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Hsa_circ_0000337 promotes proliferation, migration and invasion in glioma by competitively binding miRNA-942-5p and thus upregulates MAT2A

N.-Z. LIU[1], T. LI[2], C.-M. LIU[3], F.-R. LIU[4], Y.-X. WANG[5]

[1]Department of Neurosurgery, Weifang Brain Hospital, Weifang, China
[2]Operating Room, Yidu Central Hospital of Weifang, Weifang, China
[3]Clinical Medicine College of Jining Medical University, Jining, China
[4]Statistics College of Qufu Normal University, Qufu, China
[5]Department of Anesthesiology, Weifang Brain Hospital, Weifang, China

Abstract. – OBJECTIVE: CircRNAs are vital factors involved in the pathological processes. This study aims to elucidate the biological functions of hsa_circ_0000337 in affecting the malignant progress of glioma.

PATIENTS AND METHODS: Relative levels of hsa_circ_0000337 in 45 cases of glioma and 24 cases of normal tissues were tested. The correlation between hsa_circ_0000337 and clinical features of glioma was assessed. Proliferative and metastatic abilities of U87 and U251 cells regulated by hsa_circ_0000337 were examined by 5-Ethynyl-2'-deoxyuridine (EdU) and transwell assay, respectively. Potential molecular mechanism of hsa_circ_0000337 on regulating glioma cell functions was clarified by bioinformatic analysis, which was further verified through rescue experiments.

RESULTS: Hsa_circ_0000337 was highly expressed in glioma cases. Its level was correlated to poor prognosis of glioma. *In vitro* experiments obtained the conclusion that hsa_circ_0000337 accelerated proliferative and metastatic abilities of glioma cells. Serving as a ceRNA, hsa_circ_0000337 sponged miRNA-942-5p to upregulate MAT2A, thus inducing the malignant phenotypes of glioma.

CONCLUSIONS: Hsa_circ_0000337/miRNA-942-5p / MAT2A axis is responsible for the deterioration of glioma. Hsa_circ_0000337 may be a potential therapeutic target for glioma.

Key Words:
MiRNA-106, Pediatric osteosarcoma, PI3K/AKT signaling pathway.

Introduction

Glioma is a primary malignant tumor of the central nervous system, which is very highlighted because of the extremely high mortality[1,2]. Currently, effective screening and early stage diagnostic methods for glioma are lacked, which seriously limits the clinical treatment[3]. Surgery is the main strategy for glioma. However, glioma lesions are difficult to be completely resected because of an unobvious boundary with the normal brain tissues caused by highly invasive growth of cancer cells[4]. The rate of postoperative recurrence remains high. Moreover, glioma cells are not sensitive to traditional chemotherapy and radiotherapy. It is reported that the median survival of glioblastoma, the most malignant subtype of glioma, is only 12-15 months[4]. Seeking for molecular targets involved in the process of glioma is conductive to develop individualized targeted therapy.

CircRNAs are well concerned as tumor biomarkers. They have a unique structure as a covalent closed loop, lacking the 5' or 3' end[5,6]. Abnormally expressed circRNAs have been widely discovered in human cancers[7]. Functionally, circRNAs are capable of regulating tumor cell functions as ceRNAs[8]. It is reported that circRNA cTFRC induces the malignant progression of bladder cancer by sponging miR-107[9]. By activating autophagy, circ-DNMT1 triggers the deterioration of breast cancer[10].

Hsa_circ_0000337 is located on chromosome 11: 70200406-70202360, and its associated gene symbol is PPFIA1. Song et al[11] showed that hsa_circ_0000337 promotes the malignant progression of esophageal squamous cell carcinoma as an oncogene. This study aims to clarify the role of hsa_circ_0000337 in affecting the malignant phenotypes of glioma, and the underlying mechanism.

Corresponding Author: Yongxin Wang, BM; e-mail: 13506477221@163.com

Patients and Methods

Patients and Samples

A total of 45 cases of glioma and 24 cases of normal tissues were collected and stored at -80°C. Tumor node metastasis (TNM) staging of glioma was defined according to the criteria proposed by Union for International Cancer Control (UICC). None of recruited glioma patients had preoperative chemotherapy or radiotherapy. This investigation was approved by the research Ethics Committee of Weifang Brain Hospital and complied with the Helsinki Declaration. Informed consent was obtained from patients prior to sample collection.

Cell Culture

Human astrocyte cell line (NHA) and glioma cell lines (U251, U87, LN229 and T98G) were purchased from Cell Bank (Shanghai, China). They were cultivated in Dulbecco's Modified Eagle's Medium (DMEM; Gibco, Rockville, MD, USA) with 10% fetal bovine serum (FBS; Gibco, Rockville, MD, USA) in a humidified environment with 5% CO_2 at 37°C.

Transfection

Cells were seeded in a 6-well plate and cultivated to higher than 60% of density. Cell transfection was routinely conducted using Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA). Plasmid sequences of hsa_circ_0000337 siRNAs were: si-circ-#1: AAAAAATTGCCACCTTCCAGA; si-circ-#2: CTTCAAAAAAATTGCCACCTT; si-circ-#3: CAAAAAAATTGCCACCTTCCA.

Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR)

RNA was reversely transcribed to complementary deoxyribose nucleic acid (cDNA) and subjected to qRT-PCR using the SYBR Premix Ex Taq II (TaKaRa, Dalian, China). Relative level was calculated using the $2^{-\Delta\Delta CT}$ method. Primer sequences were as follows: hsa_circ_0000337: Forward: 5′-CTGGTGTTTCCGAGACGGAT-3′, Reverse: 5′-GGTCTAACCGAAGGGCTCTC-3′; miRNA-942-5p: Forward: 5′-CUUCUCUGUUUUGGCCAUGUG-3′, Reverse: 5′- CTCTACAGCTATATTGCCAGCCAC-3′; MAT2A: Forward: 5′- ATGAACGGACAGCTCAACGG-3′, Reverse: 5′-CCAGCAAGAAGGATCATTCCAG-3′; glyceraldehyde 3-phosphate dehydrogenase (GAPDH): Forward: 5′-CGGAGTCAACGGATTTGGTCGTAT-3′, Reverse: 5′-AGCCTTCTCCATGGTGGTGAAGAC-3′; U6: Forward: 5′-GCTGAGGTGACGGTCTCAAA-3′, Reverse: 5′-GCCTCCCAGTTTCATGGACA-3′.

Actinomycin D Assay

U87 cells were induced with 2 μg/mL Actinomycin D for indicated time points. They were collected for isolating total RNAs. Relative levels of hsa_circ_0000337 and linear PPFIA1 mRNA were detected by qRT-PCR.

Rnase R Assay

2 mg cellular RNA was induced either with 5 U/μg RNase R (Epicentre Technologies, Madison, WI, USA) at 37°C for 30 min or not, followed by purification using RNeasy MinElute (Qiagen, Hilden, Germany) and qRT-PCR[12].

EdU Assay

Cells were pre-inoculated in a 24-well plate (2×10^4 cells/well). They were incubated in 4% methanol for 30 min, followed by 10-min permeabilization in 0.5% TritonX-100 (Solarbio, Beijing, China), and 30-min reaction in 400 μL of 1×ApollorR. Afterwards, cells were dyed in 4',6-diamidino-2-phenylindole (DAPI) for another 30 min. Positive EdU-stained cells were calculated.

Transwell

Transwell chambers (Millipore, Billerica, MA, USA) were inserted in each well of a 24-well plate, where 5×10^4 cells were applied in the upper layer of the chamber, and 600 μL of medium containing 10% FBS was applied in the bottom. After 48-h incubation, cells in the bottom were fixed, dyed in crystal violet and captured. Migratory cells were counted in 5 randomly selected fields per sample. Invasion assay was conducted using transwell chamber precoated with 100 μg Matrigel.

Subcellular Distribution Analysis

Cytoplasmic and nuclear RNAs were extracted using the PARIS kit (Invitrogen, Carlsbad, CA, USA) and subjected to qRT-PCR. U1 was the internal reference of nucleus and GAPDH was that of cytoplasm.

Dual-Luciferase Reporter Assay

Binding sites between miRNA-942-5p and hsa_circ_0000337 or MAT2A were predicted using online tools. Cells were seeded in the 24-well plate. They were co-transfected with Luci-

ferase vectors and miRNA-942-5p mimics or NC for 48 h. Luciferase activity was measured using the Dual-Luciferase reporter assay system (Promega, Madison, WI, USA).

Statistical Analysis

Data processing was conducted using GraphPad Prims 7.0 (La Jolla, CA, USA) and Statistical Product and Service Solutions (SPSS) 20.0 (IBM Corp., Armonk, NY, USA). Two-paired independent *t*-test was performed for comparing differences between groups. Pearson correlation test was conducted to assess the correlation between two genes in glioma tissues. Survival analysis was performed by Kaplan-Meier curves and log-rank test for significance in GraphPad Prism 5. A significant difference was set at $p<0.05$.

Results

Upregulation of Hsa_circ_0000337 in Glioma

We collected 45 cases of glioma and 24 cases of normal tissues for detecting hsa_circ_0000337 levels. QRT-PCR data showed that hsa_circ_0000337 was upregulated in glioma tissues (Figure 1A). Through analyzing clinical data of recruited glioma patients, it is demonstrated that hsa_circ_0000337 level was higher in T3-T4 stage glioma tissues in comparison to T1-T2 tissues (Figure 1B). Kaplan-Meier survival curves revealed lower overall survival in glioma patients expressing high level of hsa_circ_0000337 compared to patients with low level (Figure 1C). Similarly, hsa_circ_0000337 was upregulated in glioma cell lines (Figure 1D). We next detected the stability of hsa_circ_0000337. In U87 cells induced with Actinomycin D, a transcription inhibitor, the half-life of hsa_circ_0000337 was over 24 h. Comparably, the half-life of its associated gene symbol, PPFIA1 mRNA, was less than 12 h (Figure 1E). Notably, an obvious decline was detected in the mRNA level of PPFIA1 in RNase-induced U87 cells, while hsa_circ_0000337 level was not affected (Figure 1F).

Silence of Hsa_circ_0000337 Inhibited Proliferative and Metastatic Abilities in Glioma

Three hsa_circ_0000337 siRNAs were synthesized, and the first line of hsa_circ_0000337 siRNA presented the best transfection efficacy in U87 and U251 cells (Figure 2A). EdU assay showed that silence of hsa_circ_0000337 markedly reduced EdU-positive rate in glioma cells (Figure 2B). Moreover, transwell assay revealed that silence of hsa_circ_0000337 weakened migratory and invasive abilities in U87 and U251 cells (Figure 2C, 2D).

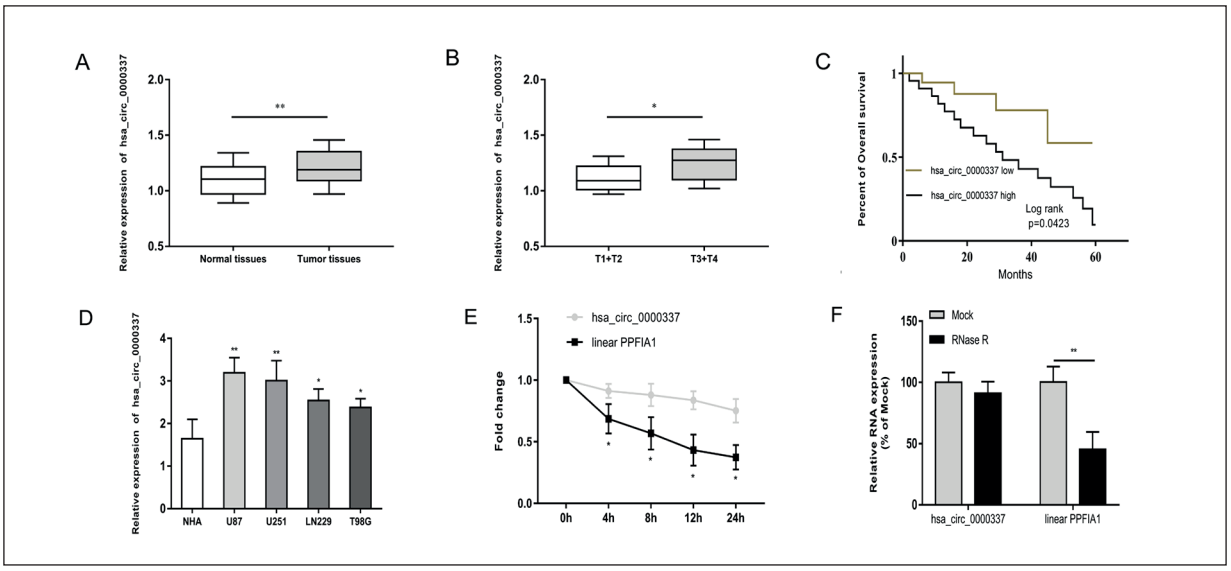

Figure 1. Upregulation of hsa_circ_0000337 in glioma. **A,** Hsa_circ_0000337 levels in glioma tissues and normal ones. **B,** Hsa_circ_0000337 levels in T1-T2 and T3-T4 glioma tissues. **C,** Overall survival in glioma patients expressing high or low level of hsa_circ_0000337. **D,** Hsa_circ_0000337 levels in glioma cell lines. **E,** The half-life of hsa_circ_0000337 and PPFIA1 in U87 cells induced with Actinomycin D. **F,** Hsa_circ_0000337 and PPFIA1 levels in U87 cells induced with RNase R. *$p<0.05$; **$p<0.01$.

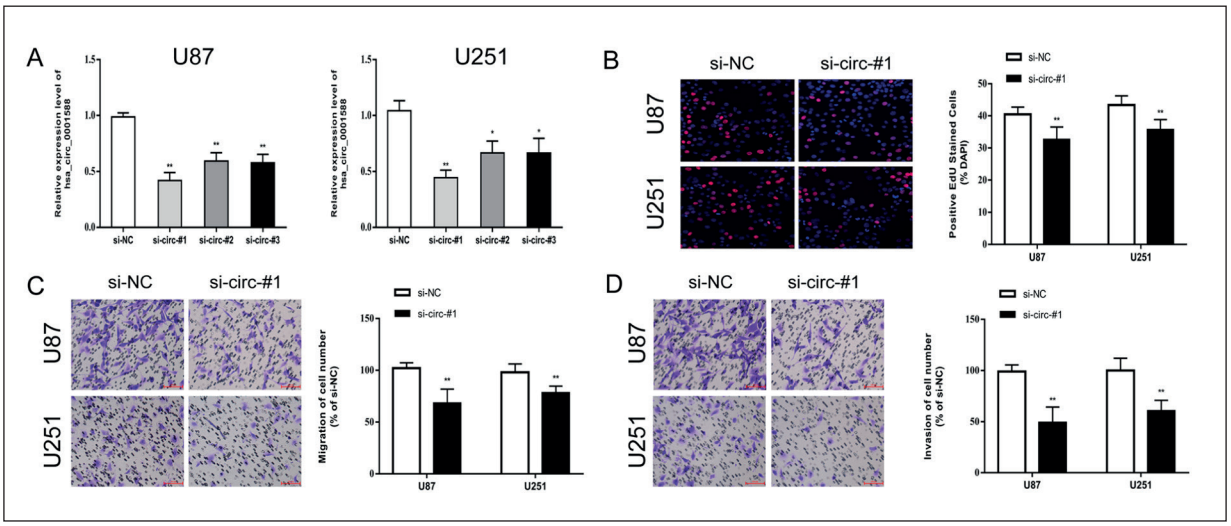

Figure 2. Silence of hsa_circ_0000337 inhibited proliferative and metastatic abilities in glioma. **A,** Transfection efficacy of hsa_circ_0000337 siRNAs in U87 and U251 cells. **B,** EdU-positive rate in U87 and U251 cells with hsa_circ_0000337 knockdown (magnification 200×). **C,** Migration in U87 and U251 cells with hsa_circ_0000337 knockdown (magnification 200×). **D,** Invasion in U87 and U251 cells with hsa_circ_0000337 knockdown (magnification 200×). *p<0.05; **p<0.01.

Hsa_circ_0000337 Could Bind MiRNA-942-5p

It is well known that circRNAs exert their biological functions mainly through sponging miRNAs. hsa_circ_0000337 was detected to be mainly distributed in the cytoplasm of U87 and U251 cells, indicating its involvement in the post-transcriptional regulation (Figure 3A). Through analyzing in circinteractome and Starbase, three miRNAs (miRNA-942-5p, miRNA-584-5p and miRNA-155-5p) were predicted to be the candidates of hsa_circ_0000337 targets (Figure 3B). Among them, miRNA-942-5p had the highest binding score, and it is previously identified to be a potential tumor-suppressor gene. According to the predicted binding sites in the 3'UTR of miRNA-942-5p and hsa_circ_0000337, Luciferase vectors were synthesized for dual-luciferase reporter assay (Figure 3C). The binding relationship between hsa_circ_0000337 and miRNA-942-5p was further confirmed (Figure 3D). Silence of hsa_circ_0000337 in U87 and U251 cells markedly upregulated miRNA-942-5p (Figure 3E). Comparably, miRNA-942-5p was downregulated in glioma ones (Figure 3F). Furthermore, miRNA-942-5p was analyzed to be negatively correlated to hsa_circ_0000337 level in glioma tissues (Figure 3G).

MiRNA-942-5p Could Bind MAT2A

Potential targets of miRNA-942-5p were predicted using microT, PITA, PicTar and miRmap. After cross-match analysis, MAT2A was finally selected to be the most optimal one (Figure 4A). The binding relationship between miRNA-942-5p and MAT2A was indicated by Dual-Luciferase reporter assay (Figure 4B, 4C). QRT-PCR data showed that MAT2A was downregulated in U87 and U251 cells overexpressing miRNA-942-5p (Figure 4D). In comparison to normal tissues, MAT2A was highly expressed in glioma ones (Figure 4E). Pearson correlation test obtained that MAT2A was positively correlated to hsa_circ_0000337 (R=0.5227, p<0.001, Figure 4F), and negatively correlated to miRNA-942-5p (R=-0.5451, p<0.001, Figure 4G).

MiRNA-942-5p Blocked Glioma to Proliferate and Metastasize by Downregulating MAT2A

To further uncover the biological functions of miRNA-942-5p and MAT2A, we synthesized miRNA-942-5p inhibitor and MAT2A siRNA. The upregulated MAT2A in glioma cells with miRNA-942-5p knockdown was reversed by co-transfection of MAT2A siRNA (Figure 5A). Transfection of miRNA-942-5p inhibitor enhanced EdU-positive rate in U87 and U251 cells, which was partially abolished by co-knockdown of MAT2A (Figure 5B). In addition, migratory and invasive abilities of glioma were stimulated after knockdown of miRNA-942-5p, which were

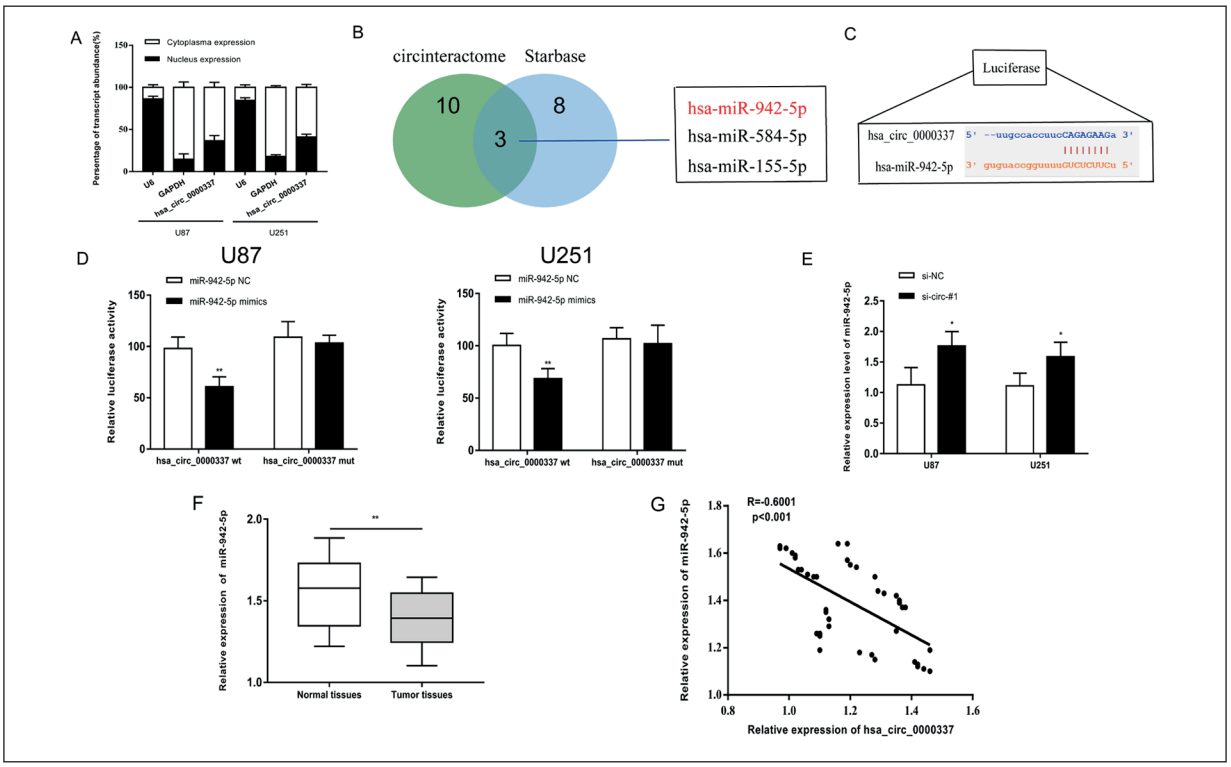

Figure 3. hsa_circ_0000337 could bind miRNA-942-5p. **A,** Subcellular distribution of hsa_circ_0000337. **B,** Potential targets of hsa_circ_0000337. **C,** Binding sites in the 3'UTR of hsa_circ_0000337 and miRNA-942-5p. **D,** Luciferase activity in U87 and U251 cells. **E,** MiRNA-942-5p level in U87 and U251 cells with hsa_circ_0000337 knockdown. **F,** MiRNA-942-5p levels in glioma tissues and normal ones. **G,** A negative correlation between hsa_circ_0000337 and miRNA-942-5p. *p<0.05; **p<0.01.

reversed by co-transfection of MAT2A siRNA (Figure 5C, 5D). The above data demonstrated that hsa_circ_0000337 may act as a ceRNA by competitively binding miRNA-942-5p to upregulate MAT2A, thereby promoting glioma cells to proliferate and metastasize.

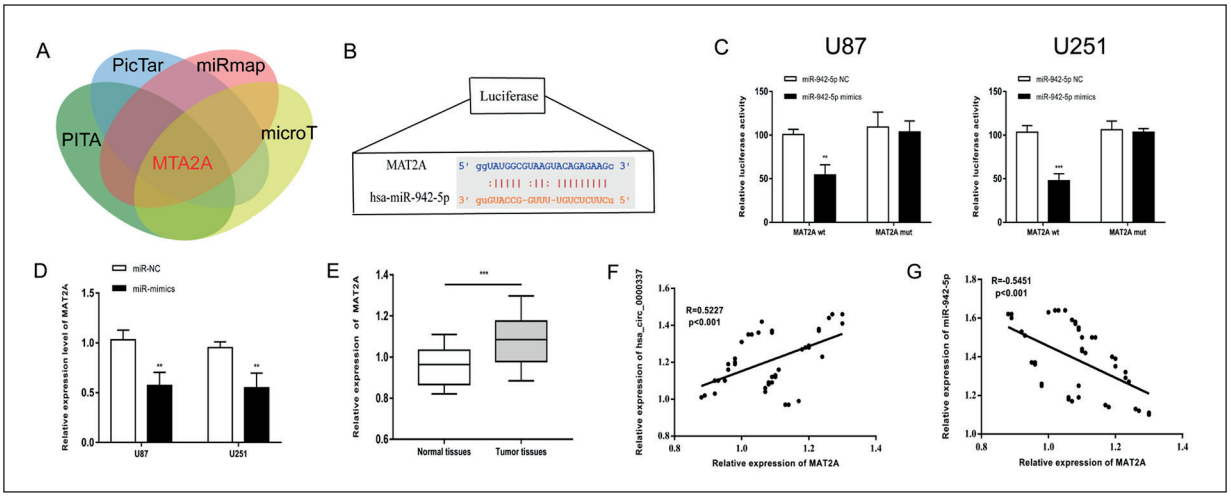

Figure 4. MiRNA-942-5p could bind MAT2A. **A,** Potential targets of miRNA-942-5p. **B,** Binding sites in the 3'UTR of miRNA-942-5p and MTA2A. **C,** Luciferase activity in U87 and U251 cells. **D,** MAT2A level in U87 and U251 cells overexpressing miRNA-942-5p. **E,** MAT2A levels in glioma tissues and normal ones. **F,** A positive correlation between MAT2A and hsa_circ_0000337. **G,** A negative correlation between miRNA-942-5p and MAT2A. **p<0.01; *** p<0.001.

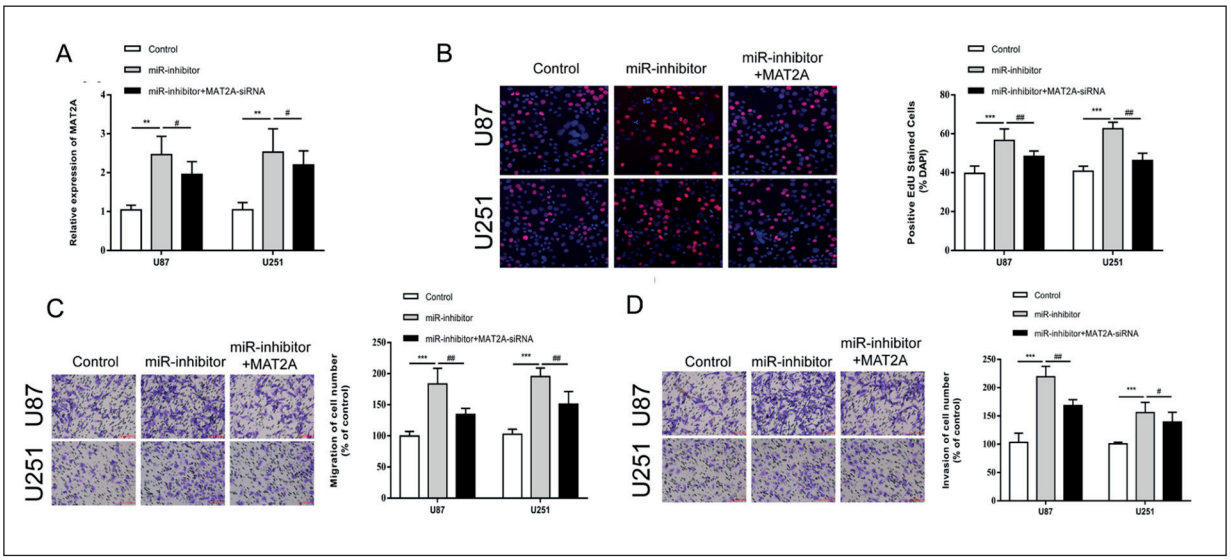

Figure 5. MiRNA-942-5p blocked glioma to proliferate and metastasize by downregulating MAT2A. **A,** Transfection efficacy of miRNA-942-5p inhibitor and MAT2A siRNA. **B,** EdU-positive rate in U87 and U251 cells regulated by miRNA-942-5p and MAT2A (magnification 200×). **C,** Migration in U87 and U251 cells regulated by miRNA-942-5p and MAT2A (magnification 200×). **D,** Invasion in U87 and U251 cells regulated by miRNA-942-5p and MAT2A (magnification 200×). **p<0.01; *** p<0.001; #p<0.05; ##p<0.01.

Discussion

Most circRNAs consist of exon sequences, which are highly conserved among species, and specifically expressed in different tissues and developmental stages[13]. CircRNAs are more stable than linear RNAs because of their resistance to exonucleases. As a result, they have significant advantages in the application of diagnostic and therapeutic targets[14]. CircRNAs are involved in gene transcription, splicing and expressions *via* sponging miRNAs[15,16]. So far, abundant circRNAs have been identified to be functional in tumor process. EIF4A3-induced circMMP9 triggers carcinogenesis of glioblastoma multiforme by sponging miR-124[17]. CircSCAF11 stimulates the tumorigenesis of glioma *via* the miR-421/SP1/VEGFA axis[18].

Our findings uncovered that hsa_circ_0000337 was highly expressed in glioma tissues. Through assessing the clinical data of recruited patients, it is found that hsa_circ_0000337 was correlated to TNM staging and overall survival of glioma. Knockdown of hsa_circ_0000337 in U87 and U251 cells weakened proliferative and metastatic abilities.

Next, we speculated that miRNA-942-5p could be a potential target binding hsa_circ_0000337 after bioinformatic analysis. MiRNA-942-5p is lowly expressed in cervical cancer cases, which is able to inhibit cancer cell growth and metastasis[19]. Through testing, we found that hsa_circ_0000337 could bind miRNA-942-5p and inhibit its expression. MiRNA-942-5p was downregulated in glioma tissues, indicating that hsa_circ_0000337 may be involved in the progression of glioma by binding to miRNA-942-5p.

Furthermore, MAT2A was identified to be the target of miRNA-942-5p following online prediction and functional analysis. MAT2A is an important target for mitogen-active cytokines, such as hepatocyte growth factor (HGF) and leptin[20]. Silence of MAT2A inhibits mitogenic response and cell proliferation and induces apoptosis[21]. The role of MAT2A in the progressions of hepatocellular carcinoma and colorectal carcinoma has been discovered[22,23]. Here, miRNA-942-5p was able to bind MAT2A, and hsa_circ_0000337 upregulated MAT2A by binding miRNA-942-5p. Knockdown of miRNA-942-5p markedly stimulated glioma cells to proliferate and metastasize, and the enhanced trends were abolished by co-knockdown of MAT2A.

The role and mechanism of circular RNA in gliomas remains unclear, this research discovered that hsa_circ_0000337 was upregulated and linked to prognosis of glioma for the first time. Hsa_circ_0000337 accelerated the malignant process

of glioma by binding miRNA-942-5p and then upregulated MAT2A. Our findings provide a novel idea for explaining the molecular mechanism of glioma, and theoretical references for clinical diagnosis and treatment.

Conclusions

Briefly, Hsa_circ_0000337/miRNA-942-5p/MAT2A axis is responsible for the deterioration of glioma. hsa_circ_0000337 may be a potential therapeutic target for glioma.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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