miR-506, downregulated in glioma, inhibits cell growth and disrupts the cell cycle by regulating YAP

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Abstract: Considered as either oncogenes or tumor suppressor genes in human cancer, microRNAs (miRNAs) play a vital role in cancer progression. The purpose of this study was to investigate the role of miR-506 in glioma and to verify whether miR-506 could regulate proliferation of rat neuroglioma C6 cell by effecting specific targets YAP (Yes-associated protein) in the Hippo pathway. Materials and methods: Quantitative reverse transcription-polymerase chain reaction (qRT-PCR) and western blot were conducted to quantify the expression levels of miR-506 in both tumor tissues and glial cell lines. Furthermore, to explore the function of miR-506, cell proliferation assays, invasion assays, migration assays, apoptosis assays and cycle assays were used after co-transfection of miR-506 mimics and LipofectamineTM 2000. Finally, luciferase reporter assays were performed to verify the directly combination of miR-506 and the 3'-untranslated region (3'-UTR) of YAP, in corroboration with western blot assays. Results: Our experiments found that miR-506 was down-regulated in human glioma tissues and rat neuroglioma C6 cells when compared with normal tissues and rat astrocytes (RA). Enforced expression of miR-506 can restrain the cell proliferation, migration and invasion as well as disrupt the cell cycle of C6 cells. Over-expression of miR-506 promotes apoptosis of C6 cells. Luciferase assays revealed that miR-506 directly bound to the 3'-untranslated region (3'-UTR) of YAP, a critical gene in Hippo pathway. Moreover, miR-506 levels are inversely correlated with that of YAP at protein levels. In brief, our research suggested that miR-506 and YAP axis may be a promising therapeutic target for glioma in the future.

Keywords: miR-506, glioma, YAP

Introduction

Glioma is one of the most lethal types of malignant primary brain tumors. Currently, despite the maximal and safe surgical resection followed by adjuvant chemotherapy and radiotherapy, the overall prognosis for glioma patients remains poor. Thus, it is essential to explore the changes at the molecular level in glioma, which may provide novel strategies for early diagnosis and treatment.

MicroRNAs (miRNAs), approximately 22 nucleotides in size, pertain to family of non-coding RNAs, which are acting mostly as suppressor of gene expression. MiRNAs affect thousands of endogenous mRNA by binding to the 3'-untranslated regions (3'-UTRs) of certain mRNAs, which allows miRNAs to have direct function in regulation of various cellular events, including proliferation, differentiation and apoptosis. Great progress has been made in identifying novel cancer-associated miRNAs and their gene regulatory targets to regulate cancer pathophysiology, including development, progression, recurrence, metastasis and resistance to treatment. Similarly, in the central nervous system, the relationship between brain tumor pathobiology and miRNA seems to be close [1, 2]. Furthermore, mis-expression of some brain-specific miRNAs is related to initiation and progression of gliomas since they may affect the PI3K/AKT, p53 or retinoblastoma protein (RB) signaling pathway [3]. In this study, we are interested in the function of miR-506 in glioma. Over-expression of miR-506 has been demonstrated to suppress proliferation directly targeting the CDK4/6-FOXM1 axis in ovarian cancer; targeting the hedgehog pathway transcription factor Gli3 in human cervical cancer;
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targeting YAP mRNA 3'UTR in hepatoma and gastric cancer, etc. [4-7]. However, so far, the concrete role of miR-506 in glioma is barely understood.

Initially defined in Drosophila, the Hippo pathway and its regulatory target, YAP, has recently emerged as an important biochemical signaling pathway, the function of which mainly includes regulation of organ size, maintaining cell proliferation and apoptosis balance and regulation of cell contact inhibition. Several studies have testified that YAP is a candidate oncogene which plays crucial roles in brain tumor progression [8]. In gliomas, Brent A. Orr found YAP was frequently expressed in infiltrating astrocytomas and oligodendrogliomas, but seldomly in pilocytic astrocytomas. Accordingly, a gain or loss of function approach had shown that YAP promoted growth of glioblastoma cell lines in vitro. Additionally, high levels of YAP expression were closely correlated with worse outcomes of glioblastoma [9, 10].

In this paper, we presented the function of miR-506 in glioma C6 cells. Intriguingly, using qRT-PCR, tumor tissues and C6 cells had lower miR-506 expression levels than adjacent normal specimens and rat astrocytes respectively. Moreover, our experiments indicated that miR-506 is able to suppress the cellular proliferation, migration of C6 cells in vitro by direct targeting YAP mRNA. These findings suggested that miR-506 may act as a novel miRNA-based therapeutic approach for glioma.

Materials and methods

Clinical glioma samples

In this study, 10 pairs of primary glioma tissues and adjacent non-tumor tissues were obtained from patients with glioma resection at the Department of Neurosurgery of Shanghai Tenth People's Hospital, China. No patients had received any chemotherapy, immunotherapy or radiotherapy prior to surgery. All samples were immediately frozen in liquid nitrogen. Patients gave written informed consent before surgery.

Cell culture and transfection

Rat neuroglioma C6 cells and rat astrocytes were purchased from the Chinese Science Institute (Shanghai, China). The cells were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS) (both from Gibco, USA), penicillin (100 U/ml) and streptomycin (100 μg/ml) (Enpromise, Hangzhou, China). Cells were incubated at 37°C in a humidified chamber supplemented with 5% CO2. Cells in the logarithmic growth phase (~80% confluence) were selected for the experiments.

MiR-506 mimics, miR-506 inhibitor, non-specific negative control (NC) oligos were purchased from GenePharma (Shanghai, China). For transfection, C6 cells (1×10^5) were added into each well of a 6-well plate and cultured in DMEM medium off with serum and antibiotics. When the cell density achieved 30-40% confluence, Lipofectamine™2000 (Invitrogen, USA) was used to respectively introduce the miRNA-506 mimics, inhibitor or NC group, which were delivered at a final concentration of 50 nM according to the manufacturer's instructions. Complete media was changed 5 h after transfection. After 24 h of incubation, cells were harvested for further analysis.

RNA extraction and Quantitative reverse transcription-polymerse chain reaction (qRT-PCR)

As to the manufacturer's direction, total RNA was extracted from the tissues and cells using TRIzol (Invitrogen, Carlsbad, CA, USA) and analyzed by ultraviolet spectrophotometer. To detect the expression of miR-506, primer design and qRT-PCR were experimented as to the manufacturer's directions. U6 mRNA and β-actin levels were used for normalization. Primers used for miR-506 real-time PCR are: miR-506 forward, 5'-TAAGGACACCTCTTGAGTAGA-3', reverse, 5'-GCCAGCACAGATTATACGAC-3'; Primers used for U6 real-time PCR are: forward, 5'-AGAGCCTGTGTTGGTTCCG-3', reverse, 5'-CATCTCAAGCACCTTCCCT-3'; Primers used for β-actin real-time PCR are: forward, 5'-CGTCTCCCTCCATCGT-3', reverse, 5'-GAAGGTGTGGTGCCAGATT-3'.

cDNA was generated by reverse transcription using the PrimeScript RT-PCR kit (Takara). With the 7900HT fast RT-PCR instrument using SYBR-Green, qRT-PCR parameters were performed as follows: 2 min at 95°C, followed by 40 cycles of 30 sec at 95°C and 40 sec at 60°C. Each sample was experimented in triplicate. The fold-change of mRNA expression was
calculated using the relative quantification equation (RQ) = 2^{\Delta\Delta Ct}.

**Cell viability assay**

At 4-5 h after miR-506 mimics, miR-506 inhibitor, NC oligo transfection, C6 cells were trypsinized and counted. Cells were seeded (1,000/well) onto each well of 96-well plates in 6 replicates and incubated at 37°C. The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (Sigma, Santa Clara, CA, USA) assay was conducted to assess cell proliferation every day from the first day until the fourth day. Briefly, 20 μL (5 mg/ml) of MTT solution was added to each well followed by incubation at 37°C in a humidified chamber supplemented with 5% CO₂ for 4 h. Subsequently, discard the supernatant and add 150 μL DMSO (Sigma) to dissolve crystals. After 10 min shaking (100 rpm), the optical density (OD) of each sample was measured with a microplate spectrophotometer (Bio-Tek, USA) at 490 nm. All experiments were performed in biological triplicate.

**Cell cycle and apoptosis assay**

After the transfection with miR-506 for 4 h and incubation for 24 h, C6 cells were trypsinized, centrifuged at 1,000 rpm for 5 min, and subsequently washed twice in cold PBS. Then add 70% ethanol to fix the cells at 4°C overnight. After removal of the ethanol, cells were incubated with RNase A at the concentration of 1 mg/ml in PBS for 30 min. Then, propidium iodide (PI) staining solution was added into each sample and incubated for 30 min at room temperature and then analyzed by a flow cytometer (FACSCanto™ II, BD Biosciences). The experiment was performed three times in triplicate.

C6 cells transfected with miR-506 mimics/inhibitor/NC were seeded in six-well plates at 10×10⁴ cells per well and cultured for 24/48 h. Cells were washed three times with ice-cold PBS and trypsinized. Cells were successively double-stained with fluorescein (FITC)-conjugated Annexin V and propidium iodide (FITC-Annexin V/PI) (BD Biosciences, San Diego, CA, USA) in the dark at room temperature. Cells were gently resuspended in the Annexin V incubation reagent at a ratio of 1×10⁵ to 10⁶ cells per 100 μL and analyzed on a flow cytometer to determine rate of apoptosis. The experiment was repeated for three times.

**Western blot**

Total protein of cells was extracted by RIPA lysis buffer after 48-72 h transfection. The concentration was quantified by BCA protein assay kit (Beyotime). Then, denature the equal amounts of protein samples with 5X sodium dodecyl sulfate (SDS) loading buffer at 100°C for 10 min. Subsequently, separate protein samples (30 μg) by 10% sodium dodecyl sulfate/polyacrylamide gel electrophoresis (SDS/PAGE). After being transferred onto 0.45-μm nitrocellulose membranes (Beyotime) and blocked in 5% fat-free milk, the target proteins were incubated overnight at 4°C with primary antibodies against YAP (1:1,000) and the β-actin (1:2,000) (Cell Signaling Technology, USA). Wash the membranes and then incubate for 60 min with specific secondary antibodies. After three washes by PBST, immune-reactive protein bands were detected with an odyssey scanning system (Li-Cor, Lincoln, NE, USA). The experiment was conducted in triplicate. Representative photographs are shown.

**Cell invasion assays**

The cell invasion assay was performed in a 24-well transwell chamber system (8 μm pore size; BD Biosciences, San Jose, CA, USA). Wash the filter with the serum-free DMEM, and place it between the lower and upper chambers. The C6 cells transfected with mimics/inhibitor/NC were trypsinized, resuspended in DMEM with FBS transferred and incubated to the upper chambers at 37°C in 5% CO₂. Lower chambers contained DMEM with 10% FBS. After 48 h of incubation, cells remaining on the upper membrane surface were removed by cotton swab scrubbing; cells on the lower surface of the membrane were fixed in 10% formalin at room temperature for 30 min and stained with 0.5% crystal violet. Five random fields of each well were counted. The stained cells were dissolved in glacial acetic acid, and the solution was transferred to a 96-well culture plate for colorimetric reading of OD at 560 nm. Each treatment was carried out in triplicate.

**Wound healing assay**

Transfected C6 cells were grown in 6-well plates until the cell confluence reached about 70-80%. Then, make a scratch in each well using a sterile pipette tip and remove the detached cells with PBS washing. Cells were...
incubated successively in DMEM supplemented with 2% FBS at 37°C in a humidified chamber supplemented with 5% CO₂. Finally, images were captured at the same site at 0, 24 after scratching to observe the process of wound healing.

**luciferase assays**

To confirm that miR-506 can bind to the predicted site YAP, we conducted a luciferase reporter assay in the 293T cell line. The 3'-untranslated region (3'UTR) of mRNA sequence of YAP containing predicted miR-506 binding site was amplified by PCR. PCR products of YAP were cloned into the Xho I site in the 3'-UTR of Renilla luciferase of psiCHECK-2 reporter vector (Promega, USA). Reporter plasmids (200 ng psiCHECK-2 reporter vector containing YAP 3'UTR) and 100 nM miR-506 mimics were cotransfected into 293T cells (80-90% confluence) with Lipofectamine 2000 (Invitrogen, USA). Besides, the control groups consist of 293T cells cotransfected with psiCHECK-2/YAP 3'-UTR (200 ng) and NC (100 nM), psiCHECK-2/YAP 3'-UTR mutant (200 ng) and miR-506 mimics (100 nM) as well as psiCHECK-2/YAP 3'-UTR mutant (200 ng) and NC (100 nM). After 48 h, add 50 μL of Luciferase Assay Reagent II to detect the firefly luciferase (FL) reporter by a microplate spectrophotometer immediately. Next, add Stop & Glo® reagent (50 μL/well) to each well to initiate the Renilla luciferase (RL). RL activity was normalized to FL activity.

**Statistical analysis**

Data from at least three independent experiments are expressed as the mean ± standard deviation (SD). Student’s t test was used to draw a comparison between groups. Differences were considered statistically significant for P-values <0.05.

**Results**

**MiR-506 was downregulated in both human glioma specimens and rat glioma C6 cells**

In order to explore the original expression level of miR-506 in human glioma, we analyzed 10 pairs of tumor tissues and adjacent normal specimens in this study. Analysis of miR-506 by real-time PCR indicated that miR-506 levels were obviously downregulated in glioma tissues compared with non-cancerous tissues (P<0.05, **Figure 1A**). Moreover, expression of miR-506 was also demonstrated to be downregulated in Rat glioma C6 cells compared to rat astrocytes (P<0.05, **Figure 1B**). These results imply a potential role of miR-506 in glioma.

**Over-expression of miR-506 inhibits proliferation of C6 cells**

After transfection with miRNA, MTT assay was conducted to assess cell proliferation from the first day until the fourth. As presented in **Figure 2A**, initially, we evaluated miR-506 expression
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in C6 cells transfected with miR-506 mimics or inhibitors (50 nM for 48 h) by qRT-PCR, which can verify the success of transcription. Additionally, in comparison with the other two groups, miR-506 mimics retards the growth rate of C6 significantly in a time dependent manner (Figure 2B). Conversely, cell proliferation was strongly promoted when cells were

Figure 2. Over-expression of miR-506 inhibits proliferation of C6 cells. A. Transfection efficiency was evaluated by qRT-PCR in C6 cells transfected with miR-506 mimics or inhibitors (50 nM for 48 h). B. MiR-506 mimics retards the growth rate of C6 significantly in a time dependent manner in comparison with the other two groups (P<0.05).

Figure 3. Over-expression of miR-506 inhibits the invasion of C6 cells. A. MiR-506 participated in preventing glioma cell invasion. B. Transwell invasion assays showed that overexpression of miR-506 induced C6 cell penetrating the membrane by 0.62-fold (P<0.05) compared to NC controls. On the contrary, miR-506 inhibitors significantly promoted invasive activity compared to the control (1.4-fold; P<0.05).
interfered with 50 nM miR-506 inhibitor as compared with the control cells ($P<0.05$). Taken together, these results indicated that forced expression of miR-506 suppresses the proliferation of glioma cells.

**Over-expression of miR-506 inhibits the invasion and migration abilities of C6 cells**

To observe whether miR-506 impact the invasive abilities of C6 cells, we transfected C6 cells with 50 nM miR-506 mimics/inhibitors/NC and compared their motility using Transwell assays. As shown in **Figure 3**, transwell invasion assays showed that overexpression of miR-506 induced C6 cell penetrating the membrane by 0.62-fold ($P<0.05$) compared to the control cells. On the contrary, miR-506 inhibitors significantly promoted invasive activity of C6 cell compared to the control (1.4-fold; $P<0.05$), suggesting that miR-506 participated in preventing glioma cell invasion. As for the wound healing assay (**Figure 4**), after 24 h incubation, the “scratch” line on the monolayer cells of the miR-506 mimics group was still clearly visible and wider than the miR-506 inhibitors group. Conversely, the scratch gap of inhibitor group almost healed at 24 h. Together these results presented that upregulation of miR-506 can suppress cellular migration and invasion ability.

**Over-expression of miR-506 can change the C6 cells cycle distribution**

The cell cycle distribution of the C6 cells with transfection of miR-506 mimics, miR-506 inhibitor and NC group was analyzed by flow cytometry. As shown in **Figure 5**, results indicated that percentage of G0/G1 phase (61.91±

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**Figure 4.** Over-expression of miR-506 inhibits the migration abilities of C6 cells. As the wound healing assay shown, after 24 h incubation, the “scratch” line in miR-506 mimics group was still clearly visible and wider than the other two groups. Conversely, the scratch gap of inhibitor group almost healed at 24 h ($P<0.05$).
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Figure 5. Over-expression of miR-506 can change the C6 cells cycle distribution. Percentage of G0/G1 phase (61.91±0.522%) increased in the miR-506 mimics group, when compared with that of the NC group (57.50±0.507%) and miR-506 inhibitor group (54.53±0.478%) (P<0.05).

Figure 6. Over-expression of miR-506 has facilitation effect on apoptosis of C6 cells. As shown above, the percentage of the early apoptotic cells of NC group (4.0%±0.02%) were lower than miR-506 mimics group (7.7%±0.06%) and higher than miR-506 inhibitor group (1.0%±0.04%), which indicating that miR-506 can induce glioma cell apoptosis in vitro.

MiR-506 directly targets the 3'UTR of YAP mRNA and represses YAP expression

In order to reveal the mechanism of miR-506 in the development of glioma, we searched for the potential target genes of miR-506 using the prediction algorithm TargetScan (http://www.targetscan.org/) (Figure 8A). One conserved target site YAP was predicted. Considered as a candidate oncogene in various cancers including brain tumors, YAP has been consistently reported to accelerate tumor growth or even confer radioresistance. As previous and our result both showed, YAP was over-expressed in glioma cells. Besides, lately articles have already reported that miR-506 can directly target the 3'UTR of YAP mRNA in hepatoma cells.

0.522%) dramatically increased in the miR-506 mimics group, when compared with that of the NC group (57.50±0.507%) and miR-506 inhibitor group (54.53±0.478%) (P<0.05, Figure 4). These findings revealed that miR-506 initiated G0/G1 phase arrest of C6 cells. Downregulation of miR-506 expression may contribute to increase of S-phase and G2/M phase cells.

Over-expression of miR-506 has facilitation effect on apoptosis of C6 cells

We assessed apoptotic cell death with flow cytometric analysis. As shown in Figure 6, the percentage of the early and late apoptotic cells of NC group were lower than miR-506 mimics group and higher than miR-506 inhibitor group. Besides, significant difference of early apoptosis was observed between the miR-506 mimics group and inhibitor group (7.7±0.06% vs. 1.0±0.04%), which indicating that miR-506 can induce glioma cell apoptosis in vitro.
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Figure 7. Relative expression of YAP protein in C6 and RA cells. In our experiment, we found YAP protein was originally up-regulated in C6 cells compared with RA cells (P<0.05).

Discussion

Gliomas, as a class of cancers notorious for aggressive proliferation, make up about 30% of all brain and central nervous system tumors and 80% of all malignant brain tumors. Patients suffering from these typically insist on receiving periodical chemotherapy and regional radiation. Yet the destructive situation has not significantly improved survival or prognosis for decades. Therefore, studies in progress to search for new ways known to be more effective and with fewer side-effects are needed. MiRNAs have been reported to influence gene expression by interfering with translation of their RNA messengers. As dys-regulation of miRNA expression plays a fundamental role in the onset, progression and dissemination of malignant tumor, several references have demonstrated its roles in human gliomas. For instance, miR-451 suppress glioma in vivo and in vitro through direct targeting of CAB39 and indirect inhibition of the PI3K/AKT pathway [12]; miR-34a could inhibit glioblastoma growth by targeting multiple oncogenes including c-MET and Notch [13]; additionally, miR-195 can inhibit glioma cell proliferation by directly targeting cyclin D1 and cyclin E1 [14]; etc. Based on these findings, it has been recommended that more effective targets or targeted drugs for diagnosing and treating glioma may involve miRNAs. In glioma, overexpression of miR-124 can not only reduce self-renewal and tumorigenicity by targeting SCP1 and PTPN12 phosphatases [15, 16], but also inhibit the malignant cell invasion [17]. Besides, miR-506, as a member in the miR-124 family, is increasingly considered to be implicated in growth, survival, motility, and invasiveness of various cancers including neuroblastoma [18]. Although most researches conceived miR-506 as a promising target to restrain the cancer progression, it remains undefined in its potential role in glioma.

In this context, we are of particular interest in whether miR-506 can affect the proliferation, migration and cell-cycle of C6 cells and its putative mechanism in cell function variation. First, we detected the expression level of miR-506 in tumor tissues and neuroglioma cell lines by qRT-PCR. As predicted, the results showed that miR-506 was significantly lower in glioma tissues and C6 cells than in normal tissues and RA cells respectively similar to other cancer types. Next, we transfected miR-506 mimics into C6 cells to achieve its overexpression, which resulted in significant inhibition of cellular proliferation as measured by MTT as determined. On the contrary, under expression of miR-506 greatly promoted cell growth in com-
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Figure 8. MiR-506 directly targets the 3'UTR of YAP mRNA and represses YAP expression. A. We searched for the potential target genes of miR-506 by the prediction algorithm TargetScan. One conserved target site YAP was predicted. B. Transfection of miR-506 mimics significantly repressed the luciferase activity in the wild type YAP 3'UTR construct, but not in the mutant 3'UTR or NC group. C. We discovered that YAP expression can be repressed by miR-506 in C6 cells with Western blot analysis.

parison with the other two groups. What’s more, cell migration and invasion ability was also significantly restrained with overexpression of miR-506. By flow cytometry we found that overexpression of miR-506 induced cell cycle arrest at the G0/1 transition. Finally, miR-506 may have facilitation effect on apoptosis of C6 cells.

To discover how miR-506 brings about these effects on the cell function, we tested conceivable targets of miR-506. One conserved target site YAP was predicted. YAP, a key driver of carcinoma tumorigenesis, is one of the two main effectors of the Hippo tumor suppressor pathway involving in the organization of size regulation, increased proliferation and decreased cell death. In the Hippo pathway, phosphorylated and activated large tumor suppressor 1 and 2 (LATS1/2) phosphorylates transcription coactivators YAP, hindering YAP into the nucleus and co-transcriptional activity [19]. Loss-of-function or mutant clones for any other genes in Hippo results in a strong activity of YAP, characterized by overexpression of its downstream transcription factor such as cyclinE and Drosophila inhibitor of apoptosis protein 1 (DIAP1) [20]. In previous research, upregulation of YAP-containing chromosome 11q22 amplicon is frequently observed in several human tumors such as medulloblastoma [8], intracranial ependymoma [21], pancreatic cancer [22] and hepatoma [23]. Similarly, a correlation between high YAP expression and poor patient prognosis has been identified in ovarian cancers, glioma, non-small cell lung cancer and esophageal squamous cell carcinoma [19]. As previous and our result both showed, YAP was over-expressed in glioma cells. Besides, lately articles have already reported that miR-506 can directly target the 3'UTR of YAP mRNA in hepatoma cells and breast cancer cells [7]. Accordingly, a gain or loss of function approach had shown that YAP promoted growth of glioblastoma cell lines in vitro [9]. Based on four databases, we found that the YAP 3'UTR contains one miR-506 matching sites. To ascertain the definite combination, we also conducted luciferase reporter assay and found YAP was a real target of miR-506. As presented above, transfection of miR-506 mimics significantly repressed the luciferase activity in the wild type YAP 3'UTR construct, but not in the mutant 3'UTR or NC group. Additionally, we found that the protein levels of YAP were significantly
reduced in miR-506-overexpressing cells when compared with those transfected with inhibitor group or NC. In a word, these results show that enforced expression of miR-506 in C6 cells triggered an evident and direct inhibitory effect on YAP expression. However, this experiment had some disadvantages such as the unstable transient transfection and failing to elucidate the role of miR-506 in vivo. Further study need to be investigated.

On the whole, our findings indicate that miR-506 is down-regulated in glioma tissues and C6 cells. Over-expression of miR-506 is able to inhibit cellular proliferation, cell migration and invasion as well as disrupt the cell cycle via direct target on YAP. Furthermore, its expression has a negative correlation with YAP, which is highly direct correlation with tumorigenesis and tumor progression. Taken together, our results showed that miR-506 serves as a tumor suppressor in glioma by directly targeting YAP. This newly identified miR-506/YAP axis in glioma provides further insight into the pathogenesis of glioma and indicates a potential novel therapeutic agent for treatment.

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Disclosure of conflict of interest

None.

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