Int J Clin Exp Pathol 2018;11(9):4405-4413
www.ijcep.com /ISSN:1936-2625/IJCEP0079288

*Original Article*

# miR-505 functions as a tumor suppressor in glioma by targeting insulin like growth factor 1 receptor expression

Hua Shi[1], Hua Yang[2], Shu Xu[2], Yan Zhao[3], Jian Liu[2]

*[1]Teaching and Research Department of Pathology and Pathophysiology, Guizhou Medical University, Guiyang, China; [2]Department of Neurosurgery, Hospital Affiliated to Guizhou Medical University, Guiyang, China; [3]Teaching and Research Department of Molecular Biology, Guizhou Medical University, Guiyang, China*

Received May 8, 2018; Accepted June 21, 2018; Epub September 1, 2018; Published September 15, 2018

**Abstract:** MicroRNAs (miRNAs) are small non-coding RNA molecules that regulate gene expression at the post-transcriptional level. Compelling evidence shows that there are causative links between miRNAs abnormal regulation and the development of cancer. miR-505 has been reported to be aberrant expression and functions as a tumor suppressor in many human cancers, but its roles and potential molecular mechanism in glioma remain unclear. Here, we found that the expression levels of miR-505 were down-regulated in glioma tissues and cell lines. Exogenous over-expression of miR-505 resulted in inhibited cell proliferation and invasion in glioma *in vitro*. Furthermore, dual luciferase reporter assay and western blot analysis confirmed that IGF1R (Insulin like growth factor 1 receptor) was a direct target gene of miR-505 in glioma. More importantly, over-expression of IGF1R rescued miR-505-mediated inhibition of cell proliferation and invasion in glioma *in vitro*. Taken together, our results suggest that miR-505 acts as a tumor suppressor in glioma via direct negative regulation of IGF1R, which may provide a novel therapeutic strategy.

**Keywords:** miRNAs, miR-505, glioma, suppressor, IGF1R

## Introduction

Glioma is the most common malignant primary brain tumor in the central nervous system, which exhibits a spectrum of aggressive phenotypes with high morbidity and mortality [1]. Despiteadvances in therapeutic treatment, such as surgery, chemotherapy, and radiotherapy, the overall survival of patients with glioma is still unsatisfactory [2, 3]. Therefore, it is necessary to identify the potential molecular mechanism involved in the development of glioma and find novel therapeutic targets.

MicroRNAs (miRNAs) are small non-coding RNAs that control gene expression by antisense complementarity to the 3'-untranslated regions (3'-UTRs) of mRNA, leading to either mRNA degradation or translational inhibition [4-6]. Accumulating evidence has been reported that miRNAs are aberrantly expressed and play oncogenic or tumor suppressor gene roles in various types of human tumors [7, 8]. Studies also find that miRNAs are involved in various biologic processes of cancer, including cell growth, migration, invasion, and apoptosis [9, 10].

miR-505 is derived from the pre-miR-505, which has been reported deregulated in different types of human tumors. For example, miR-505 acts as a tumor suppressor gene in endometrial cancer by targeting TGF-α [11]. MiR-505 has been identified to function as a tumor suppressor in breast cancer [12]. A recent study shows that miR-505 inhibits cell metastasis and epithelial mesenchymal transition (EMT) in nasopharyngeal carcinoma [13]. However, little is known about the biological function and potential molecular mechanism of miR-505 in glioma.

Here, we found that miR-505 was significantly down-regulated in glioma tissues and cell lines. Further experiments revealed that miR-505 acts as a tumor suppressor in glioma cell lines

**Table 1.** The information of primers for quantitative real-time PCR

| Gene | Forward (5'-3') | Reverse (5'-3') |
|---|---|---|
| miR-505 | GGGAGCCAGGAAGTATTGAUGT | Universal primer |
| U6 | CTCGCTTCGGCAGCAC | ACGCTTCACGAATTTGC |
| IGF1R | GCCTTGGTCTCCTTGTCC | TCCCAGTCCCACAGTTGC |
| GAPDH | CAAGGTCATCCATGACAA | GTCCACCACCCTGTTGCTG |

and exogenous over-expression of miR-505 resulted in inhibited cell proliferation and invasion in glioma *in vitro*. The IGF1R (Insulin like growth factor 1 receptor) was predicted by bioinformatics analysis as a target gene of miR-505, which was validated by dual luciferase reporter assay and western blot analysis. In addition, we also found overexpression of IGF1R partly reversed miR-505-mediated inhibition of cell proliferation and invasion in glioma *in vitro*. These data indicated that miR-505 acts as a tumor suppressor in glioma by targeting IGF1R and its restoration might be a possible therapeutic strategy against this disease.

## Material and methods

### *Clinical specimen collection and total RNA isolation*

Forty tissue specimens of glioma were obtained from the Department of Neurosurgery, People's Hospital Affiliated of Guizhou Medical University (Guiyang, China) between January 2011 and December 2014. The matched normal brain tissues were taken from the distal end of the operative excisions (far from the tumor). All specimens were confirmed by pathological diagnosis and classified with 2007 World Health Organization (WHO) criteria [14]. Twelve of the 40 tissue specimens were classified as low-grade (3 in I, 9 in II), and 28 tissue specimens were classified as high-grade (16 in III, 12 in IV). This study was approved by Tissue Committee and Research Ethics Board of People's Hospital Affiliated of Guizhou Medical University. All patients provided written informed consent in compliance with ethics of the World Medical Association (Declaration of Helsinki). All samples were snap-frozen in liquid nitrogen immediately, and then stored at -80°C until use. Total RNA was isolated from tissues and cells by TRIzol (Invitrogen, Carlsbad, CA, USA), according to the manufacturer's protocols. The RNA was immediately frozen stored at -80°C until further experiments.

### *Cell culture and cell transfection*

Human U87 and U251 glioma cell lines and a normal neuronal cell line primary human fetal glial cell (PHFG) were purchased from Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences (Shanghai, China). These cells were incubated in Dulbecco's modified Eagle's medium (DMEM; Invitrogen, Carlsbad, CA, USA) supplemented with 10% fetal bovine serum (FBS; Invitrogen, Carlsbad, CA, USA), 100 μg/ml streptomycin and 100 U/ml penicillin, and cultured in a humidified atmosphere of 5% $CO_2$ at 37°C.

miR-505 mimics (mimics) and corresponding negative control (NC), the human IGF1R overexpressed plasmid (pCDNA3.1+ IGF1R) and empty vector (pCDNA3.1+) were brought form GenePharma Co., Ltd (Shanghai, China). These molecular products were transfected into U87 and U251 cells by Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA) when cells were grown to 70-75% confluence, according to the supplier's protocols.

### *Quantitative real-time PCR*

For detect miR-505 expression, reverse transcription was performed by TaqMan MicroRNA Reverse Transcription kit (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's protocols. To detect IGF1R mRNA expression, the complementary DNA (cDNA) was synthesized by using a Reverse Transcriptase M-MLV (Takara, Dalian, China). Quantitative real-time PCR was performed by using a Taqman MicroRNA Assay Kit (Applied Biosystems, Foster City, CA, USA) on ABI PRISM 7900 Sequence Detection System (Applied Biosystems, Foster City, CA, USA). U6 and GAPDH were used as internal controls. The primer sequences are shown in **Table 1**. The miR-505 and IGF1R mRNA expression levels were normalized to those of U6 and GAPDH, respectively, by using the $2^{-\Delta\Delta Ct}$ method [15].

### *Target gene prediction and dual luciferase reporter assay*

Based on bioinformatics analysis (http://www.microrna.org), IGF1R was selected as candidate target gene of miR-505. The 3'-UTR se-

quences of IGF1R containing putative binding sites of miR-505 was amplified and cloned into the dual-luciferase reporter vector pGL4.15 (Promega, Madison, WI, USA) termed as: wild-type (WT)-IGF1R. A mutant plasmid in miR-505 binding sites of IGF1R 3'UTR region was generated by Quick Change Site-Directed Mutagenesis Kit (Takara, Dalian, China), and also cloned into pGL4.15 vector termed as: mutant (MUT)-IGF1R. The WT and MUT recombinant reporter vectors were confirmed by Sanger DNA sequencing. For dual luciferase reporter assay, U87 and U251 cells were co-transfected with the mimics or NC by Lipofectamine 3000 in a 24-well plate followed by the WT and MUT recombinant reporter vectors. Twenty-four hours later, luciferase activity was measured by using a Dual-Luciferase Reporter Assay Kit (Promega, Madison, WI, USA) according to the protocols provided by manufacturer. The Firefly luciferase activity was used to normalize the Renilla luciferase activity for each individual analysis.

*Western blot analysis*

Total protein of cells was isolated by ice-cold RIPA buffer (Invitrogen, Carlsbad, CA, USA), and quantitated by a BCA kit (Millipore, MA, USA) according to the manufacturer's protocols. The protein samples were separated in 12% SDS-PAGE and transferred onto a polyvinylidene fluoride membrane (PVDF; Millipore, Billerica, MA, USA). After that, the membrane was blocked in 5% non-fat milk overnight and incubated with the mouse against human IGF1R monoclonal antibody (ab16890; 1:1000; Abcam, Cambridge, MA, USA) and mouse against human GAPDH monoclonal antibody (sc-365062; 1: 5000; Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA) at 37°C for 2 h. After washing with TBST buffer (Beyotime, Shanghai, China), the membrane was incubated with the HRP-conjugated goat anti-mouse secondary antibody (sc-2005; 1:2000; Santa Cruz Biotechnology, Inc. Santa Cruz, CA, USA) for 1 h at 37°C. The protein band was detected by using an enhanced chemiluminescence (ECL)-based detection system (Millipore, MA, USA).

*MTT assay*

To determine miR-505 on cell proliferative capacity in glioma *in vitro*, U87 and U251 cells were examined by using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Human U87 and U251 cells were seeded in 96-well plates at a density of 6000 cells per well and allowed to grow for 24 h, and then transfected with mimics and NC or pCDNA3.1+ IGF1R or empty vector on the next day. After transfection, 30 μl MTT (5 mg/ml; Sigma, USA) was added in each well and incubated at 37°C for 4 hours. The MTT assay was used to determine relative cell viability at 0, 24, 48 and 72 h. After dissolving the formazine granular of each well with 200 μl DMSO (Sigma, USA), the optical density (OD) at 570 nm was measured by using a microplate reader (Model 354; Thermo Fisher Scientific; Waltham, MA, USA).

*Cell invasion assay*

Cell invasion ability was evaluated by using trans-well assay. In briefly, transfected cells (about $6 \times 10^4$ cell/well) in DMEM medium were seeded into the upper well of the matrigel-coated invasion chamber (8-μm pore; BD Biosciences; Franklin Lakes, NJ, USA). The lower chamber was filled with DMEM medium with 10% FBS as the nutritional attractant. After cells had been cultured at 37°C for 48 h, cells remaining on the upper side of the membrane were removed, while cells that had migrated to the lower surface of the membrane were fixed with 75% ethanol (Sigma, USA) for 30 min and stained with 0.1% crystal violet (Sigma, USA) for 15 min. The invaded cells were photographed under × 200 magnification and counted in five randomly selected fields for each well using a light microscope (Olympus, Japan).

*Statistical analysis*

The SPSS 18.0 software (SPSS Inc; Chicago, IL, USA) was used to perform statistical analysis. Data was shown as the mean ± standard deviation (SD) from at least three times independently experiments. Student's t-test or ANOVA was used to determine statistical significance. A value of $P<0.05$ was considered significant.

## Results

*Expression levels of miR-505 in glioma tissues and glioma cell lines*

The expression of miR-505 in 40 pairs of patient specimens was determined by quantitative real-time PCR. As shown in **Figure 1A**, the expression of miR-505 in glioma tissues was

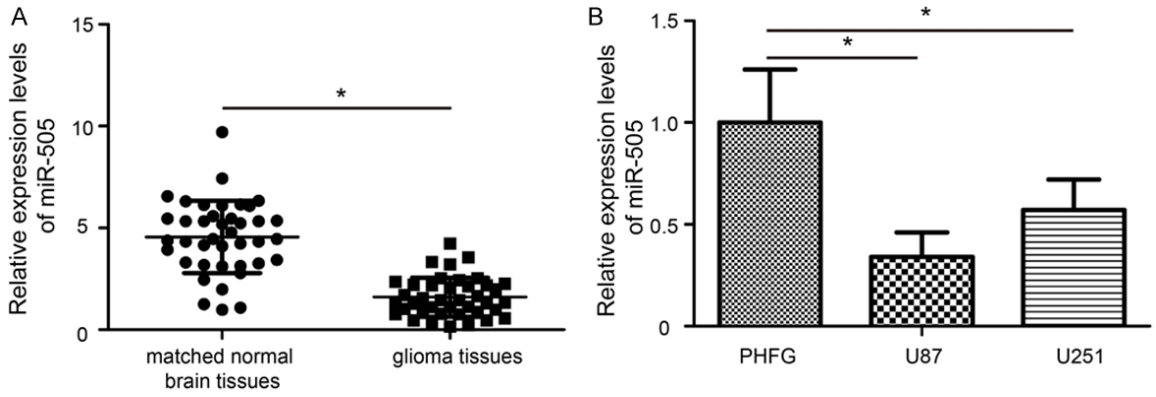


**Figure 1.** Expression levels of miR-505 in glioma tissues and glioma cell lines. A. Quantitative real-time PCR analysis of miR-505 expression in glioma tissues and matched normal brain tissues. B. Expression levels of miR-505 in human glioma cell lines (U87 and U251) and a primary human fetal glial cell (PHFG). U6 was used as an internal control. *P<0.05.

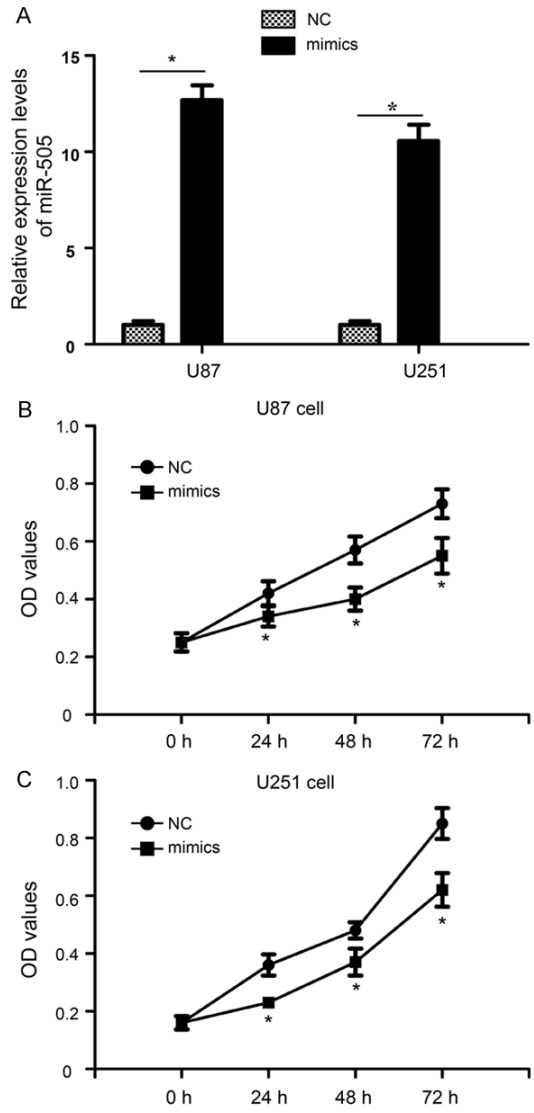


**Figure 2.** Restoration of miR-505 inhibited cell growth in glioma *in vitro*. (A) The expression levels of miR-505 were detected in mimics or NC transfected cells by quantitative real-time PCR. Mimics: miR-505 mimics; NC: corresponding negative control. The U87 (B) and U251 (C) cells were transfected with the mimics or NC, and MTT assay was used to determine cell growth ability at 0, 24, 48 h and 72 h. MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide. *P<0.05.

significantly decreased compared with matched normal brain tissues (P<0.05).

In addition, quantitative real-time PCR was also applied to detect miR-505 expression in human U87 and U251 glioma cell lines and a primary human fetal glial cell (PHFG). Interestingly, the data showed that the expression levels of miR-505 was lower in U87 and U251 cells than that in PHFG cell (**Figure 1B**, P<0.05).

*Restoration of miR-505 inhibited cell growth in glioma in vitro*

To illustrate the role of miR-505 in the growth of glioma cells, U87 and U251 cells were transfected with mimics or NC, then cell proliferation ability was determined by MTT assay. Increased expression of miR-505 in both U87 and U251 cells transfected with the mimics was confirmed by quantitative real-time PCR assay (**Figure 2A**, P<0.05). The data revealed that over-expression of miR-505 significantly decreased the proliferation of U87 (**Figure 2B**) and U251 (**Figure 2C**) cells compared with cells treated with NC (P<0.05).

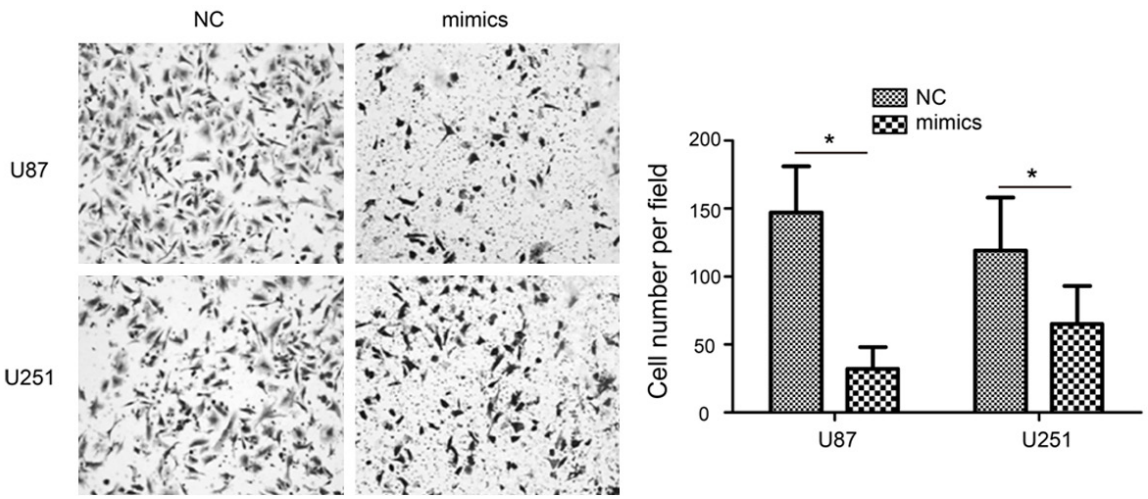


**Figure 3.** Over-expression of miR-505 suppressed cell invasion in glioma in vitro. Invasion of U87 and U251 cells following mimics or NC transfection was analyzed by transwell assay. Representative photographs were shown (magnification, 200 ×). *P<0.05.

*Over-expression of miR-505 suppressed cell invasion in glioma in vitro*

In parallel, we analyzed trans-well assay to evaluate the effect of miR-505 on the invasion capacity of glioma cells. The results showed that restoration of miR-505 markedly inhibited invasion in U87 and U251 cells compared with cells treated with NC (**Figure 3**, P<0.05). These results indicated that miR-505 served as a tumor suppressor in glioma.

*miR-505 targeted the 3'-UTR of IGF1R transcript and negatively regulated its expression*

To explore the potential molecular mechanism of miR-505 in glioma cells, bioinformatics analysis was used to identify the target gene of miR-505. Considering the associated genes that accounted for cell growth and invasion, insulin like growth factor 1 receptor (IGF1R), was chosen for further experiments.

Base-pairing complementation revealed that the 3'-UTRs of IGF1R mRNA contained a putative binding site of miR-505 (**Figure 4A**). To determine whether IGF1R was a directly target gene of miR-505, dual luciferase reporter assay was performed. The mimics or NC was then co-transfected with the WT and MUT recombinant reporter vectors into U87 and U251 cells. Interestingly, we found that co-transfection of mimics and the WT recombinant reporter vector caused a significant decrease in luciferase activity in U87 cell compared with the controls. However, cotransfection of the MUT recombinant reporter vector and mimics failed to alter the luciferase activity (**Figure 4B**, P<0.05). Similar findings were observed in U251 cell (**Figure 4B**, P<0.05).

Quantitative real-time PCR and western blot analysis were used to determine whether miR-505 retarded endogenous IGF1R expression in glioma cells. Over-expression of miR-505 dramatically suppressed the endogenous mRNA and protein levels of IGF1R in U87 and U251 cells (**Figure 4C**, P<0.05). These data strongly support IGF1R as a target gene of miR-505 in glioma.

*Up-regulation of IGF1R rescued the inhibitory effect effects of miR-505 on glioma cells*

To confirm the functional relevance of IGF1R targeting by miR-505, we evaluated whether IGF1R over-expression could rescue the inhibitory effects of miR-505 on glioma cells. U87 and U251 cells were co-transfected with mimics and pCDNA3.1+ IGF1R over-expression plasmid or pCDNA3.1+ empty vector. Quantitative real-time PCR and western blotwere also applied to validate IGF1R expression. Increased expression of IGF1R in U87 and U251 cells transfected with the pCDNA3.1+ IGF1R over-expression plasmid was confirmed (**Figure 5A**, P<0.05). In addition, our results revealed that the enforced expression of IGF1R rescued the inhibitory effects of miR-505 on cell proliferation and invasion in glioma *in vitro* (**Figure 5B**

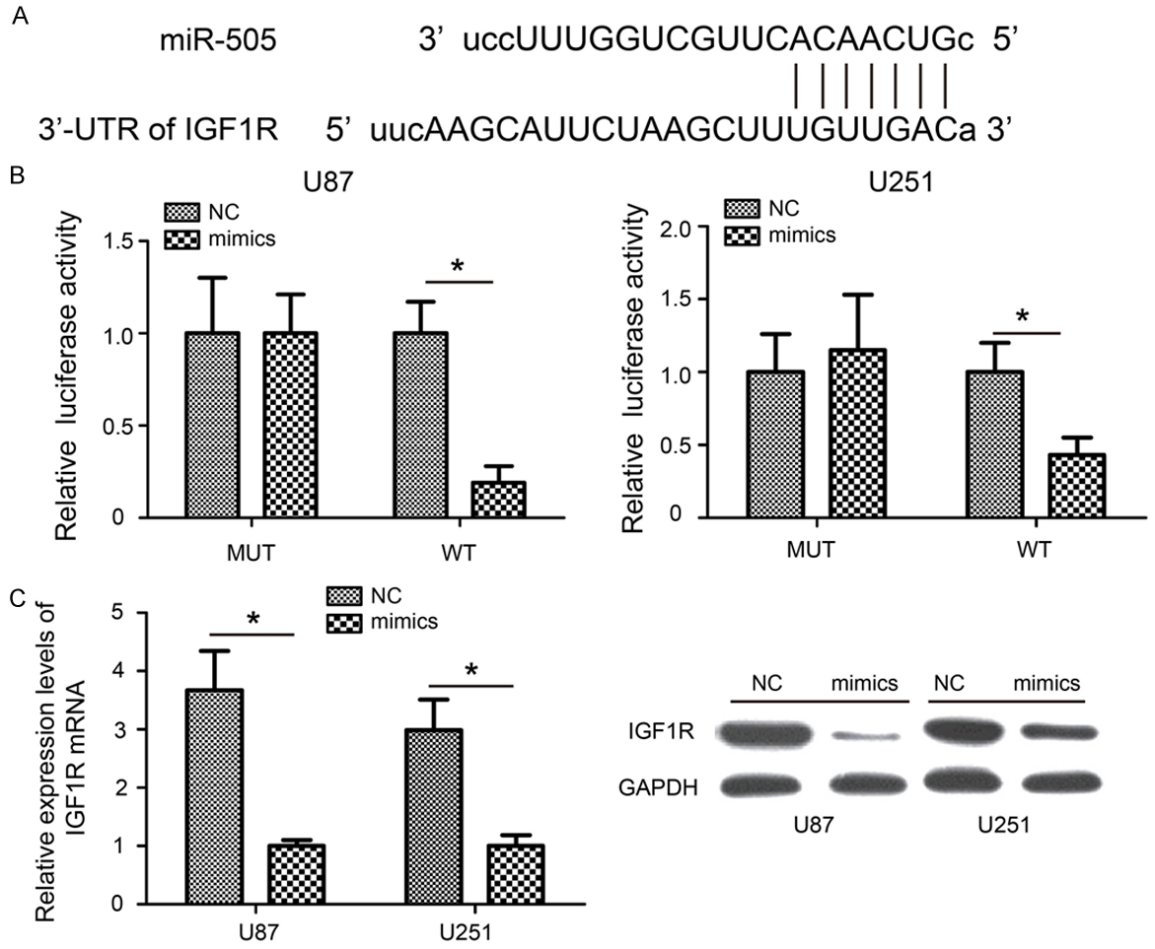


**Figure 4.** MiR-505 targeted IGF1R and negatively regulated its expression. A. The predicted miR-505 binding site on the IGF1R mRNA 3'-UTR are shown. B. U87 and U251 cells were transfected with the WT and MUT recombinant reporter vectors as well as the mimics or NC. C. Measurement of IGF1R mRNA and protein expression levels by quantitative real-time PCR and Western blot analysis. The endogenous expression levels of GAPDH was used an internal control. WT: wild-type; mutant: MUT; 3'-untranslated regions: 3'-UTR. *P<0.05.

and **5C**, P<0.05). These results suggested that miR-505 inhibited cell growth and invasion in glioma by suppressing IGF1R expression.

## Discussion

Glioma is one of the most devastating tumors because it often exhibits locally aggressive behaviors [1]. Development of glioma as a result of genetic alteration that accumulates throughout tumor cell progression. Therefore, elucidation of a molecular mechanism, in particular the one associated with cell growth and metastasis, is critical to understand glioma prognosis and response to its treatment.

In recent years, accumulated evidence has shown that miRNAs play fundamental roles in the growth and metastasis of glioma cells, acting as either tumor suppressor or oncogene. miR-10b [16], miR-17 [17], miR-19a [17], miR-23a [18] and miR-92b [19, 20] have been shown to promote the development and progression of glioma. In contrast, miR-145 [21], miR-204 [22], miR-214 [23], miR-217 [24] and miR-495 [25] have been implicated as tumor suppressors in glioma. However, the role and potential mechanism of miR-505 in glioma has not been identified.

The suppressive miR-505 has been reported to be down-regulated in various types of tumors [11-13]. In present study, we showed that miR-505 was significantly down-regulated in glioma tissues and cell lines. Restoration expression of miR-505 inhibited cell growth and invasion

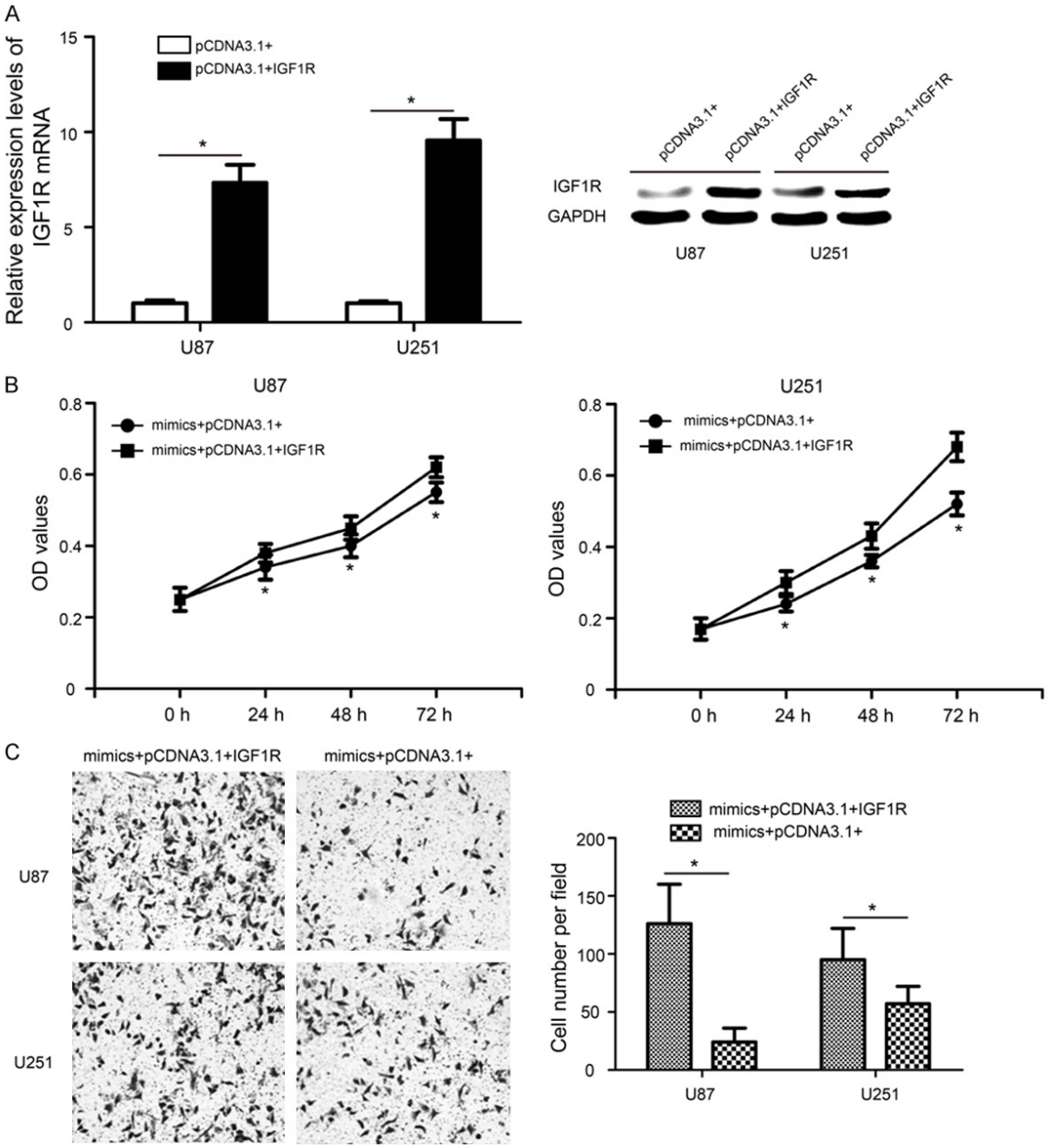


**Figure 5.** Over-expression of IGF1R rescued the inhibitory effects of miR-505 on glioma cells. A. IGF1R expression on mRNA and protein levels in U87 and U251 cells transfected with pCDNA3.1+ IGF1R over-expression plasmid or pCDNA3.1+ empty vector was detected by quantitative real-time PCR and Western blot, respectively. B. Cell proliferation was determined in U87 and U251 cells transfected with mimics with pCDNA3.1+ IGF1R over-expression plasmid or pCDNA3.1+ empty vector. C. The invasion of U87 and U251 cells was detected by transwell assay after treated with mimics with pCDNA3.1+ IGF1R over-expression plasmid or pCDNA3.1+ empty vector. Representative photographs were shown (magnification, 200 ×). *P<0.05.

in glioma *in vitro*. Our results supported that miR-505 act as a tumor suppressor in glioma. To further investigate the molecular mechanism of miR-505 in glioma, bioinformatic analysis was used to identify the potential target gene of miR-505. 3'-UTR of IGF1R was found to exist a binding site for miR-505. Dual luciferase reporter assay, quantitative real-time PCR and western blot confirmed that IGF1R was a target gene of miR-505.

IGF1R is a member of the insulin receptor family of receptor tyrosine kinases, which is up-regulated and acts as an oncogene in many

cancers [26]. Recently, evidence has supported a tumor promoter role of IGF1R in carcinogenesis [27]. Additionally, some studies have noted the role of miRNAs in the regulation of IGF1R expression in cancers. For example, Yen et al., [28] reports that miR-99a functions as a tumor suppressor gene by targeting IGF1R in oral squamous cell carcinoma. Qian et al. showed [29] that miR-143 inhibited tumor cell growth and angiogenesis by suppressing IGF1R in colorectal cancer. Gong et al. [27] illustrates that tumor suppressor role of miR-133a in gastric cancer by regulating IGF1R. In this study, we observed that restoration of miR-505 dramatically suppressed the endogenous mRNA and protein levels of IGF1R in glioma cells. Furthermore, over-expression of IGF1R rescued the inhibitory effects of miR-505 on glioma cells. These results suggested that miR-505 exerted tumor suppressor role in glioma, at least in part, by suppressing IGF1R expression.

In summary, the present study is, to the best of our knowledge, the first to report that miR-505 inhibited cell proliferation and invasion in glioma and exerted inhibitory roles by directly targeting IGF1R expression. Our data provided a novel insight into the molecular mechanism of the pathogenesis of glioma. Targetingthe miR-505/IGF1R axis may be a promising therapeutic strategy to treat patients with glioma in the future.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Jian Liu, Department of Neurosurgery, Hospital Affiliated to Guizhou Medical University, Yunyan District, Guiyang 550001, China. Tel: 86-851-88416022; E-mail: liujianmed@126.com

## References

[1] DeAngelis LM. Brain tumors. N Engl J Med 2001; 344: 114-123.
[2] Furnari FB, Fenton T, Bachoo RM, Mukasa A, Stommel JM, Stegh A, Hahn WC, Ligon KL, Louis DN, Brennan C, Chin L, DePinho RA and Cavenee WK. Malignant astrocytic glioma: genetics, biology, and paths to treatment. Genes Dev 2007; 21: 2683-2710.
[3] Zhou BB, Zhang H, Damelin M, Geles KG, Grindley JC and Dirks PB. Tumour-initiating cells: challenges and opportunities for anticancer drug discovery. Nat Rev Drug Discov 2009; 8: 806-823.
[4] Kim VN. Small RNAs: classification, biogenesis, and function. Mol Cells 2005; 19: 1-15.
[5] Ambros V. The functions of animal microRNAs. Nature 2004; 431: 350-355.
[6] He L and Hannon GJ. MicroRNAs: small RNAs with a big role in gene regulation. Nat Rev Genet 2004; 5: 522-531.
[7] Kwak PB, Iwasaki S and Tomari Y. The microRNA pathway and cancer. Cancer Sci 2010; 101: 2309-2315.
[8] Malzkorn B, Wolter M, Liesenberg F, Grzendowski M, Stuhler K, Meyer HE and Reifenberger G. Identification and functional characterization of microRNAs involved in the malignant progression of gliomas. Brain Pathol 2010; 20: 539-550.
[9] Hwang HW and Mendell JT. MicroRNAs in cell proliferation, cell death, and tumorigenesis. Br J Cancer 2007; 96 Suppl: R40-44.
[10] Hwang HW and Mendell JT. MicroRNAs in cell proliferation, cell death, and tumorigenesis. Br J Cancer 2006; 94: 776-780.
[11] Chen S, Sun KX, Liu BL, Zong ZH and Zhao Y. MicroRNA-505 functions as a tumor suppressor in endometrial cancer by targeting TGF-alpha. Mol Cancer 2016; 15: 11.
[12] Yamamoto Y, Yoshioka Y, Minoura K, Takahashi RU, Takeshita F, Taya T, Horii R, Fukuoka Y, Kato T, Kosaka N and Ochiya T. An integrative genomic analysis revealed the relevance of microRNA and gene expression for drug-resistance in human breast cancer cells. Mol Cancer 2011; 10: 135.
[13] Qin Z, He W, Tang J, Ye Q, Dang W, Lu Y, Wang J, Li G, Yan Q and Ma J. MicroRNAs provide feedback regulation of epithelial-mesenchymal transition induced by growth factors. J Cell Physiol 2016; 231: 120-129.
[14] Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW and Kleihues P. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007; 114: 97-109.
[15] Schmittgen TD and Livak KJ. Analyzing real-time PCR data by the comparative C(T) method. Nat Protoc 2008; 3: 1101-1108.
[16] Sun L, Yan W, Wang Y, Sun G, Luo H, Zhang J, Wang X, You Y, Yang Z and Liu N. MicroRNA-10b induces glioma cell invasion by modulating MMP-14 and uPAR expression via HOXD10. Brain Res 2011; 1389: 9-18.
[17] Murphy BL, Obad S, Bihannic L, Ayrault O, Zindy F, Kauppinen S and Roussel MF. Silencing of the miR-17~92 cluster family inhibits medulloblastoma progression. Cancer Res 2013; 73: 7068-7078.

[18] Hu X, Chen D, Cui Y, Li Z and Huang J. Targeting microRNA-23a to inhibit glioma cell invasion via HOXD10. Sci Rep 2013; 3: 3423.
[19] Wang K, Wang X, Zou J, Zhang A, Wan Y, Pu P, Song Z, Qian C, Chen Y, Yang S and Wang Y. miR-92b controls glioma proliferation and invasion through regulating Wnt/beta-catenin signaling via Nemo-like kinase. Neuro Oncol 2013; 15: 578-588.
[20] Wu ZB, Cai L, Lin SJ, Lu JL, Yao Y and Zhou LF. The miR-92b functions as a potential oncogene by targeting on Smad3 in glioblastomas. Brain Res 2013; 1529: 16-25.
[21] Shi L, Wang Z, Sun G, Wan Y, Guo J and Fu X. miR-145 inhibits migration and invasion of glioma stem cells by targeting ABCG2. Neuromolecular Med 2014; 16: 517-528.
[22] Ying Z, Li Y, Wu J, Zhu X, Yang Y, Tian H, Li W, Hu B, Cheng SY and Li M. Loss of miR-204 expression enhances glioma migration and stem cell-like phenotype. Cancer Res 2013; 73: 990-999.
[23] Tang SL, Gao YL and Chen XB. MicroRNA-214 targets PCBP2 to suppress the proliferation and growth of glioma cells. Int J Clin Exp Pathol 2015; 8: 12571-12576.
[24] Zhu Y, Zhao H, Feng L and Xu S. MicroRNA-217 inhibits cell proliferation and invasion by targeting Runx2 in human glioma. Am J Transl Res 2016; 8: 1482-1491.
[25] Zhang B, Yuan F, Liu J, Li Y, Zhou F, Liu X, Hao Z, Li Q, Zheng Y and Wang W. Hsa-miR-495 acts as a tumor suppressor gene in glioma via the negative regulation of MYB. Mol Med Rep 2016; 14: 977-982.
[26] Hartog H, Wesseling J, Boezen HM and van der Graaf WT. The insulin-like growth factor 1 receptor in cancer: old focus, new future. Eur J Cancer 2007; 43: 1895-1904.
[27] Gong Y, Ren J, Liu K and Tang LM. Tumor suppressor role of miR-133a in gastric cancer by repressing IGF1R. World J Gastroenterol 2015; 21: 2949-2958.
[28] Yen YC, Shiah SG, Chu HC, Hsu YM, Hsiao JR, Chang JY, Hung WC, Liao CT, Cheng AJ, Lu YC and Chen YW. Reciprocal regulation of microRNA-99a and insulin-like growth factor I receptor signaling in oral squamous cell carcinoma cells. Mol Cancer 2014; 13: 6.
[29] Qian X, Yu J, Yin Y, He J, Wang L, Li Q, Zhang LQ, Li CY, Shi ZM, Xu Q, Li W, Lai LH, Liu LZ and Jiang BH. MicroRNA-143 inhibits tumor growth and angiogenesis and sensitizes chemosensitivity to oxaliplatin in colorectal cancers. Cell Cycle 2013; 12: 1385-1394.