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Long non-coding RNA SNHG11 promotes cell proliferation, invasion and migration in glioma by targeting miR-154-5p

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Abstract. – OBJECTIVE: Long non-coding RNAs (lncRNAs) play critical roles in tumour progression. However, the function of lncRNA small nucleolar RNA host gene 11 (SNHG11) in glioma has not been mentioned before. Our study aims to uncover the biological roles of SNHG11 in the progression of glioma and throw light for clinical treatment of glioma.

MATERIALS AND METHODS: The Gene Expression Profiling Interactive Analysis (GEPIA) dataset was used to analyze the SNHG11 expression between glioma and normal tissue, as well as survival benefit. The quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) was used to detect SNHG11 and miR-154-5p expression. Celltiter-Glo, colony formation, and transwell assays were utilized to detect the influence of SNHG11 to the malignancy of U87 and U251 cells. The underlying pathways affected by SNHG11 were measured using Western blot. Furthermore, Luciferase reporter assay was applied to verify the interaction between SNHG11 and miR-154-5p.

RESULTS: SNHG11 was upregulated in glioblastoma tissues and five malignant glioma cell lines. SNHG11 expression was negatively correlated with overall survival of glioma patients. Moreover, silencing of SNHG11 could decrease glioma cell viability both *in vitro* and *in vivo*. Furthermore, the inhibition of SNHG11 suppressed proliferation, invasion and migration via regulating epithelial-mesenchymal transition (EMT). In addition, SNHG11 could bind miRNA-154-5p and negatively regulate its level.

CONCLUSIONS: SNHG11 functioned as an oncogene in glioma and promoted proliferation, invasion, and migration via EMT by sponging miR-154-5p. These findings provided a new therapeutic target for glioma.

Key Words:
Long non-coding RNA, SNHG11, Glioma, Epithelial-mesenchymal transition, MiR-154-5p.

Introduction

Glioma is the most common and aggressive intracranial malignant tumour of adults with poor overall survival worldwide[1]. Although a combined approach of maximal safe resection, radiation, and chemotherapy has been improved in the last decades, the prognosis for patients with malignant glioma remains bleak[2]. Thus, investigating the molecular mechanism and searching effective therapeutic targets of gliomas are significant for patients.

LncRNAs, a class of non-protein coding transcripts which are longer than 200 nucleotides, have attracted considerable attention in recent years[3]. To date, numerous scholars[4] have demonstrated that lncRNAs function as competing endogenous RNAs to decoy miRNA, decreasing the amount of available miRNAs and contributing to translation. Moreover, many lncRNAs were found to be aberrantly expressed in tumours compared to normal tissue and suggesting their critical roles in tumour progression[5]. Previous studies have demonstrated that SNHG11 is a prognosis biomarker in colorectal cancer[6] and promotes hepatocellular carcinoma progression[7]. However, few studies focused on the role of SNHG11 in glioma[8].

In our study, we identified that SNHG11 was highly expressed in glioblastoma compared to normal brain and as a biomarker for short overall survival. Moreover, suppression of SNHG11 inhibited the proliferation, migration, and invasion of glioma cells *via* regulating epithelial-to-mesenchymal transition. In addition, the interaction between SNHG11 and miR-154-5p was validated by Luciferase assay in glioma cells. These data suggested that SNHG11 could be a potential biomarker and therapeutic target of malignant glioma.

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Materials and Methods

Bioinformatic Analysis

Differential expression and prognosis of SNHG11 in glioma tissues were evaluated by analyzing Gene Expression Profiling Interactive Analysis (GEPIA) database (http://GEPIA.cancer-pku.cn/index.html). The number of patients is showed in Figure 1.

Cell Culture

The human glioma cell lines (U87, U251, and U343) were kindly gifts from Dr. Xin Chen[9], and HEB astrocyte cell line was purchased from Beijing winter song Boye Biotechnology (Beijing, China). U87, U251, U343 and HEB cell lines were cultured in Dulbecco's Modified Eagle's Medium (DMEM; Corning, NY, USA) containing 10% fetal bovine serum (FBS; HyClone, Logan, UT, USA) and 1% penicillin and streptomycin (Gibco, Rockville, MD, USA) in a 5% carbon dioxide incubator at 37°C. Patient-derived diffuse intrinsic pontine glioma cell lines TT150630 and TT150714 were cultivated as previously described[10]. All cell lines used in our study were tested and confirmed to be negative for mycoplasma.

Lentiviral Construction and Cell Transfection

Lentiviral short heparin RNA (shRNA) plasmids and lentiviruses were generated as previously described[11]. The three SNHG11 shRNAs sequences (sh-SNHG11-1 CCTTGGGTCTGGAAACTGTTA, sh-SNHG11-2 CCGTGTGTGTTATATCATGAT, and sh-SNHG11-3 GCCTACAAAGTGTCGGTCATT) were designed from Sigma-Aldrich (https://www.sigmaaldrich.com/life-science/functional-genomics-and-rnai/sirna/mission-predesigned-sirna.html). The empty FUGW-H1 vector was used as the shRNA control.

The piggyBac plasmid was used as a vector (PB-CTR) to overexpress SNHG11 (PB-SNHG11) and transfected into U87 and U251 cells with Lipofectamine 2000 reagent (Invitrogen, Carlsbad, CA, USA).

RNA Isolation and Quantitative Real Time-Polymerase Chain Reaction

Cells were lysed by TRIzol reagent for RNA isolation. Next, cDNA was generated with a commercial reverse transcription kit (ABM, Zhenjiang, Jiangsu, China). qRT-PCRs were performed using SYBR Green (CWBIO, Beijing, China). Relative expression of SNHG11 was assessed using the $2^{-\Delta\Delta Ct}$ method and normalized to GAPDH. The level of miR-154-5p was normalized to the level of U6. qRT-PCR primers used in this research are listed below. SNHG11-Forward: 5'-TGGGAGTTGTCATGTTGGGA-3'; SNHG11-Reverse: 5'-ACTCGTCACTCTTGGTCTGT-3'; MiR-154-5p-Forward: 5'-GCCTTCGCTCAACTGAATTG-3'; MiR-154-5p-Reverse: 5'-CTCAACTGGTGTCGTGGAGTC-3'; U6-Forward: 5'-CTCGCTTCGGCAGCACATA-3'; U6-Reverse: 5'-CGCTTCACGAATTTG-

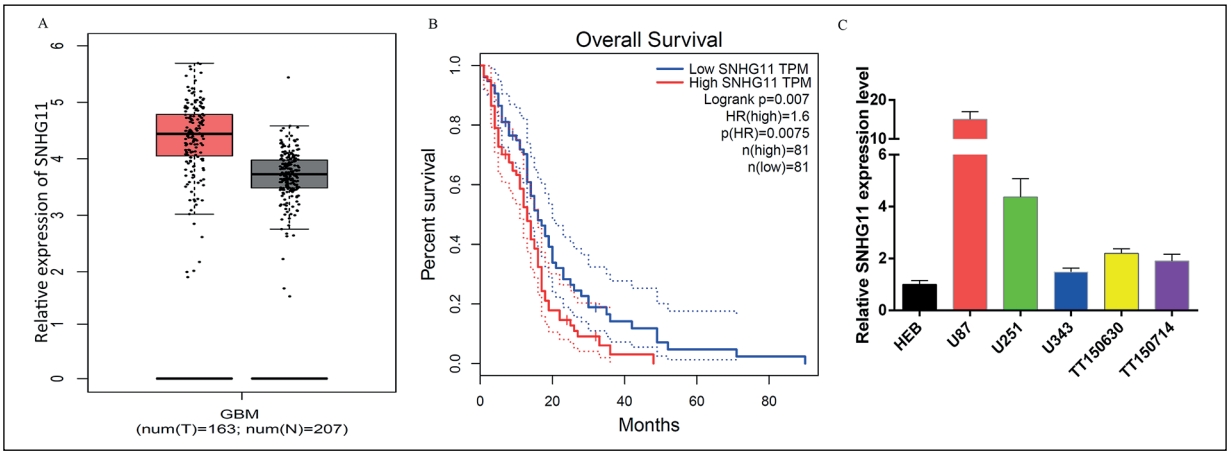

Figure 1. The expression level and survival risk of lncRNA SNHG11 in glioma. **A,** The expression level of SNHG11 in glioma tissues (red bar, n=163) and normal tissues (black bar, n=207) analyzed by GEPIA dataset. **B,** The 162 glioma patients into high and low SNHG11 level groups (n=81) with the median expression level of SNHG11 in glioma tissues as the cutoff value. Survival curves were compared by the log-rank test. **C**, SNHG11 levels in human astrocytes HEB and glioma cells U87, U251, U343, TT150630, and TT150714. (*$p < 0.05$).

CGTG-3'; GAPDH-Forward: 5'-GATCATCAGCAATGCCTCCT-3'; GAPDH-Reverse: 5'-TGAGTCCTTCCACGATACCA-3'.

Cell Viability

2,000 cells were seeded in triplicate in 96-well plates. At indicated time points, cell viability was assessed by Celltiter Glo assay (Promega, Madison, WI, USA) and the bioluminescence was measured by a TECAN Infinite 2000 plate reader (TECAN, Maennedorf, Zürich, Switzerland).

Colony Formation Assay

2,000 cells were cultured in three replicates in 6-well plates. After seven days, cells were fixed by methanol and incubated with 0.5% crystal violet for 10 minutes. Subsequently, the plates were rinsed in water to remove excessive crystal violet. The plates were scanned by an electronic scanner and a group of at least 50 cells was defined as a colony.

Wound Healing Assay

4×10^5 cells per well were plated into 6-well plate and incubate 24 hours in DMEM medium. Wounds were created by scratching the cell monolayer with a 1000 ul pipette tip. Cells were cultured in the DMEM containing 2% fetal bovine serum (FBS) for another 24 hours and images were captured under a microscope (Zeiss, Jena, Germany). This experiment was performed in triplicate independently.

Transwell Assay

5×10^4 cells suspended in serum-free DMEM were plated onto 8 μm pore size inserts (Corning, NY, USA) for cell migration assay [without Matrigel (Corning, NY, USA)] and cell invasion assay (pre-coated with Matrigel for 2 hours). Then, the DMEM containing 10% FBS was added to the lower chamber to induce cell migration or invasion. After incubation at 37°C for 24 h, the inserts were fixed by 4% paraformaldehyde for 30 minutes, and then, stained by 0.5% crystal violet for 10 minutes. Cells remaining on the upper surface of the membrane were gently removed with a cotton swab. The number of migration or invasion cells in the lower surface were counted in four random field at a magnification of 40×.

Western Blot

The cell lysates were extracted by RIPA buffer containing complete tablets (Roche, Basel, Switzerland) and phosphatase inhibitor (Sangon Biotech, Shanghai, China) on a shaker at 4°C overnight. The polyvinylidene difluoride (PVDF) membranes (Thermo Fisher Scientific, Inc., Waltham, MA, USA) were incubated in the 5% bovine serum albumin (Sangon Biotech, Shanghai, China) with the following primary antibody overnight: GAPDH (1:2000, G041, abm), E-cadherin (Cell Signaling Technology, Danvers, MA, USA), N-cadherin (BD Biosciences, San Jose, CA, USA), and Vimentin (Thermo Fisher Scientific, Inc., Waltham, MA, USA). The dilution of the primary antibody for WB is 1:1000 except for the additional instructions. The protein bands were visualized using the enhanced chemiluminescence (ECL) detection kit (Thermo Fisher Scientific, Inc., Waltham, MA, USA) and ChemiDoc Touch imaging system (Bio-Rad, Hercules, CA, USA). The intensities were measured by Image J software.

Glioma Xenograft Mouse Models

All *in vivo* experiments were approved by the Ethics Committee of the of Animal Experiments of Beijing Tiantan Hospital and performed in accordance with the guidelines for the Care and Use of Laboratory Animals of the Ethics Committee of Animal Experiments, Beijing Tiantan Hospital.

10^6 active U87 cells infected with sh-SNHG11 or empty vector lentivirus were suspended in 200 μl PBS and subcutaneously injected into a group of six nude mice, respectively. After 30 days, the mice were sacrificed and xenografts were excised, weighed and took photos.

Dual-Luciferase Reporter Gene Assay

To determine the relationship between SNHG11 and miR-154-5p, the fragment of SNHG11-WT or SNHG11-MU was inserted into the pGL4 vector (Promega, Madison, WI, USA). Then, these vectors were co-transfected with miR-NC or miR-154-5p (5'-UAGGUUAUCCGUGCCUUCG-3') into the U87 and U251 cells using Lipofectamine 2000 reagent.

Statistical Analysis

GraphPad Prism 7.0 (GraphPad Software, La Jolla, CA, USA) was used to analyze the data and perform the figures. Data were showed as the mean ± standard deviation (SD) of at least three independent experiments and analyzed using Student's *t*-test. Kaplan-Meier method and log-rank test were carried out for survival analysis. $p < 0.05$ was considered a significant difference.

Results

Aberrant Expression and Prognostic Significance of SNHG11 in Glioma Patients

To address the role of lncRNA SNHG11 in glioma, we first compared SNHG11 expression between glioblastoma tissues and normal brain tissues based on the TCGA database. SNHG11 expression was higher in GBM than in normal brain by analyzing the GEPIA dataset (Figure 1A). Furthermore, we evaluated the correlation between SNHG11 expression and patient clinical outcome. As shown in Figure 1B, survival analysis demonstrated that both low-grade glioma (LGG) and glioblastoma (GBM) patients with high SNHG11 expression levels had a significantly poor prognosis, according to the TCGA database. In addition, compared with the level in human astrocyte, SNHG11 was highly expressed in several glioma cell lines by conducting qRT-PCR analysis (Figure 1C). These data suggested that SNHG11 was highly expressed in GBM and its expression was negatively correlated with glioma patient survival.

Silencing of SNHG11 Suppressed the Malignant Behavior of Glioma Cells via EMT

To investigate the biological role of SNHG11 in glioma, we used two glioma cell lines highly expressing SNHG11 (U87 and U251) for further experiments. Three different SNHG11 shRNAs, sh-SNHG11-1, sh-SNHG11-2 and sh-SNHG11-3 were designed and transfected into the above-mentioned cell lines. The expression levels of SNHG11 were assessed by qRT-PCR and sh-SNHG11-2 (sh-SNHG11) was selected for the following experiments as its best efficiency (Figure 2A).

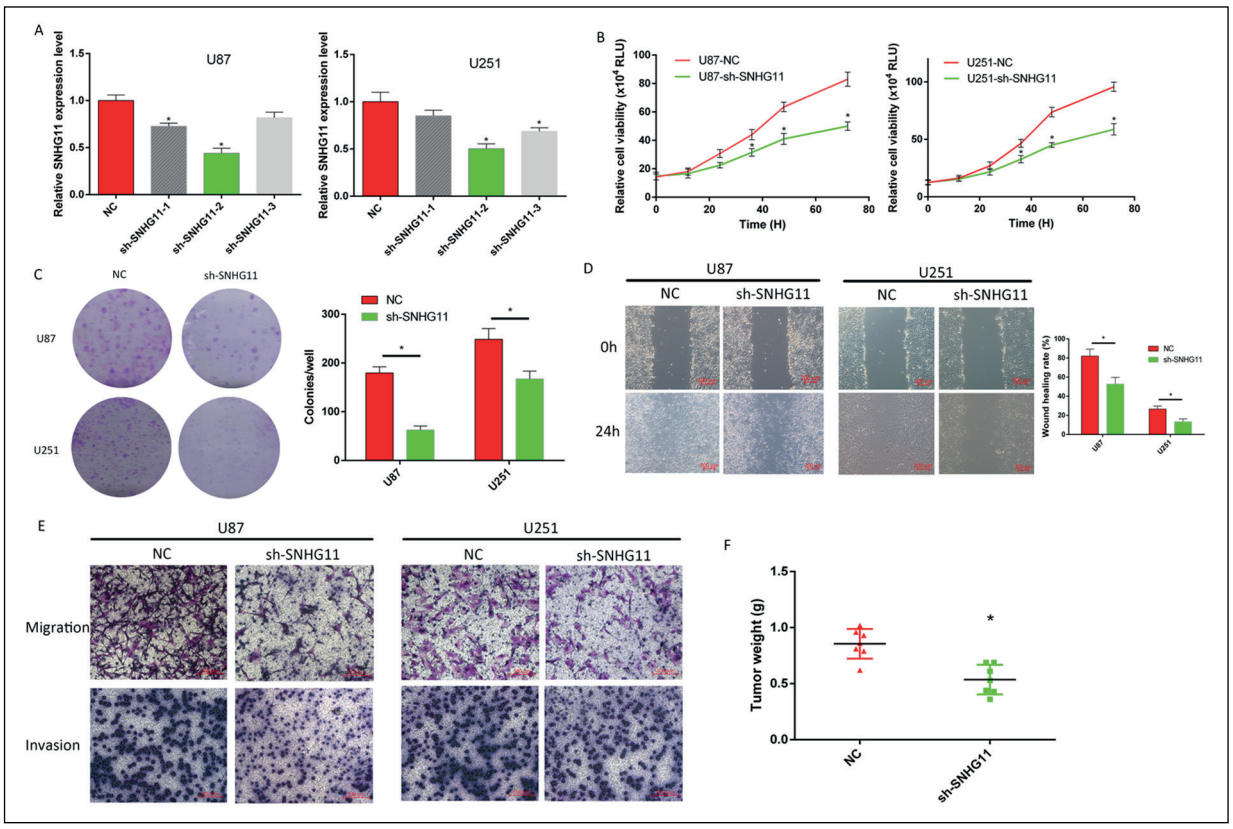

Figure 2. Inhibition of SNHG11 suppressed proliferation, invasion and migration in glioma. **A,** The SNHG11 knockdown efficiencies by three shRNAs were detected by qRT-PCR. **B,** CellTiter Glo assay showed that knockdown of SNHG11 inhibited cell growth ability in glioma cells. **C-E,** Representative images from colony formation assays **(C, left)**, wound healing assays **(D, left,** magnification: 10×, scale bar: 200 μm**)**, and transwell assays **(E,** magnification: 20×, scale bar: 500 μm**)** for glioma infected by NC and shSNHG11 lentiviruses. Graphic representation of the quantification of the colony number after seven days **(C, right)** and wound healing rate after 24 hours **(D, right)**. **F,** Tumor weights were measured from sacrificed mice. (*$p < 0.05$).

Due to lncRNAs participation in diverse biological processes, the following experiments were conducted to investigate the role of SNHG11 in glioma. CellTiter Glo assays demonstrated that the cell proliferation capacity was significantly decreased in cells transfected with sh-SNHG11 (Figure 2B). Likewise, colony formation assays suggested that SNHG11 knockdown reduced colony number (Figure 2C). Subsequently, the wound healing and transwell assays were used to explore the influence of lncRNA SNHG11 in cell migration and invasion. As expected, the results of these two assays revealed that both cell migration and invasion were sharply decreased in the sh-SNHG11 group, compared with that in the control shRNA (NC) group (Figure 2D and 2E).

To further determine whether SNHG11 is critical for malignant behavior of glioma, xenograft mouse models were established to evaluate the role of SNHG11 *in vivo*. U87 transfected with sh-SNHG or NC were separately implanted to the flank of immunodeficient mice. Compared with the NC group, the knockdown of SNHG11 significantly reduced glioma tumour growth *in vivo* (Figure 2F).

EMT considered an important biological progression in promoting tumor migration and invasion[12]. Here, we measured the expression level of EMT markers between sh-SNHG11 and NC glioma cells. As a result, the significant decreases of both N-cadherin and vimentin in sh-SNHG11 groups indicated that the weakened EMT progression after SNHG11 was silenced (Figure 3). Collectively, these data suggested that the knockdown of lncRNA SNHG11 significantly suppressed the malignant behavior of glioma cell lines by regulating EMT.

MiR-154-5p Was a Direct Target of SNHG11 in Glioma

The bioinformatic analysis website (starBase v2.0) was used to predict the potential miRNA interaction with SNHG11. MiR-154-5p, containing a complementary base with SNHG11 (Figure 4A) and inhibiting EMT in prostate cancer[13], was selected for our further studies. We used the Luciferase reporter gene assay to investigate the interaction between SNHG11 and miR-154-5p. As shown in Figure 4B, the Luciferase activities were significantly reduced when the SNHG11-WT bound to miR-154-5p, whereas no change was observed in glioma cells co-transfected with SNHG11-MU and miR-154-5p. Moreover, the miR-154-5p expression was significantly increased by the suppression of SNHG11 while the overexpression of SNHG11 downregulated miR-154-5p expression in both the U87 and U251 glioma cell lines (Figure 4C).

Discussion

Some scholars[14] have reported that a group of lncRNAs, small nucleolar RNA host genes (SNHG), participate in the glioma progression. For instance, the SNHG1 promotes glioma progression by sponging miR-194[15], and the oncogene SNHG16 affects PI3K/Akt signalling pathway by binding to miR-4518[16], as well as the critical role of SNHG18 in glioma radioresistance[17]. Also, there are several studies defined SNHG11 as a risk factor in colorectal and pancreatic cancer[6,18]. However, the function and mechanisms of SNHG11 in glioma remain unclear.

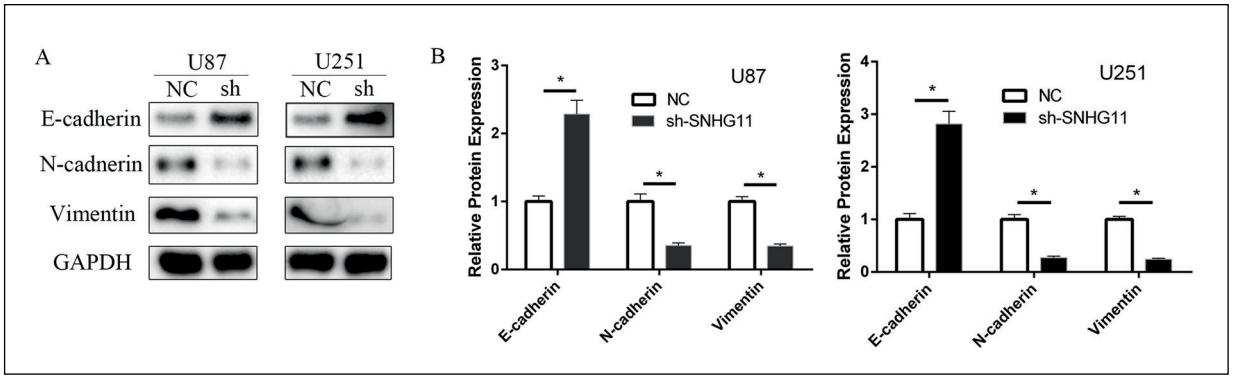

Figure 3. SNHG11 promoted EMT in glioma. **A,** Western blot for protein levels of three EMT markers, E-cadherin, N-cadherin and Vimentin from U87 and U251 cells infected by NC or SNHG11 lentiviruses. GAPDH was used as a loading control. **B,** Graphic representation of the quantification of the three EMT markers. (*$p < 0.05$).

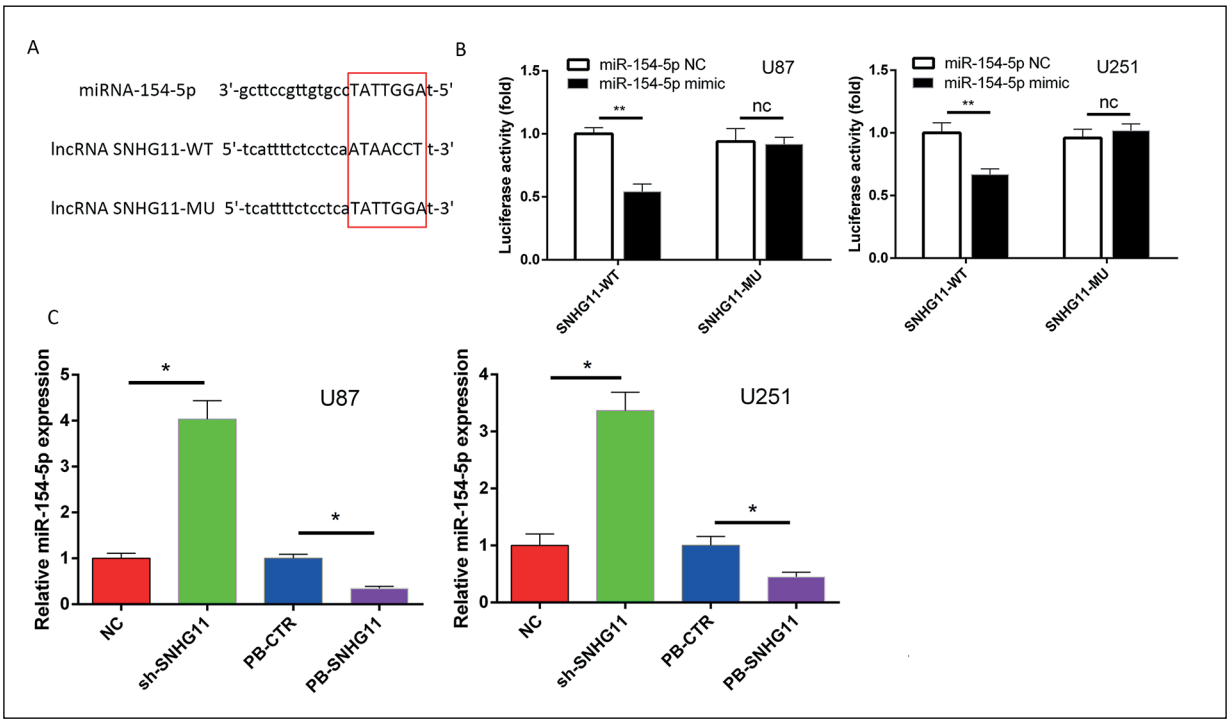

Figure 4. MiR-154-5p was identified as a target miRNA of SNHG11 in glioma. **A,** The predicted miR-154-5p binding sites on SNHG11 and schematic of wild and mutant pGL4-SNHG11 constructs. **B,** The relative Luciferase activity was decreased after co-transfecting with miR-154-5p mimics and pGL4-SNHG11-WT in U87 and U251 cells. **C,** The efficiency of miR-154-5p expression after glioma cells transfected with NC, shSNHG11, PB-CTR and PB-SNHG11 in glioma. (*$p <$ 0.05, **$p < 0.01$).

In the present study, SNHG11 was found to be upregulated in glioma tissues, as well as several glioma cell lines. The upregulated expression of SNHG11 was correlated with poor prognosis of glioma. Moreover, SNHG11 knockdown could decrease glioma cell viability both *in vitro* and *in vivo*. Furthermore, silencing SNHG11 suppressed proliferation, invasion and migration by regulating EMT in glioma cell lines.

EMT is a transformation process that the static epithelial cells create motile cells by reusing some parts of the molecular program. It is well accepted that EMT contains three subtypes[19]. Type 1 EMT participates in primitive epithelial cells transitioning to motile mesenchymal cells[20]. Type 2 EMT involves secondary epithelial cells transitioning to resident tissue fibroblasts. Both situations participate in normal development or body protection, such as primitive neuroepithelial cells generating migrating neural crest cells and fibroblasts responding to inflammation. However, type 3 EMT involves in epithelial carcinoma cells forming migratory metastatic tumor cells, which is a major part of glioma progression.

E-cadherin, N-cadherin, and vimentin play crucial roles in EMT. Cadherins keep the balance between suppression and promotion of migration and invasion in cancer cells. Among them, E-cadherin, also called uvomorulin, links plasma membranes of adjacent cells and maintains the rigidity of the cell layer, and functions as an invasion suppressor[21,22]. On the other hand, cancer cells that express intermediate filament protein vimentin are constitutively more motile and invasive *in vitro* and more metastatic *in vivo*[23]. These vimentin-positive cell lines all lack functional E-cadherin and highly express N-cadherin[24]. Consistent with our results, the knockdown of SNHG11 inhibited the malignant behavior of glioma cells, accompanied by the downregulation of N-cadherin and upregulation of vimentin.

We also discovered that miR-154-5p was a direct target of SNHG11, which indicated that miR-154-5p might play a critical role in EMT. Previous investigations have demonstrated that miRNA-154-5p functions as a tumor suppressor in osteosarcoma[25] and is a target of circ_101064

which promotes glioma proliferation. Notably, Zhu et al[13] demonstrated that miR-154 inhibits EMT by targeting HMGA2, which give us the hints to further investigate the regulatory network of SNHG11.

Conclusions

In summary, the abundance of lncRNA SNHG11 was abnormally increased in glioma tissue and cell lines. Our study first demonstrated silencing SNHG11 inhibited glioma cell proliferation, invasion and migration via regulating EMT. Meanwhile, our study first discovered the SNHG11/miR-154-5p axis in glioma, providing new insight into the mechanism of glioma progression and a promising therapeutic target.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Funding Interests

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