings provide valuable clues toward fully understanding the molecular mechanisms underlying tumorigenesis and progression of glioma, and may present an opportunity to develop novel therapeutic targets for glioma treatments.

Materials and methods

Clinical specimens. Seventy-nine paired glioma tissues and adjacent normal tissues were obtained from surgical resections of glioma in the Department of Neurosurgery, Tangdu Hospital, Fourth Military Medical University, Shanxi, China. The adjacent normal tissue was defined as 2 cm away from the tumor tissue. All tissues were derived from glioma cases who had not been treated with chemotherapy or radiotherapy before operation. After excision, tissue samples were immediately frozen in liquid nitrogen and stored at -80 °C until use. This study was approved by the Ethics Committee of Tangdu Hospital.

Cell culture. Human glioma cell lines (U251, U87, U373, LN229, A172) and normal human glial cell line (HEB) were obtained from American Type Culture Collection (ATCC, Manassas, VA, USA). Human embryonic kidney (HEK) 293T cell line was purchased from Cell Bank of the Chinese Academy of Sciences (Shanghai, China). All cell lines were grown in Dulbecco's modified eagle's medium (Gibco, Carlsbad, CA, USA) supplemented with 10% fetal bovine serum (FBS; Gibco) and 1% penicillin/streptomycin (Gibco) at 37 °C in a humidified atmosphere with 5% CO₂.

Oligonucleotides and cell transfection. miR-302a mimics, miRNA mimics negative control (NC), siRNA targeting GAB2 (si-GAB2) and its negative control (si-NC) were chemically synthesized by GenePharma (Shanghai, China). Overexpression plasmid of GAB2 and its negative control (pCDNA3.1-GAB2 and pCDNA3.1) were purchased from RiboBio (Guangzhou, China). Cells were transfected with these oligonucleotides by using Opti-MEM I and Lipofectamine 2000 reagents (Invitrogen, Carlsbad, CA, USA) at approximately 50-70% confluence according to the manufacturer's instructions.

Quantitative reverse transcription polymerase chain reaction (qRT-PCR). Total RNA from tissues and cells was isolated using TRIzol reagent (Invitrogen). miR-302a expression was detected using TaqMan microRNA assays (Applied Biosystems, Foster City, CA) following the manufacturer's instructions. U6 was used as an internal control. For mRNA expression, single-stranded cDNA was synthesized from 1 μg of total RNA using an M-MLV Reverse Transcription system (Promega Corp., Madison, WI, USA) following the manufacturer's protocol. Real-time quantitative PCR was performed to measure GAB2 mRNA expression by using SYBR Premix Ex Taq (Takara, Dalian, China) and run in triplicate in an ABI Prism 7500 Sequence detection system (Applied Biosystems). GAPDH was used as an internal control. The relative gene expression was analyzed using the 2⁻ΔΔCt method.

Cell Counting Kit-8 assay. Transfected cells were harvested, seeded into 96-well plates at a density of 2000 cells/well and cultured for 24, 48, 72, and 96 h. At each time point, Cell Counting Kit-8 (CCK8) assay (Dojindo, Japan) was performed according to the manufacturer's instructions. Briefly, 10 μl of CCK8 solution was added into each well and incubated for 2 h at 37 °C in a humidified atmosphere with 5% CO₂. The absorbance at 450 nm was determined with a microplate reader (Thermo Scientific, Hudson, NH, USA).

Cell migration and invasion assays. Transwell chambers (24-well) with 8 μm pore size polycarbonate membrane (Millipore, Billerica, MA, USA) were used to carry out cell migration and invasion assays. For cell migration assays, cells were collected 48 h post-transfection and suspended in FBS-free culture medium. Cells (5x10⁴) were seeded on the top side of the Transwell chambers, culture medium containing 20% FBS was added to the low side of the Transwell chambers. After 48 h incubation in a humidified atmosphere with 5% CO₂ at 37 °C, cells remaining on the upper chambers were removed with cottons swabs. The migrated cells were fixed with 100% methanol, stained with 0.5% crystal violet, photographed and counted under an IX71 inverted microscope (Olympus, Tokyo, Japan). The procedures of cell invasion assays were similar to cell migration assays, except that the Transwell chambers were pre-coated with Matrigel (BD, Franklin Lakes, NJ, USA).

Bioinformatics analysis and luciferase reporter assay. The candidate target genes of miR-302a were generated using three publicly available databases: TargetScan (www.targetscan.org/), miRanda (www.microrna.org) and PicTar (http://pictar.mdc-berlin.de/).

The 3'UTR sequence of GAB2 predicted to interact with miR-302a as well as a mutated sequence with the predicted target sites were synthesized and inserted into pGL3 plasmid. HEK293T cells were seeded into 24-well plates and transfected with pGL3-GAB2-3'UTR Wt or pGL3-GAB2-3'UTR Mut, together with miR-302a mimics or NC by using FuGENE HD transfection reagent (Promega, Manheim, Germany). After 48 h of incubation, firefly and renilla luciferase activities were measured with Dual-Luciferase reporter assay system (Promega) following to the manufacturer's protocol. Firefly luciferase activities were used as an internal control for renilla luciferase activities.

Western blot analysis. The primary antibodies used were mouse anti-human monoclonal GAB2 antibody (1:1000 dilution; sc-365590; Santa Cruz Biotechnology, Santa Cruz, CA,
USA) and mouse anti-human monoclonal GADPH antibody (1:1000 dilution; sc-137179; Santa Cruz Biotechnology). Cells were collected at 72 h post-transfection, washed with ice-cold PBS (Gibco) and treated with RIPA protein lysis buffer supplemented with protease inhibitor. The homogenates were then centrifuged for 30 min at 4°C, 12,000 rpm, and the supernatants were collected as protein samples. Equal proteins were separated by 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis, transferred onto polyvinylidene fluoride membranes (Millipore) and probed with primary antibodies at 4°C overnight followed by incubation with goat anti-mouse horseradish peroxidase (HRP)-conjugated secondary antibody (1:5000 dilution; Santa Cruz Biotechnology). Finally, the blot was developed with the enhanced chemiluminescence (ECL) kit (Pierce Biotechnology, Rockford, IL, USA), and images were captured using the FluorChem imaging system (Alpha Innotech, San Leandro, CA, USA).

**Statistical analysis.** Data are expressed as mean ± SD. Statistical analyses were performed with SPSS 19.0 software (SPSS, Chicago, IL, USA) using Student’s t-tests or Chi-square tests. P<0.05 was considered to be statistically significant.

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**Figure 1.** Expression levels of miR-302a in glioma tissues and cell lines. (A) qRT-PCR was performed to measure miR-302a expression in paired glioma tissues and adjacent normal brain tissues. (B) qRT-PCR was performed to detect miR-302a expression in glioma cell lines (U251, U87, U373, LN229, A172) and a normal human glial cell line (HEB). Each assay was repeated at least three times. *P<0.05 compared with respective control.

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**Figure 2.** miR-302a overexpression inhibits U251 and U87 cell proliferation, migration and invasion. (A) qRT-PCR was performed to determine miR-302a expression in U251 and U87 cells following miR-302a mimics or NC transfection. (B) The proliferation of U251 and U87 cells transfected with miR-302a mimics or NC was determined by CCK8 assay. (C and D) Migration and invasion abilities of U251 and U87 cells transfected with miR-302a mimics or NC were evaluated by cell migration and invasion assays. Each assay was repeated at least three times. *P<0.05 compared with respective control.
Results

miR-302a is greatly downregulated both in glioma tissues and cell lines. To identify the roles of miR-302a in glioma, we first measured its expression in paired glioma tissues and adjacent normal brain tissues using qRT-PCR. Compared with adjacent normal tissues, glioma tissues showed reduced expression levels of miR-302a (Fig. 1A, P<0.05). Similarly, miR-302a expression was lower in glioma cell lines (U251, U87, U373, LN229, A172) compared with normal human glial cell line (heB) (Fig. 1B, P<0.05). Thus, the above results indicated that the downregulation of miR-302a may be critically involved in glioma occurrence and development.

Correlation between miR-302a expression and clinico-pathological features in gliomas. We next investigated the correlation between the miR-302a expression and clinico-pathological features in gliomas. As shown in Table I, low miR-302a expression was significantly correlated with KPS score (P=0.008) and WHO grade (P=0.035). However, there was no association between miR-302a expression and gender (P=0.709), age (P=0.593), family history of cancer (P=0.150), tumor size (P=0.442), and tumor location (P=0.427).

miR-302a suppresses U251 and U87 cell proliferation, migration and invasion in vitro. miR-302a was downregulated in glioma tissues and cell lines, hence the functions of miR-302a were investigated using miR-302a mimics in U251 and U87 cells. The transfection efficiencies were evaluated by measuring miR-302a expression in U251 and U87 cells after transfection with miR-302a mimics or NC. As shown in Fig. 2A, miR-302a expression levels were increased markedly compared with NC groups (P<0.05).

To investigate the effect of miR-302a overexpression on proliferation of glioma cells, CCK8 assay was performed. The results showed that restoration of miR-302a expression decreased U251 and U87 cell proliferation abilities (Fig. 2B, P<0.05). To explore whether the upregulation of miR-302a could influence the metastasis of glioma cells in vitro, cell
migration and invasion assays were used. As shown in Fig. 2C and D, ectopic of miR-302a expression reduced the number of migrated and invaded cells compared with those of NC groups (P<0.05). These results indicated that miR-302a had tumor-suppressive roles that could suppress glioma cell growth and metastasis.

GAB2 is a direct target of miR-302a. To investigate the molecular mechanism underlying the tumor suppressive roles of miR-302a in glioma, bioinformatic analysis was performed with publicly available databases. As shown in Fig. 3A, a binding site of miR-302a was observed in the 3’UTR of GAB2. Therefore, GAB2 could be a potential target of miR-302a.

To test this hypothesis, luciferase reporter assay was used. As shown in Fig. 3B, upregulation of miR-302a decreased the luciferase activities of pGL3- GAB2-3’UTR Wt in HEK293T cells (P<0.05) without change in luciferase activities of pGL3- GAB2-3’UTR Mut.

Furthermore, qRT-PCR and western blot analysis were performed to investigate whether miR-302a overexpression could downregulate GAB2 expression in glioma cells. We found that miR-302a could decrease GAB2 at mRNA (Fig. 3C, P<0.05) and protein (Fig. 3D, P<0.05) levels in U251 and U87 cells. These findings demonstrate that miR-302a negatively regulated GAB2 expression by directly binding 3’UTR of GAB2.

GAB2 is upregulated and inversely correlated with miR-302a expression in glioma tissues. Further experiments were performed to determine GAB2 mRNA and protein expression in paired glioma tissues and adjacent normal brain tissues. Results of qRT-PCR showed that GAB2 mRNA was significantly upregulated in clinical glioma tissues compared with

Table I. Correlation between miR-302a expression and clinico-pathologic characteristics in human glioma.

<table>
<thead>
<tr>
<th>Clinico-pathologic characteristics</th>
<th>Case no.</th>
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<th>P-value</th>
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<tr>
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</tr>
<tr>
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<tr>
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<tr>
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<tr>
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</tr>
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<tr>
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</tr>
<tr>
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<td></td>
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</tr>
<tr>
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<tr>
<td>III-IV</td>
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WHO, World Health Organization; KPS, Karnofsky performance score.
those in adjacent normal brain tissues (Fig. 4A, P<0.05). In addition, spearman's correlation analysis was adopted to analyze the relationship between miR-302a and GAB2 mRNA expression in glioma tissues and found that the expression level of miR-302a was inversely correlated with GAB2 mRNA in glioma tissues (Fig. 4B, r= -0.5642, P<0.0001). Furthermore, western blot analysis indicated that GAB2 protein expression was increased in glioma tissues in comparison with adjacent normal brain tissues (Fig. 4C, P<0.05).

**Knockdown of GAB2 exhibits similar effects with miR-302a overexpression in glioma cells.** To investigate the biological roles of GAB2 in glioma, siRNA targeting GAB2 was used to knock down GAB2 expression in U251 and U87 cells. The efficiency of si-GAB2 transfection was assessed by using western blot analysis. As shown in Fig. 5A, GAB2 protein was downregulated in both U251 and U87 cells (P<0.05). The effects of GAB2 underexpression on glioma cell proliferation, migration and invasion were determined using CCK8 assay and cell migration and invasion assays, respectively. As shown in Fig. 5B-C, downregulation of GAB2 significantly inhibited U251 and U87 cells proliferation (P<0.05), migration and invasion (P<0.05) in vitro. These results suggested that the knockdown of GAB2 had similar biological roles with
miR302a overexpression in glioma cells, further confirming that GAB2 was a functional downstream target of miR-302a.

Upregulation of GAB2 reverses the inhibitory effects of miR-302a in glioma cells. To explore whether the suppressive roles of miR-302a in glioma cells were mediated by GAB2, U251 and U87 cells were transfected with pCDNA3.1-GAB2. As shown in Fig. 6A, GAB2 protein was upregulated in U251 and U87 cells after transfection with pCDNA3.1-GAB2 (P<0.05). Rescue experiments were performed in U251 and U87 cells co-transfected with miR-302a mimics or NC, and pCDNA3.1-GAB2. As shown in Fig. 6B-D, upregulation of GAB2 reversed the inhibition effects of miR-302a on U251 and U87 cells migration and invasion abilities. Each assay was repeated at least three times. *P<0.05 compared with respective control.

Figure 6. GAB2 re-introduction rescues the inhibitory effects of miR-302a in glioma. (A) GAB2 protein expression was determined by western blotting in U251 and U87 cells transfected with pCDNA3.1-GAB2 or pCDNA3.1. (B) Restoration of GAB2 rescued the inhibition effects of miR-302a on U251 and U87 cells proliferation. (C and D) Upregulation of GAB2 reversed the inhibition effects of miR-302a on U251 and U87 cells migration and invasion abilities.
GAB2 effectively reversed the inhibition effects of miR-302a on U251 and U87 cell proliferation (P<0.05), migration and invasion (P<0.05). These findings suggested that miR-302a inhibited growth and metastasis in glioma cells, at least in part, by suppression of GAB2.

Discussion

Fully understanding the mechanisms underlying glioma occurrence and development is essential for providing novel therapeutic strategies for glioma patients to improve prognosis (25). The aim of the present study was to investigate the expression and roles of miR-302a in glioma and the possible molecular mechanisms. We found that expression levels of miR-302a were reduced in both glioma tissues and cell lines. Low miR-302a expression was significantly correlated with adverse clinicopathological characteristics in glioma. miR-302a overexpression inhibited cell proliferation, migration and invasion of glioma. Additional in vitro studies demonstrated that GAB2 was the direct target gene of miR-302a in glioma. Thus, miR-302a could suppress glioma growth and metastasis through directly targeting GAB2, suggesting that miR-302a functions as a tumor suppressor in glioma and play essential roles in the carcinogenesis and progression of glioma.

Previous studies have revealed that miR-302a was abnormally expressed in several human cancers. Guo et al reported that miR-302a was decreased in ovarian cancer tissues and cell lines. miR-302a expression was significantly correlated with TNM stage of ovarian cancer patients (26). Wei et al found that miR-302a expression was lower in colorectal cancer cell lines than that in normal colon epithelium cell line (27). In prostate cancer, miR-302a has been found at low level in tumor tissues. Moreover, expression level of miR-302a was associated with Gleason score (28). These studies suggested that a low expression pattern of miR-302a may be universal regardless of ethic background and be involved in the occurrence and development of human cancer.

Dysfunction of miR-302a has been found to be involved in the development and progression of human cancers. In ovarian cancer, restoration of miR-302a expression inhibited tumor cell proliferation, transition from G1 phase to S phase and induced apoptosis through directly targeting SDC1 (26). In colorectal cancer, miR-302a decreased cell proliferation and invasion and has been confirmed as a tumor suppressor through regulation of MAPK and PI3K/Akt signaling pathways (27). Zhang et al demonstrated that, in prostate cancer, miR-302a was found to improve G1/S cell cycle arrest and reduce cell growth in vitro and in vivo (28). Liang et al reported that miR-302a was downregulated in metastatic breast cancer cells and tumor tissues. Ectopic miR-302a expression suppressed invasion and metastasis of breast cancer cells in vitro and in vivo by negative regulation of CXCR4 (29). Moreover, miR-302a overexpression enhanced the chemosensitivity of breast cancer cells to adriamycin and mitoxantrone through directly targeting MEK1 and BCRP, respectively (30,31). However, the biological roles of miR-302a in glioma remain unknown. In the present study, we found that the upregulation of miR-302a inhibited glioma cell proliferation, migration and invasion in vitro, suggesting that miR-302a is a novel tumor-suppressive miRNA that plays significant roles in the regulation of glioma growth and metastasis.

Since the potential molecular mechanism of miR-302a as a tumor suppressor in glioma was unknown, we explored the potential mechanism. In the present study, an important molecular association between miR-302a and GAB2 was identified. Firstly, bioinformatics analysis indicated that GAB2 could be a potential target of miR-302a. Subsequently, GAB2 was found to highly expressed in clinical glioma tissues and inversely correlated with miR-302a expression. Importantly, upregulation of miR-302a decreased GAB2 expression in glioma cells. This hypothesis was further supported by the luciferase reporter assay, in which the results demonstrated that miR-302a directly targeted the 3’UTR of GAB2. Moreover, the knockdown of GAB2 had similar biological roles with miR-302a overexpression in glioma cells. Finally, rescue experiments showed that restoration of GAB2 reversed the inhibitory effects of miR-302a in glioma cells. These results strongly demonstrated that GAB2 was a novel direct and functional target of miR-302a in glioma. GAB2, a member of the DOS/Gab family of scaffolding adapters, contains an N-terminal pleckstrin homology domain and C-terminal portion with multiple tyrosine phosphorylation sites and proline rich motifs (32,33). GAB2 integrate and amplify signals from cytokines, growth factors and antigen receptors, as well as from cell adhesion molecules. In addition, GAB2 diversify signals by channeling the input information from activated receptors into signal pathways with distinct biological functions (34,35). Previous studies showed that GAB2 was highly expressed in various kinds of human cancer, such as hepatocellular carcinoma (36), ovarian cancer (37), colorectal cancer (38) and breast cancer (39). In glioma, GAB2 was obviously upregulated in tumor tissues and cell lines. In addition, upregulation of GAB2 expression was correlated with WHO grade of glioma patients. Gliomas with high GAB2 level had shorter survival time than patients with low GAB2 (40). Functionally, GAB2 underexpression inhibited glioma cell proliferation, migration and invasion (40,41). In the present study, we also found that knockdown of GAB2 significantly suppressed the proliferation, migration and invasion of glioma cells, indicating the oncogenic role of GAB2 in glioma. Therefore, GAB2 downregulation by miR-302a may stress the mechanism by which miR-302a decreased glioma growth and metastasis.

In summary, the present study for the first time, to the best of our knowledge, demonstrated an inhibitory role of miR-302a in glioma by directly targeting GAB2 and suggests that miR-302a is a novel therapeutic target for treatment of glioma.

References


