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ORIGINAL ARTICLE

lncRNA SNHG16 Exerts Oncogenic Functions in Promoting Proliferation of Glioma Through Suppressing p21

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Abstract
Glioma is a malignant brain tumor that accounts for 30% of all brain tumors and 80% of malignant brain tumors. This poor clinical outcome makes the study of molecular mechanisms in glioma as an urgent subject. However, the certain mechanism remains unclear. Long non-coding RNAs (lncRNAs) plays a key role in glioma development and progression. In the present study, we aimed to explore the potential mechanisms of lncRNA SNHG16 in glioma. The levels of lncRNA SNHG16 were qualified in both glioma tissues and cell lines using qRT-PCR assay. The ability of cell proliferation was tested via CCK-8 and colony formation assays. Transfections were performed to knockdown SNHG16 and its target gene p21. The cell cycles and cell apoptosis were evaluated using flow cytometry, and the expression of SNHG16, p21 and apoptosis biomarkers were qualified with qRT-PCR and western blot assays. The expression of SNHG16 were up-regulated in both glioma tissues and cell lines. Knockdown of SNHG16 was associated with poor proliferation, decreased monoclonal formation rates, but increased apoptosis rates, which also caused the high expression of p21. Moreover, p21 could mediate cell proliferation and monoclonal formation, promote cell apoptosis in glioma, which was negatively correlated with lncRNA SNHG16. The molecule mechanism experiments revealed that SNHG16 could not only inhibit the expression of p21 but also suppressed the level of caspase 3 and 9, while promoted cyclinD1 and cyclinB1 expression. lncRNA SNHG16 could promote the cell proliferation and inhibit the apoptosis of glioma through suppressing p21, indicating that lncRNA SNHG16 might be quite vital for the diagnosis and progression of glioma and could even be a novel therapeutic target for glioma.

Keywords Long non-coding RNA · SNHG16 · p21 · Glioma

Introduction

Glioma is a malignant brain tumor that accounts for 30% of all brain tumors and 80% of malignant brain tumors [1, 2]. Despite the improvement in therapeutic approaches in the past decade, the etiology of these tumors is still unknown, and the prognosis of patients remains poor. Common gliomas are divided into astrocytoma and oligodendroglioma, which have the same pathological grade but different histological and molecular causes. For each type of glioma, there are tumors that span a broad spectrum of biological invasiveness [3, 4]. Gliomas are difficult to cure, whose 5-year survival rate is less than 10% and the median survival period is only 14 months [5]. This pessimistic clinical outcome makes the study of molecular mechanisms in glioma as an urgent subject.

In recent years, long non-coding RNAs (lncRNAs) was focused by scholars. It is well-known that lncRNAs are a kind of non-coding RNAs with size over 200 nucleotides, which can regulate gene expression at pre-transcriptional, post-transcriptional and epigenetic levels [6]. They have been identified as vital regulators in the development and progression of multiple tumors [6–8]. For example, the level of lncRNA PAR5 was down-regulated in glioma patients, and the rescued PAR5 inhibited the proliferation, invasion and migration of glioma cells by regulating an oncogene EZH2 [9]. The lncRNA HOXA11-AS and ATB were significantly up-regulated in glioma tissue, promoting glioma progression by binding to miR-140-5p and miR-200a respectively [10, 11]. Hao Li et al. Also identified a total of 1545 lncRNAs which were aberrantly expressed greater than 2-fold in differentiated human glioblastoma stem cells [12]. It implied lncRNAs may

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involve in the regulating of giloma differentiation. These lncRNAs have been reported to correlate with the development and progression of glioma, indicating that lncRNAs might be the potential biomarkers for glioma diagnose and treatment. However, more evidence is needed to explain the mechanisms of glioma for finding the effective therapy.

Clinical evidences have been showed the aberrant level of lncRNA SNHG16 was associated with glioma prognostic [13]. lncRNA SNHG16 was first reported to be up-regulated in lung adenocarcinoma in recent years [14]. The subsequently studies showed this lncRNA was high expressed in glioma tissues and cells [13]. It may regulate cancer development by binding with miR-20a-5p or miR-4518 [13, 15]. However, the certain mechanism was still unclear.

In the present study, we found that SNHG16 was showed an increasing level in glioma cell lines. Moreover, its down-regulation was subjected to suppress cell proliferation and promote apoptosis. Our study demonstrated that SNHG16 functions as an oncogene through inhibiting p21 expression in glioma. Taken together, we investigated that SNHG16 might be taken a novel therapeutic target in glioma.

Materials and Methods

Clinical Tissue Collection

The glioma tissue ($n = 40$) and normal brain ($n = 40$) samples were collected from patients suffer from traumatic brain injury who were received surgical surgeries at the First Affiliated Hospital of University of South China from 2012 to 2017. The experimental protocol was approved by the ethnical committee of the hospital. The participants were fully informed and understood, and signed an informed consent.

Cell Culture and Transfection

The human glioma cell line U251, H4 SW1783, LN229 and normal human astrocytes NIHAS obtained from ATCC. The cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with with 2 mmol/L glutamine (Sigma) and 10% of FBS (fetal bovine serum, Gibco) at 37 °C, 5% of CO_2. The medium was renewed every three days. The small interfering RNAs (siRNAs, including si-SNHG16, si-p21 and their negative controls: siNC) and over-expression plasmids (including pcDNA-SNHG16, pcDNA-p21 and their negative control: pcDNA) were synthesized by GenePharma, Co., Ltd. (Shanghai, China). The cells was transfected with siRNAs or over-expression plasmids using Lipofectamine 2000 (Invitrogen, USA) according to the manufacturer's instruction [16].

RNA Extraction and Quantitative PCR

Total RNA was extracted using TRIZOL (Invitrogen, USA). Subsequently, cDNA was synthesized using SuperScript II RT kit (Invitrogen, USA) according to the manufacturer's instruction. PCR was performed using ABI 7500 (Life Tech, USA). The relative expression levels of mRNA were determined using a SYBR-Green PCR master mix kit (Thermo Fisher, USA). Gene expression was normalized to GAPDH and fold changes were calculated using the $2^{-\Delta\Delta Cq}$ method. The primer sequences were: SNHG16 F: 5′-GCAGAATGCCATGG TTTCCC-3′; R: 5′-GGACAGCTGGCAAGAGACTT-3′; p15 F: 5′-CCAGAAGCAATCCAGGCACG-3′; R: 5′-CGTT GGCAGCCTTCATCG-3′; p16 F: 5′-GAAG AAAGAGGAGGGGCTC-3′; R: 5′- GCGCTACCTGATTC CAATTC-3′; p21 F: 5′-CGATGGAACTTCGACTTTGT CA-3′; R: 5′-GCACAAGGGTACAAGACAGTG-3′; p27 F: 5′- TCTGTAGTAGAACTCGGGCAA-3′; R: 5′-AGTT CAAACGTGCGAGTGTC-3′; GAPDH F: 5′-AGAA GGCTGGGGCTCATTTG-3′, R: 5′-AGGGGCCATCCACA GTCTTC-3′ [15].

Cell Proliferation Assay

Cell counting kit-8 (CCK8, Univbio, China) was utilized for cell proliferation assay [17]. The cells were cultured with the previously mentioned condition in a 96 well plate (2.5×10^3 cells for each well). At the 0/24/48/72 h after seeding, 100 μL of CCK-8 solution were added for staining. The absorbance at 450 nm was measured via a microplate reader (Thermofisher, USA) after a 2-h incubation at room temperature. The wells with serum-free medium were set as blank control group. Triplicates were performed for each group.

Colony Formation Assay

The cells in logarithmic growth phase was prepared for clone formation assay [18]. The single cell suspensions were added to 60 mm petri dishes with the concentration of 500 cells per dish. After 14 days, the cells were washed once with PBS, fixed with methanol, and stained with Gimsa, and colonies of cells with a cell count of 50 cells or more were counted under a microscope (Zeiss, Germany). Triplicates were performed for each group.

Cell Cycle and Apoptosis Assay

The cell cycles and apoptosis were tested using flow cytometry [18]. For apoptosis, FITC Apoptosis Detection Kits (BD Biosciences, USA) was performed according to the manufacturer's guide. For cell cycle, the cells were fixed with ethanol and collected after trypsinization. The RNA was degraded with RNase (Sigma, USA). 50 μg/ml of PI was added and incubated at room temperature for 30 min. Finally, the cells were resuspended and analyzed using flow cytometry (BD Biosciences, USA).

Western Blot Analysis

The western blot assay was performed as the classic protocol [19]. The total protein in cultured cells were extracted by EpiQuik Whole Cell Extraction Kit (Epigentek, USA). Briefly, 200 μL of RIPA buffer (1 mM PMS, 1 mM NaF, 2 μg/mL of Aprotinin, 2 μg/mL of Leupetin) was added in cells. Then the cells were incubated on ice for 20 min. After performing the centrifugation of 10,000 rpm, 15 min, 4 °C, the supernatant were collected. The concentration of protein was measured using a Commassie Blue Staining Kit (Beyotime, China). Subsequently, 150 μL of lysate protein were mixed with 50 μL of 4× loading buffer and boiled for 5 min. Equal amounts of total protein were separated by 10% SDS gel (sodium dodecyl sulphate-polyacrylamide) electrophoresis and transferred onto polyvinylidene difluoride membranes (Beyotime, China). The membranes were immunoblotted respectively with following primary mouse-anti-human antibodies: caspase3 (1:1000), caspase9 (1:1000), cyclinD1 (1:500), cyclinB1 (1:500), p21 (1:600), and β-actin (1:5000). After incubation overnight at 4 °C, the antibodies were blocked with 0.5% of goat serum albumin. The horseradish peroxidase linked secondary goat-anti-mouse antibodies were applied and DAB (3,3-diaminobenzidine tetrahydrochloride) (Beijing Liuyi Biotechnology Co., Ltd., Beijing, China) was used to visualize blot. All of the antibodies were obtained from Santa Cruz, USA. The amount of total protein was semiquantified as ratio to β-actin on each gel.

Statistical Analysis

The data of this study were performed using SPSS 19.0 software (SPSS, USA). Analysis of variance was calculated by the Student's test (t-test) or One-way ANOVA for two groups or among multiple groups, respectively. The data were presented as mean ± SD. $P < 0.05$ was considered to indicate a statistically significant result. All experiments were repeated at least three times.

Results

SNHG16 Is Significantly Up-Regulated in Glioma Tissues and Cell Lines

To explore the expression pattern of SNHG16 in the glioma, qRT-PCR assay was applied to determine the level of SNHG16 in glioma tissues and cell lines. As shown in Fig. 1a, the SNHG16 expression level was significantly increased in glioma tissues compared with the normal brain tissues (Fig. 1a). Consistently, the expression level of SNHG16 was also obviously up-regulated in glioma cell lines (Fig. 1b). These data indicated that the aberrant expression of SNHG16 might be connected with the development of glioma. Among four glioma cell lines, the LN229 cells expressed the highest levels of SNHG16, which was about three times of control group. The U251 cells were showed with the lowest level of SNHG16. We next knocked down the SNHG16 expression via transfecting with si-SNHG16 for further exploration (Fig. 1c).

Knockdown of SNHG16 Suppresses the Proliferation and Promotes Apoptosis of Glioma Cells

To determine the special biological role of SNHG16 in glioma, we chose the cells with high expression of SNHG16 (LN229) and low expression of SNHG16 (U251) for the experiments. In both two cell lines, the cell proliferation was significantly suppressed with knocking down SNHG16 expression (Fig. 2a). Meanwhile, the colony formation assay showed that the number of monoclonal cells was significantly reduced after knocking down the expression of SNHG16 (Fig. 2b). Moreover, as shown in Fig. 2c and d, the flow cytometry analysis presented that the cell cycle was arrested in G1 phase when SNHG16 was knockdown and the proportion of apoptotic cells was significantly increased after silencing SNHG16. These results suggested that lncRNA SNHG16 promoted the proliferation of glioma cells through modulating its influence on cell cycle and apoptosis.

lncRNA SNHG16 Mediates Cell Proliferation Via Inhibiting p21

To further explore the effects of SNHG16 on cell cycle, CDK inhibitors (CKIs) such as p15, p16, p21, p27 were measured. We investigated the expression of kinase inhibitory proteins p15, p16, p21 and p27 using qRT-PCR. As illustrated in Fig. 3a, only the expression of p21 was significantly increased in glioma cells after knocking down SNHG16. And western blot analysis verified the result that p21 protein level was also up-

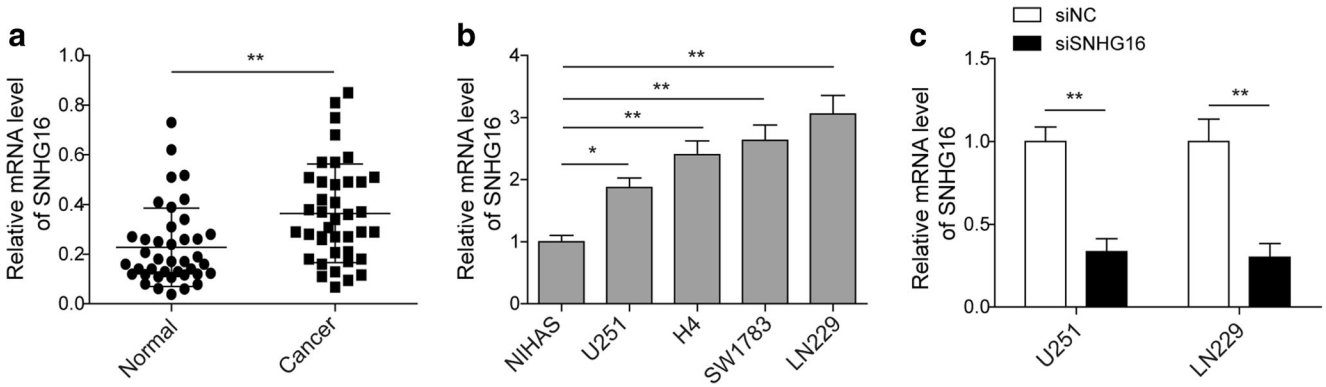


Fig. 1 The expression of lncRNA SNHG16 in glioma tissues and cell lines. a and **b**: The expression level of lncRNA SNHG16 in both glioma tissues and cell lines, compared with normal tissues and normal human astrocytes. $^{**}P < 0.01$ vs. Normal. $^{*}P < 0.05$ and $^{**}P < 0.01$ vs. NIHAS. **c** The expression of SNHG16 was detected by qRT-PCR assay. $^{**}P < 0.01$ vs. siNC

regulated (Fig. 3b). Additionally, the colony formation assay showed that the number of monoclonal cells was markedly decreased, and the cell cycle was also arrested in G1 phase after over-expression of p21 (Fig. 3c-d), which was the same

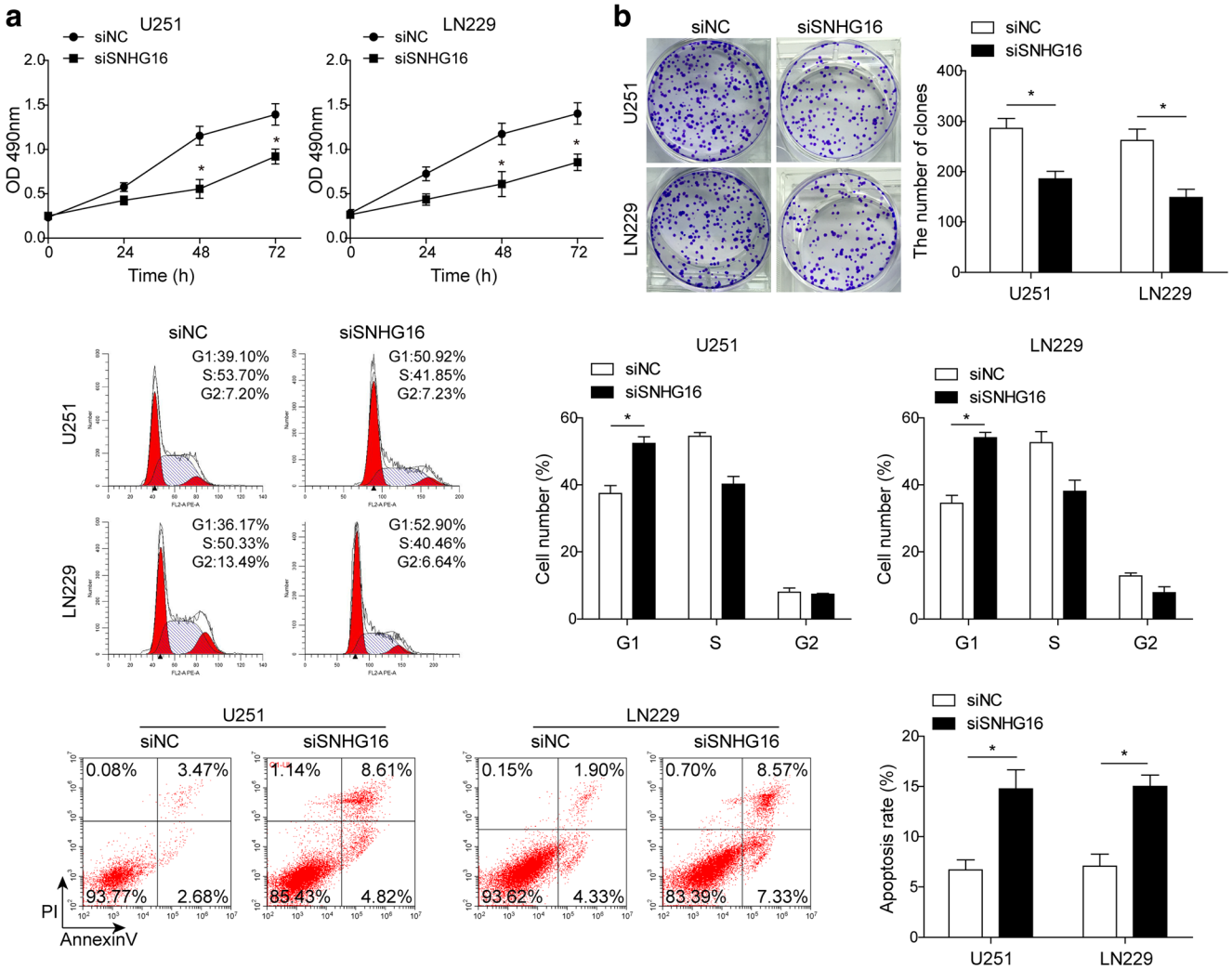


Fig. 2 Effects of knocking down lncRNA SNHG16 on cell proliferation and apoptosis. a: CCK-8 assay was performed to measure cell proliferation with knocking down lncRNA SNHG16. $^{*}P < 0.05$ vs. siNC. **b**: The monoclonal cell formation was determined under SNHG16 knockdown by colony formation. $^{*}P < 0.05$ vs. siNC. **c** and **d**: The flow cytometry assay was performed to assess the cell cycle and cell apoptosis when cells were transfected with siSNHG16. $^{*}P < 0.05$ vs. siNC

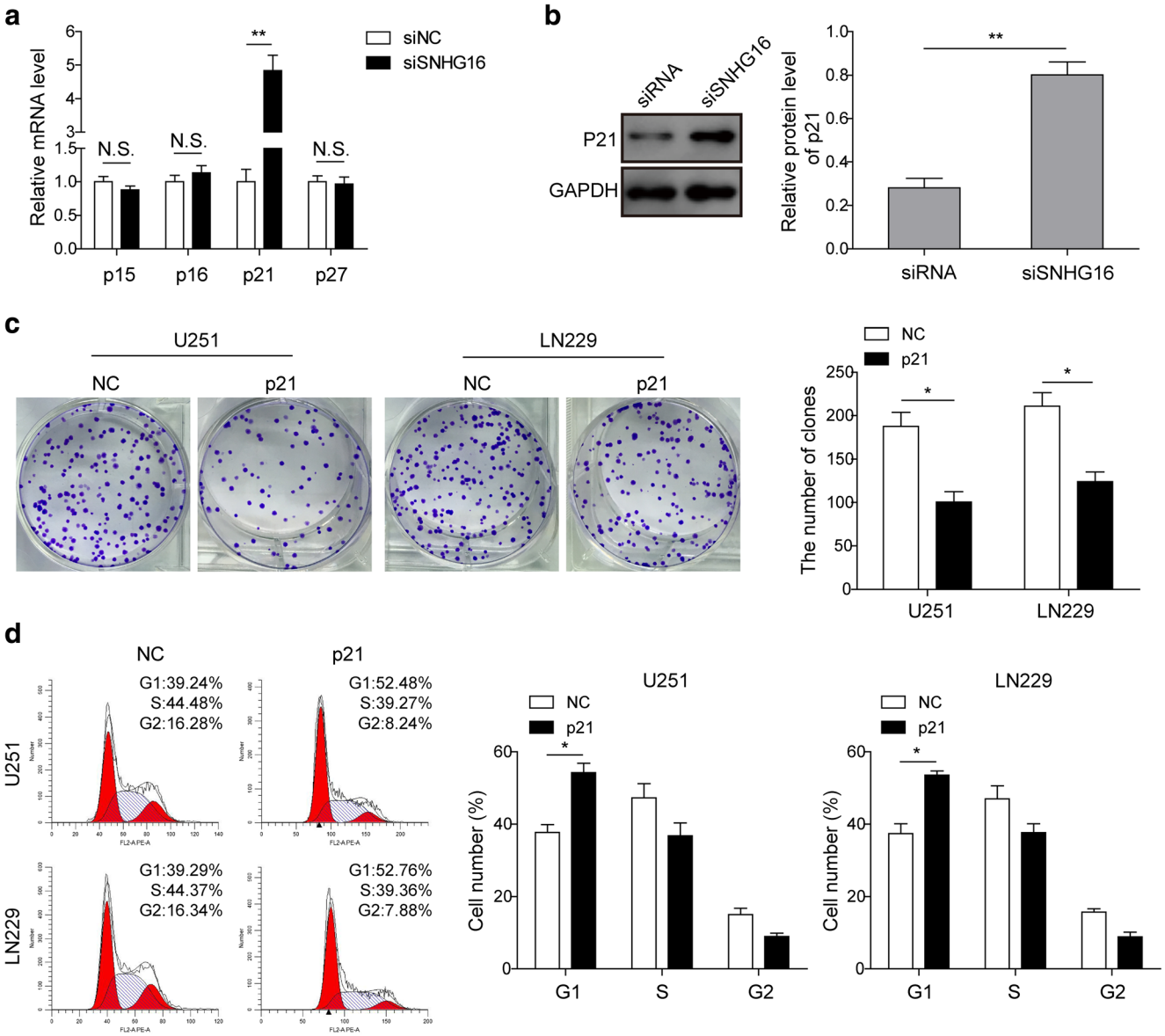
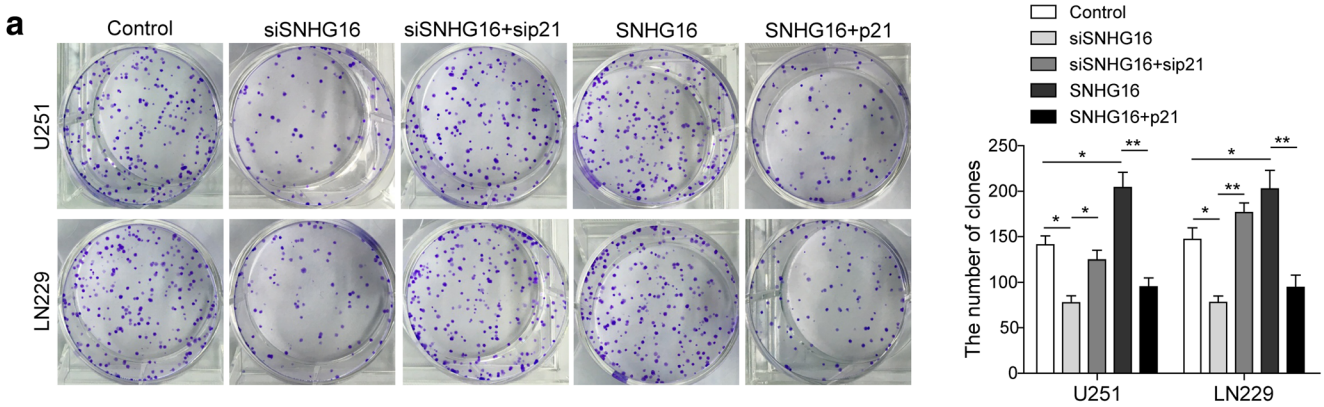


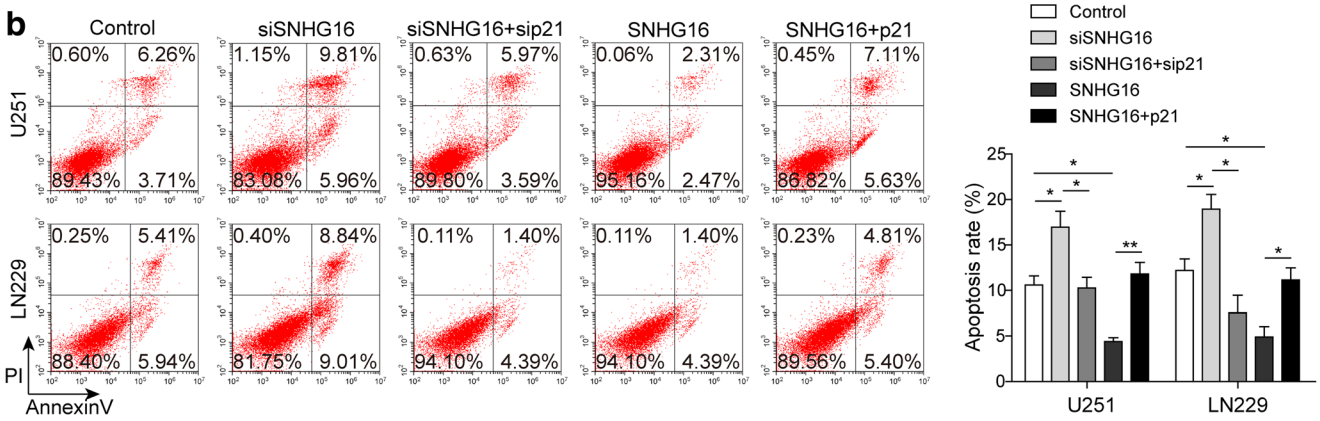
Fig. 3 lncRNA SNHG16 mediates glioma cells proliferation of via inhibiting the expression of p21. a: The expression levels of CKIs (p15, p16, p21, p27) were measured by qRT-PCR assay in response to SNHG16 knockdown. $^{**}P < 0.01$ vs. siNC. **b**: Western blot analysis was presented to measure the expression of p21 protein level after SNHG16 knockdown.$^{**}P < 0.01$ vs. siNC. **c**: Colony formation to assess the number of monoclonal cells in response to p21 over-expression. $^{*}P < 0.05$ vs. NC. **d**: Flow cytometry was performed to test the cell cycle within p21 over-expression $^{*}P < 0.05$ vs. NC

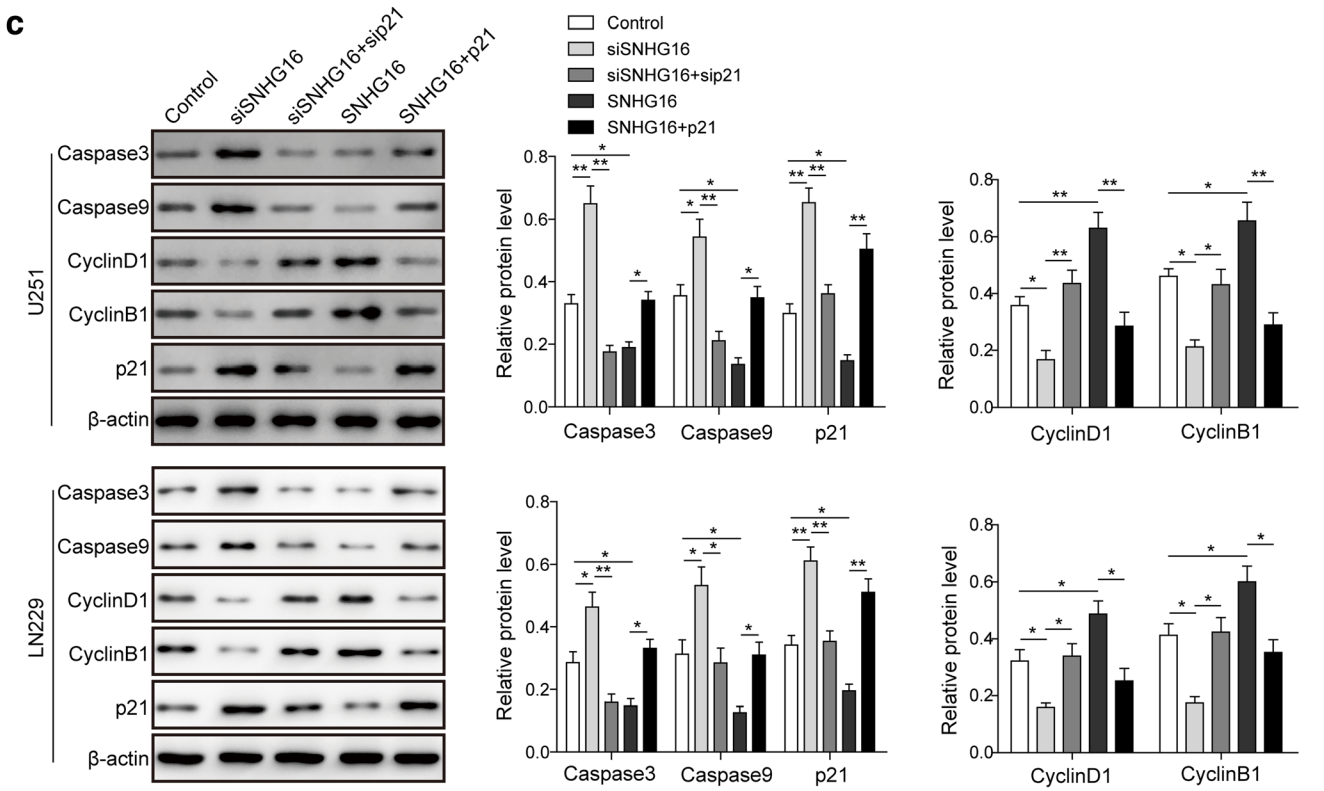
as the phenomenon of SNHG16 knockdown. These data demonstrated that SNHG16 might mediate the proliferation of glioma cells via suppressing the expression of p21.

p21 Is Involved in lncRNA SNHG16-Mediated Cell Proliferation and Apoptosis of Glioma Cells

Next, we further confirmed whether p21 was involved in lncRNA SNHG16-mediated glioma progression. As shown in Fig. 4a, colony formation assay showed the cell proliferation was inhibited with SNHG16 knockdown, but partly rescued by silencing p21; and the number of monoclonal clones increased with SNHG16 over-expression, while this effect was reversed by p21 over-expression (Fig. 4a). Similarly, the proportion of apoptosis was increased after knocking down SNHG16, and significantly reduced when p21 was knocked down; on the contrary, the proportion of apoptosis was reduced after over-expression of SNHG16 but increased when p21 was over-expressed (Fig. 4b). For the signaling pathway of apoptosis, knockdown of SNHG16 caused the up-regulation of p21 and apoptosis-related proteins caspase 3, 9 and the down-regulation of cyclinD1, cyclinB1; whereas this effect was rescued by suppressing p21 expression, which showed that the expression of caspase3, 9 was down-


a
Control
siSNHG16
siSNHG16+sip21
SNHG16
SNHG16+p21
U251
LN229
The number of clones
U251
LN229


b
Control
siSNHG16
siSNHG16+sip21
SNHG16
SNHG16+p21
U251
LN229
PI
AnnexinV
0.60% 6.26% 89.43% 3.71%
1.15% 9.81% 83.08% 5.96%
0.63% 5.97% 89.80% 3.59%
0.06% 2.31% 95.16% 2.47%
0.45% 7.11% 86.82% 5.63%
0.25% 5.41% 88.40% 5.94%
0.40% 8.84% 81.75% 9.01%
0.11% 1.40% 94.10% 4.39%
0.11% 1.40% 94.10% 4.39%
0.23% 4.81% 89.56% 5.40%
Apoptosis rate (%)
U251
LN229


c
Control
siSNHG16
siSNHG16+sip21
SNHG16
SNHG16+p21
Caspase3
Caspase9
CyclinD1
CyclinB1
p21
β-actin
U251
LN229
Relative protein level
Caspase3
Caspase9
p21
CyclinD1
CyclinB1

◀ **Fig. 4 p21 mediates the function of lncRNA SNHG16 in glioma.** lncRNA SNHG16 knocked down or over-expressed U251 and LN229 cells were transfected with si-p21 or p21 vector. **a**: The ability of cell proliferation was measured by colony formation. $*P < 0.05$ vs. Control. $*P < 0.05$ and $**P < 0.01$ vs. siSNHG16. $**P < 0.01$ vs. SNHG16. **b**: The cell apoptosis was using the flow cytometry analysis. **c**: The expression of p21, apoptosis-related proteins and cell cycle-related proteins were analyzed by western blot assay. $*P < 0.05$ and $**P < 0.01$ vs. Control. $*P < 0.05$ and $**P < 0.01$ vs. siSNHG16. $*P < 0.05$ and $**P < 0.01$ vs. SNHG16

regulated, and the expression of cyclin D1 and cyclin B1 was up-regulated. Consistently, SNHG16 over-expression inhibited the expression of p21, caspase 3 and 9 and promoted the expression of cyclinD1 and cyclinB1. Nevertheless, p21 up-regulation could reverse the effect of SNHG16 over-expression (Fig. 4c). Taken together, we could deduce that SNHG16 modulated the proliferation of glioma cells by negatively regulating the expression of p21.

Discussion

The incidence and characteristics of glioma (high incidence, easy to relapse), indicating that the current treatment effect is not optimistic, thus the diagnosis and treatment of glioma is a thorny problem needed to be solved [20, 21].

Glioma is the most common primary intracranial tumor in central nervous system (CNS) and associated with a high morbidity rate and recurrence. Most patients with glioma have a poor prognosis, the 5-year survival rate is less than 10% and the median survival period is only 14 months [5]. Currently, radiotherapy, chemotherapy and surgical resection are the standard therapeutic strategies for clinical glioma treatment, however, the outcomes are unsatisfactory [22]. Althought themozolomide (TMZ) has been proposed as a standard chemotherapy, the drug resistance of glioma cells to TZM as well as the blood-brain barrier greatly limit the therapeutic effect of TZM [23, 24]. Therefore, exploring new therapeutic markers and better understanding of the pathway related to cancer initiation and progression is warranted to improve the prognosis of patients with glioma.

Long non-coding RNAs (lncRNAs) are a novel class of non-protein-coding transcripts that have been proved to be key players in human carcinogenesis [25–27]. lncRNAs have been found to be correlated with a diverse range of functions in cell biology [28, 29], and altered lncRNAs expression patterns have been associated with carcinoma. For example, lncRNA DANCR expression was increased in colorectal cancer and tumors with high lncRNA DANCR expression was correlated with TNM stage, histologic grade and lymph node metastasis [30]. A growing number of recent papers have demonstrated that lncRNAs expressions were correlated with biogenesis, development and differentiation of human gliomas [31, 32] . Further studies revealed that lncRNA SNHG16 was highly expressed in glioma tissues and cell lines and participated in glioma pathogenesis [15]. Small nucleolar RNA host gene 16 (SNHG16), a newly identified potential oncogene, has been reported involved in various biological activities, such as cell proliferation, invasion, and migration. Previous studies found that SNHG16 was correlated with the malignancy and poor prognosis of glioma patients, and SNHG16-miR-4518-PRMT5 pathway regulatory axis affects the glioma pathogenesis [15]. However, the certain mechanism remains unknown.

In the present study, we demonstrated that high expression level of SNHG16 was observed in both glioma tissues and cell lines. Functionally, we also found that knockdown of SNHG16 suppressed cell proliferation, cell cycle arrest and promoted cell apoptosis. Mechanistically, p21 acted as a downstream gene of lncRNA SNHG16, which was negatively regulated by lncRNA SNHG16, indicating that p21 was involved in lncRNA SNHG16-mediated cell proliferation, cell cycle and apoptosis. In summary, lncRNA SNHG16 exerts oncogenic function in modulating the development and progression of glioma via p21, providing a novel therapeutic target for the treatment of glioma.

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Compliance with Ethical Standards

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Conflict of Interest The authors declares that they have no conflict of interest.

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