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Long non-coding RNA SUMO1P3 promotes glioma progression *via* the Wnt/β-catenin pathway

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Abstract. – OBJECTIVE: Long non-coding RNA SUMO1P3 has been reported to act as an oncogene in the tumorigenesis of several types of human malignancy. However, to the best of our knowledge, the exact biological functions and potential mechanism of lncRNA SUMO1P3 in glioma remains unknown. Therefore, the aim of this study was to investigate the potential role of SUMO1P3 in glioma and to explore the underlying mechanism.

PATIENTS AND METHODS: The present study examined SUMO1P3 expression in glioma tissues and cell lines using reverse transcription-quantitative polymerase chain reaction. Cell Counting Kit-8 (CCK-8) and transwell assays were used to examine the effects of SUMO1P3 on the proliferation and invasion of glioma cells, respectively. Furthermore, Western blot was used to detect the expression levels of proteins in the epithelial-mesenchymal transition (EMT) process.

RESULTS: The expression level of SUMO1P3 was higher in glioma tissues compared with corresponding adjacent normal tissues. In addition, a high expression level of SUMO1P3 was significantly associated with clinical progression and poor survival for patients with glioma. Furthermore, the knockdown of SUMO1P3 inhibited the proliferation, migration and invasion of U87 and U251 cells. In addition, the knockdown of SUMO1P3 inhibits glioma growth *in vivo*. Finally, the knockdown of SUMO1P3 inhibited the epithelial-mesenchymal transition and reduced the expression levels of active β-catenin, C-myc, and cyclin D1 in U87 and U251 cells. By contrast, the overexpression of SUMO1P3 promoted glioma cell proliferation, migration, and invasion.

CONCLUSIONS: SUMO1P3 promotes glioma cell proliferation, migration, and invasion, and may be involved in Wnt/β-catenin signaling.

Key Words:
SUMO1P3, Glioma, Proliferation, Invasion, Wnt/β-catenin pathway.

Introduction

Glioma, arising from astrocytes or astroglial precursors, is the most common and aggressive type of malignancy in the central nervous system[1]. An increasing number of studies have been performed with the aim to elucidate the etiology and mechanism of glioma. Additionally, the comprehensive treatment strategies for glioma, including surgery, chemotherapy, radiotherapy, and targeted therapy, have improved over the past few decades[2,3]. However, patients with glioma remain to have a poor prognosis with an overall survival time of 12-15 months, which can be attributed to the invasiveness of glioma and the high rate of relapse following surgery[4,5]. Therefore, there is a requirement to improve understanding regarding the mechanisms underlying glioma initiation and progression, and to establish precise diagnostic and therapeutic targets for the optimized management of glioma.

Long non-coding RNAs (lncRNAs) serve crucial regulatory roles in a large number of physiological and pathological processes, including the development of cancer[6-8]. LncRNAs function via different mechanisms, including regulation of gene transcription, post-transcriptional regulation, and epigenetic regulations[9,10]. Pseudogenes, including small ubiquitin-like modifier 1 pseudogene 3 (SUMO1P3), constitute a separate class of lncRNAs and serve key roles in the initiation and progression of human cancer.

SUMO1P3 (NR_002190.1) was originally reported as an important novel diagnostic biomarker and therapeutic target for gastric cancer[11]. Subsequently, it was revealed that the expression level of SUMO1P3 is significantly higher in blad-

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der cancer tissues, and SUMO1P3 promotes bladder cancer growth and metastasis[12]. In addition, SUMO1P3 can facilitate the progression of breast cancer[13], colon cancer[14], pancreatic cancer[15], and hepatocellular carcinoma[16]. However, to the best of our knowledge, the relative expression, function, and molecular mechanism of SUMO1P3 in glioma remain unknown.

The present investigation reported that SUMO1P3 expression was higher in glioma tissues and cell lines. The increased expression level of SUMO1P3 was positively associated with tumor size and advanced tumor stage, and it negatively associated with the prognosis of patients with glioma. In addition, SUMO1P3 knockdown inhibited the proliferation, migration and invasion of glioma cells, and suppressed the Wnt/β-catenin pathway. By contrast, SUMO1P3 overexpression promoted glioma cell proliferation, migration, and invasion. In summary, the current results revealed the oncogenic functions of SUMO1P3 in glioma, which suggests it may serve as a promising prognostic marker and therapeutic target for patients with glioma.

Patients and Methods

Clinical Samples

A total of 66 pairs of glioma tissue samples and paired normal tissue samples were obtained from the Department of Neurosurgery, The First Affiliated Hospital of Gannan Medical University (Ganzhou, China) between 2006 and 2010. All patients were pathologically confirmed to have glioma and had not received preoperative chemotherapy or radiation. The tissue samples were collected during surgery and stored in liquid nitrogen. The current study was performed with approval from the Ethics and Research Committees of the First Affiliated Hospital of Gannan Medical University (Ganzhou, China). Written informed consent was obtained from all patients involved in the research. The clinical characteristics of all patients are summarized in Table I.

Reverse Transcription-Quantitative Polymerase Chain Reaction (RT-qPCR)

According to the manufacturer's protocol, TRIzol (Invitrogen; Thermo Fisher Scientific, Inc., Waltham, MA, USA) was used to isolate RNA from tissues or cells. The isolated RNA was then reverse transcribed using the PrimeScript RT Reagent kit (Invitrogen; Thermo Fisher Scientific, Inc., Waltham, MA, USA), and qPCR was performed using SYBR Premix Ex Taq (Takara Biotechnology Co., Ltd., Dalian, China). GAPDH was used as internal control. RT-qPCR was performed using the ABI PRISM 7500 PCR system (Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, MA, USA). The primer sequences for SUMO1P3 and GAPDH are presented in Table II. The median expression level was used as the cut-off value to divide patients with glioma into high and low SUMO1P3 expression groups.

Cell Culture

Human glioma cell lines (SHG-44, U-118MG, and U251), a glioblastoma cell line of unknown origin (U87), and a human astroglial cell line (HA) was purchased from the American Type

Table I. Association of LINC00675 with clinicopathological characteristics of ESCC patients.

Clinicopathological parameters	N²	SUMO1P3 expression		χ^2	*p*-value
		H	L		
All	66	33	33		
Age (years)				0.149	0.773
<40	23	13	10		
≥ 40	43	20	23		
Sex				0.186	0.811
Male	40	21	19		
Female	26	12	14		
Tumor size				4.863	**0.037**
< 4 cm	28	11	17		
≥ 4 cm	38	22	16		
TNM stage				6.133	**0.021**
I-II	15	1	14		
III	51	32	19		

Table II. Real Time-PCR primers.

Gene	Forward primer	Reverse primer
SUMO1P3	ACTGGGAATGGAGGAAGA	TGAGAAAGGATTGAGGGAAAAG
GAPDH	CGCTCTCTGCTCCTCCTGTTC	ATCCGTTGACTCCGACCTTCAC

Culture Collection (ATCC, Manassas, VA, USA). All cell lines were cultured in Dulbecco's modified Eagle's medium (DMEM; Gibco; Grand Island, NY, USA) supplemented with 10% fetal bovine serum (FBS; Gibco, Grand Island, NY, USA), and 50 U/ml penicillin and 0.1 mg/ml streptomycin. All cells were incubated at 37˚C and 5% CO_2.

SUMO1P3 Short Hairpin RNA (shRNA) and Plasmid Transfection

SUMO1P3 shRNA (sh-SUMO1P3) and SUMO1P3 overexpression plasmid were obtained from Shanghai GenePharma Co., Ltd. (Shanghai, China). Lipofectamine 3000 kit (Invitrogen, Thermo Fisher Scientific, Inc., Waltham, MA, USA) was used to perform the transfections, according to the manufacturer's protocol. RT-qPCR was used to evaluate the knockdown efficiency.

Cell Counting Kit-8 Assay

Cell proliferation was examined every 24 h, according to the manufacturer's protocol. Cells were plated in 96-well plates at a density of ~3,000 cells/well. Subsequently, 10 µl CCK8 (Dojindo Molecular Technologies, Kumamoto, Japan) was added, and the cells were incubated for 2 h. Finally, the absorbance at 450 nm was determined.

Wound-Healing Assay

Cells transfected with sh-SUMO1P3 or sh-NC were cultured in 6-well plates (Sigma-Aldrich, St. Louis, MO, USA) until a confluency of 95% was reached. The cell layer was then scratched using a 10 µl pipette tip, gently washed with PBS, and cultured in fresh serum-free DMEM for 24 h. Finally, a microscope was used to observe and analyze the migrated distance.

Cell Invasion Assay

Cell invasion ability was determined using BD 24-well transwell chambers (Costar; Corning Inc., Corning, NY, USA) pre-coated with Matrigel, according to the manufacturer's protocol. Firstly, 1×10^5 cells suspended in 200 µl serum-free medium were seeded in the upper chamber, and 800 µl DMEM supplemented with 10% FBS was placed in the lower chamber. Following incubation for 18 h, cells on the lower chamber membrane were fixed with 4% formaldehyde and stained with 1% crystal violet. Finally, cells in five random fields of the membrane were counted by microscopy.

In Vivo Tumor Xenografts Experiments

4-week-old BALB/c nude mice were purchased from SLAC Laboratories Animal, Shanghai, China. Cells (1×10^7 cells/ml) stably transfected with sh-NC or sh- SUMO1P3 were harvested and re-suspended in serum-free medium and subcutaneously injected in the right flank of mice. Three to four weeks later, the mice were sacrificed, and the tumors were dissected, photographed, and weighed. Treatments of the animal were performed on the basis of the Guide for the Care and Use of Laboratory Animals.

Western Blot Analysis

RIPA buffer (Beyotime Institute of Biotechnology, Haimen, China) was used to extract proteins from the cells. The proteins were then subjected to 10% SDS-PAGE and electrophoretically transferred to polyvinylidene difluoride membranes (Bio-Rad Laboratories, Inc., Hercules, CA, USA). Following blocking with 5% non-fat milk, the membranes were incubated with primary antibodies. Finally, electrochemiluminescence kit (Santa Cruz Biotechnology, Santa Cruz, CA, USA) was used to detect the immunoblots, which were visualized following X-ray film exposure.

Statistical Analysis

Experimental data from a minimum of three independent experiments are presented as the mean ± standard deviation. SPSS 18.0 software (SPSS, Inc., Chicago, IL. USA) was used to perform statistical analysis. The associations between SUMO1P3 expression level and clinicopathological factors were assessed by χ^2-tests. Differences between groups were evaluated by Student's *t*-test

for continuous variables and χ^2-test for categorical variables. $p<0.05$ was considered to indicate a statistically significant difference.

Results

SUMO1P3 Expression Level is Higher in Glioma Tissues and Cell Lines

The RT-qPCR analysis was performed to measure the relative expression of SUMO1P3 in 66 pairs of glioma tissue and adjacent normal tissue. The results revealed that SUMO1P3 expression was significantly higher in glioma tissues compared with corresponding adjacent normal tissues (Figure 1A). The SUMO1P3 expression level was further analyzed in four human glioma cell lines and the human astroglial cell line HA. It was identified that the expression level of SUMO1P3 was higher in glioma cell lines compared with the HA cell line (Figure 1B).

A High Expression Level of SUMO1P3 is Associated With Disease Progression and Poor Prognosis for Patients With Glioma

The associations between SUMO1P3 expression level and clinicopathological factors of 66 patients with glioma were investigated (Table I). This revealed that a high expression level of SUMO1P3 was associated with tumor size and clinical stage; however, no significant associations were identified between SUMO1P3 expression level, and age and sex. In addition, Kaplan-Meier survival curves indicated that patients with a high SUMO1P3 expression level had significantly poorer survival rates compared with patients with a low expression level of SUMO1P3 (Figure 1C).

SUMO1P3 Knockdown Inhibits Glioma Cell Proliferation, Migration, and Invasion

The SUMO1P3 expression level was significantly lower in cells transfected with the specific

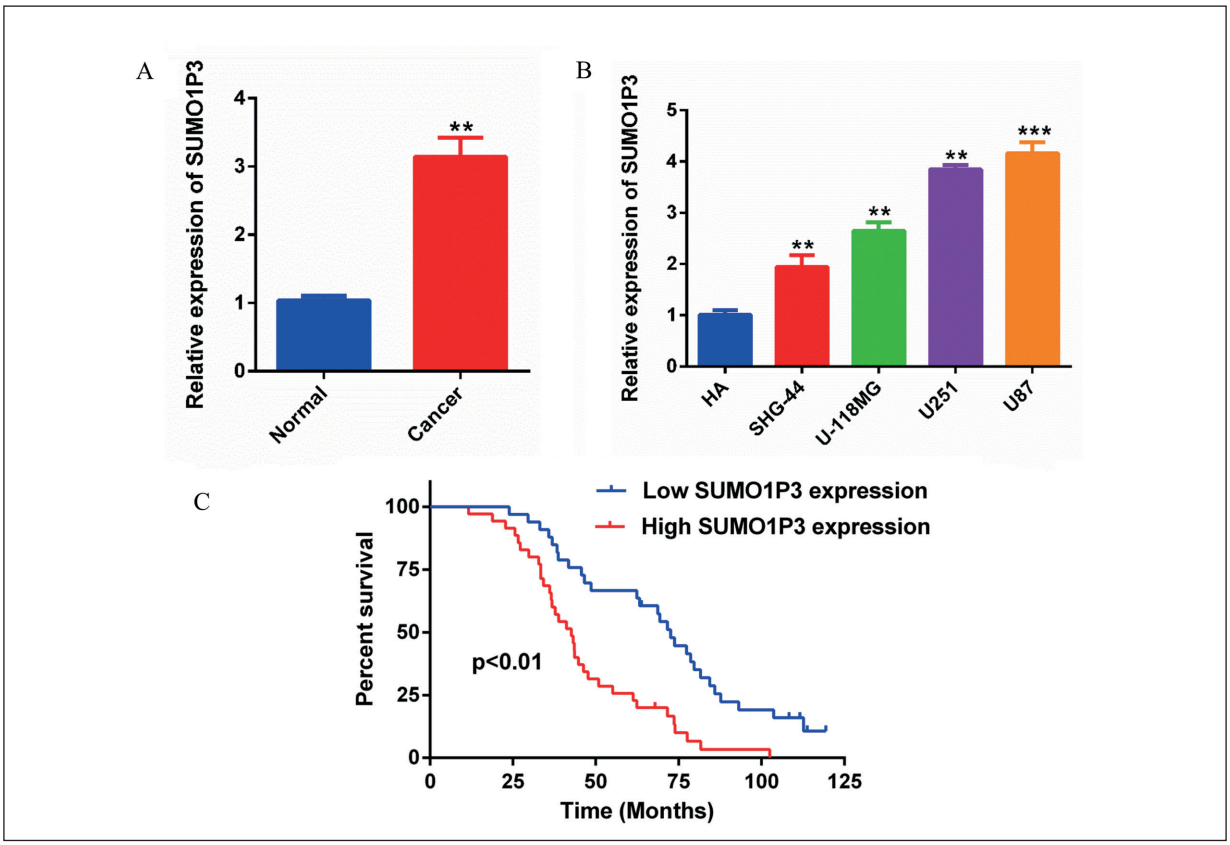

Figure 1. Expression pattern of SUMO1P3 in glioma and its clinical significance. **A,** Relative expression levels of SUMO1P3 in 66 pairs of glioma tissue and adjacent non-tumor tissues were measured by reverse transcription-quantitative polymerase chain reaction. $^{***}p<0.001$. **B,** Relative expression levels of SUMO1P3 in glioma cell lines. $^{*}p<0.05$, $^{**}p<0.01$. **C,** Kaplan-Meier survival curves for patients with glioma with high and low expression levels of SUMO1P3.

SUMO1P3 shRNA compared with cells transfected with the negative control (Figure 2A and B). In addition, SUMO1P3 knockdown markedly suppressed the proliferation ability of U87 (Figure 2C) and U251 cells (Figure 2D). Wound-healing assays demonstrated that SUMO1P3 silencing significantly impaired the migration ability of U87 (Figure 2E) and U251 cells (Figure 2F). Additionally, cell invasion assays indicated that knockdown of SUMO1P3 significantly suppressed the cell invasion ability of U87 and U251 cells (Figure 2G).

Overexpression of SUMO1P3 Enhances Glioma Cell Proliferation, Migration, and Invasion

The expression level of SUMO1P3 was markedly higher in cells transfected with the specific SUMO1P3 overexpression plasmid compared with cells transfected with the negative control (Figure 3A and B). SUMO1P3 overexpression significantly enhanced the proliferative ability of U87 (Figure 3C) and U251 cells (Figure 3D). Wound-healing assays demonstrated that SUMO1P3 overexpression markedly promoted the migration ability of U87 (Figure 3E) and U251 cells (Figure 3F). In addition, cell invasion assays indicated that SUMO1P3 overexpression significantly enhanced the invasion ability of U87 and U251 cells (Figure 3G).

SUMO1P3 Knockdown Suppresses Glioma Growth In Vivo

To assess the effect of SUMO1P3 on glioma growth *in vivo*, U87 cells stable transferred with sh-NC or sh-SUMO1P3 were injected into nude mice, and the tumor growth was measured. Our results suggested that tumor growth was slower in sh- SUMO1P3 compared with sh-NC group (Figure 4A). Moreover, the tumor size and weight were obviously reduced in sh- SUMO1P3 group compared with sh-NC group (Figure 4B and 4C). We also determined the expression of SUMO1P3 in xenograft tumor and found that SUMO1P3 knockdown leads to a decrease of SUMO1P3 expression (Figure 4D) in xenograft tumor.

SUMO1P3 Knockdown Suppresses the Wnt/Đ-catenin Pathway in Glioma Cells

A number of studies have confirmed that the Wnt/β-catenin pathway is constitutively active in numerous types of human malignancy, including glioma. To further investigate whether SUMO1P3 regulates glioma development via Wnt/β-catenin pathway activation, western blot assays were used to evaluate the relative expression levels of associated genes in glioma cells. As demonstrated in Figure 5, knockdown of SUMO1P3 significantly increased E-Cadherin expression but markedly reduced the expression levels of N-cadherin, β-catenin, Vimentin, Slug, Snail, C-myc, and cyclin D1. These results indicate that SUMO1P3 may be involved in the Wnt/β-catenin pathway in human glioma cells.

Discussion

LncRNA SUMO1P3, an important member of the SUMO pseudogene family, was originally identified to be upregulated in gastric cancer[11]. Subsequently, certain studies revealed that SUMO1P3 expression was high in bladder, colon and breast cancer, and this high expression level of SUMO1P3 was revealed to be associated with disease progression and poor prognosis. Furthermore, SUMO1P3 has been revealed to promote the growth, invasion, and metastasis of different cancer types[12-14]. Zhou et al[16] reported that SUMO1P3 enhanced tumor growth and invasion and repressed radiosensitivity in hepatocellular carcinoma. These previous studies indicate that SUMO1P3 serves oncogenic roles in human cancer; however, to the best of our knowledge, the function of SUMO1P3 in glioma remains unclear.

The present investigation identified that SUMO1P3 expression was significantly higher in glioma tissues and cell lines, and this high expression of SUMO1P3 in glioma tissues was positively associated with the progression of glioma and a poor prognosis for patients. It was then revealed that SUMO1P3 knockdown repressed cell proliferation, migration, and invasion of glioma cells. By contrast, SUMO1P3 overexpression promoted glioma cell proliferation, migration, and invasion. These results were consistent with the previously published data. Finally, we demonstrated that SUMO1P3 knockdown inhibited the epithelial-mesenchymal transition (EMT) and the Wnt/β-catenin signaling pathway in glioma.

EMT is an important pathological process in the initiation and development of numerous types of human malignancy, including glioma[17,18]. During this pathological process, cell-cell adhesion and cell polarity are reduced in cancer cells, and mesenchymal characteristics, including

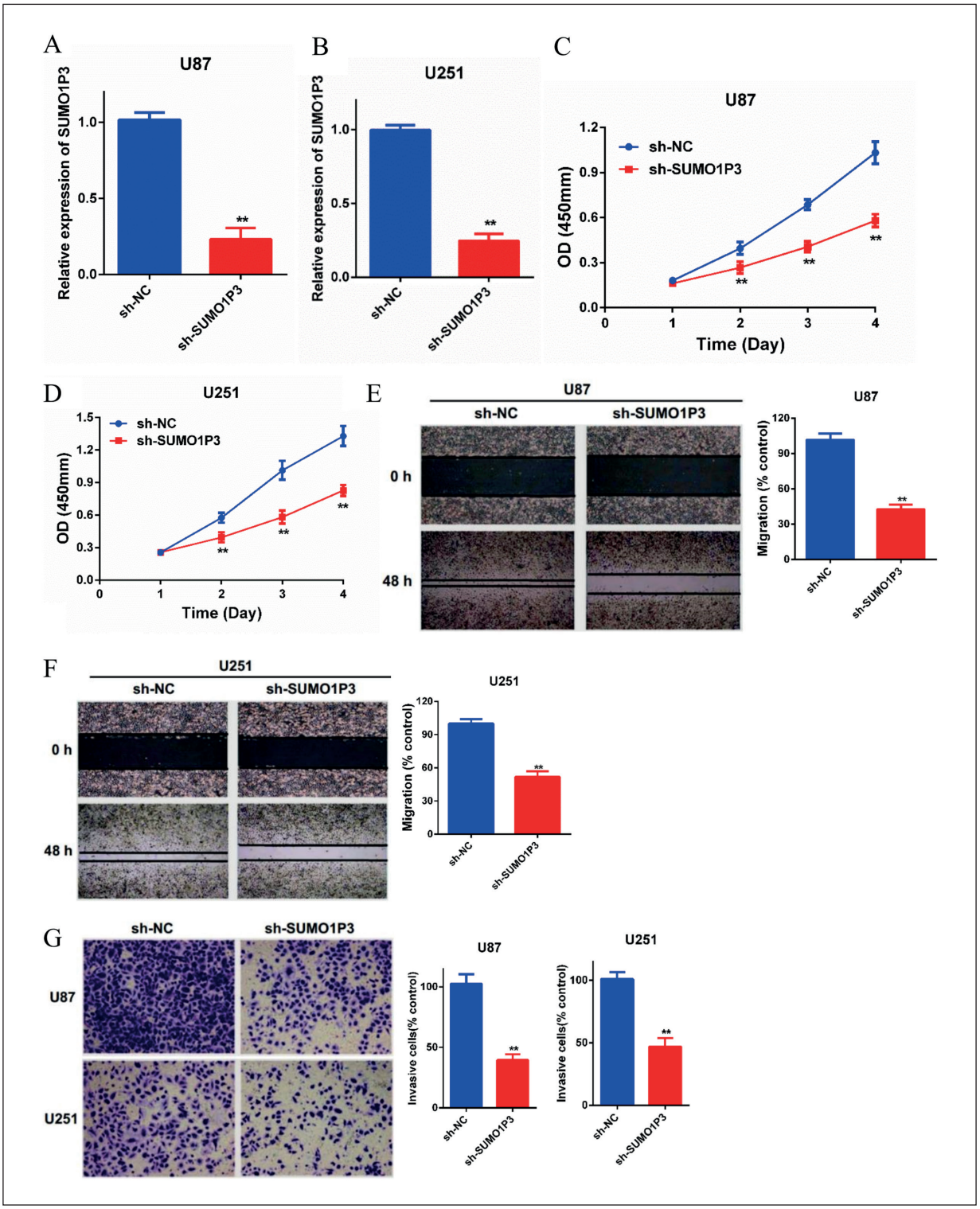

Figure 2. SUMO1P3 silencing inhibits proliferation, migration and invasion of glioma cells. **A,** The inhibitory efficiency of sh-SUMO1P3 on SUMO1P3 expression level in U87 cells was evaluated by RT-qPCR analysis. $^{**}p < 0.01$. **B,** The inhibitory efficiency of sh-SUMO1P3 on SUMO1P3 expression in U251 cells was evaluated by RT-qPCR analysis. $^{**}p < 0.01$. **C,** A CCK-8 assay was used to determine the proliferation ability of U87 cells. (D) A CCK-8 assay was used to determine the proliferation ability of U251 cells. **E,** Wound-healing assays were used to determine the migration ability of U87 cells (magnification: 40×). **F,** Wound-healing assays were used to determine the migration ability of U251 cells (magnification: 40×). **G,** Cell invasion assays were used to determine the invasive abilities of U87 and U251 cells (magnification: 40×).

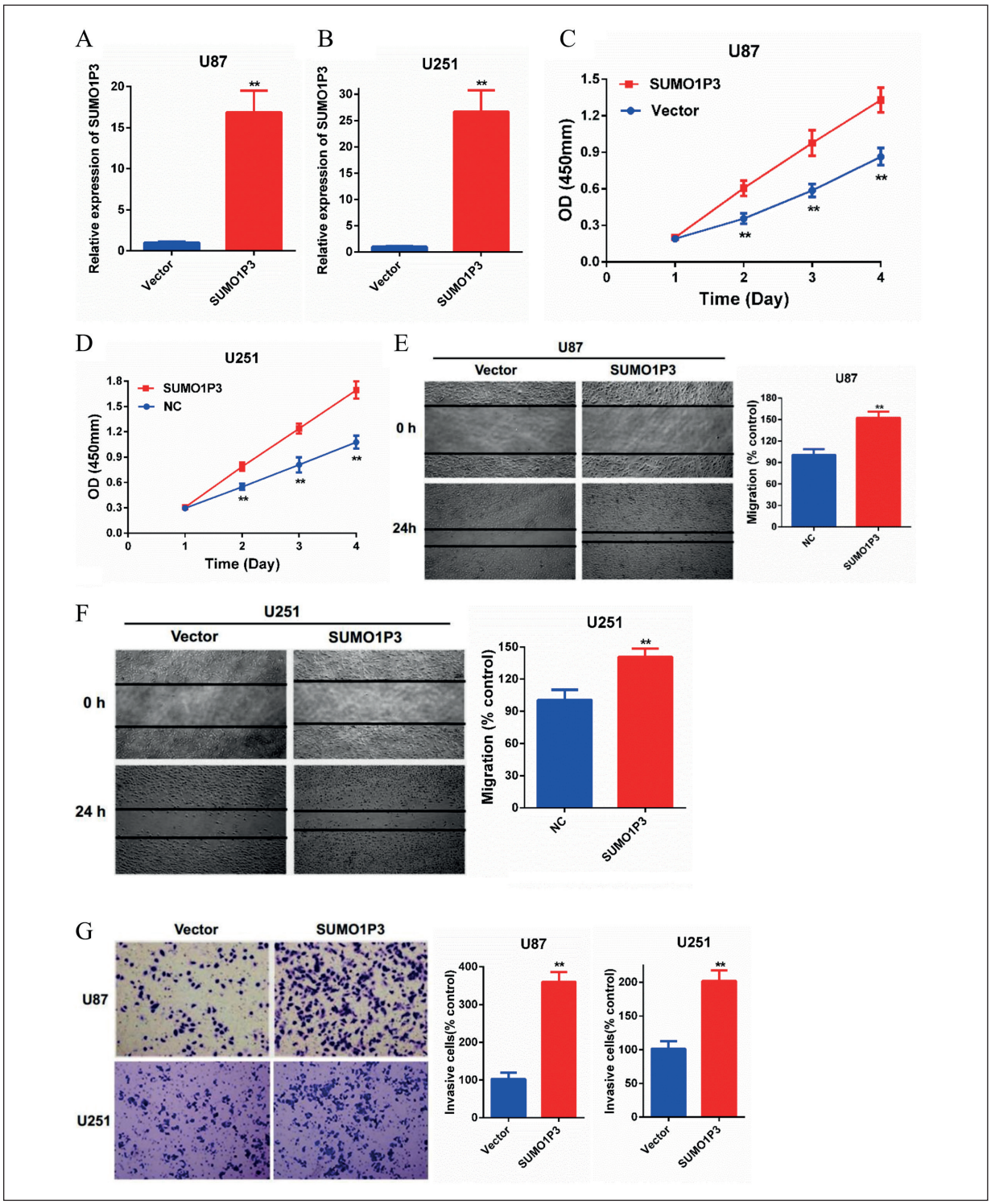

Figure 3. SUMO1P3 overexpression promotes proliferation, migration and invasion of glioma cells. **A,** The expression level of SUMO1P3 was significantly higher in U87 cells transfected with SUMO1P3 plasmid compared with cells transfected with the empty vector. $^{**}p < 0.01$. **B,** The expression level of SUMO1P3 was significantly higher in U251 cells transfected with SUMO1P3 plasmid compared with cells transfected with the empty vector. $^{**}p < 0.01$. **C,** A CCK-8 assay was used to determine the proliferation ability of U87 cells. **D,** A CCK-8 assay was used to determine the proliferation ability of U251 cells. **E,** Wound-healing assays were used to determine the migration ability of U87 cells (magnification: 40×). **F,** Wound-healing assays were used to determine the migration ability of U251 cells (magnification: 40×). **G,** Cell invasion assays were used to determine the invasive abilities of U87 and U251 cells (magnification: 40×).

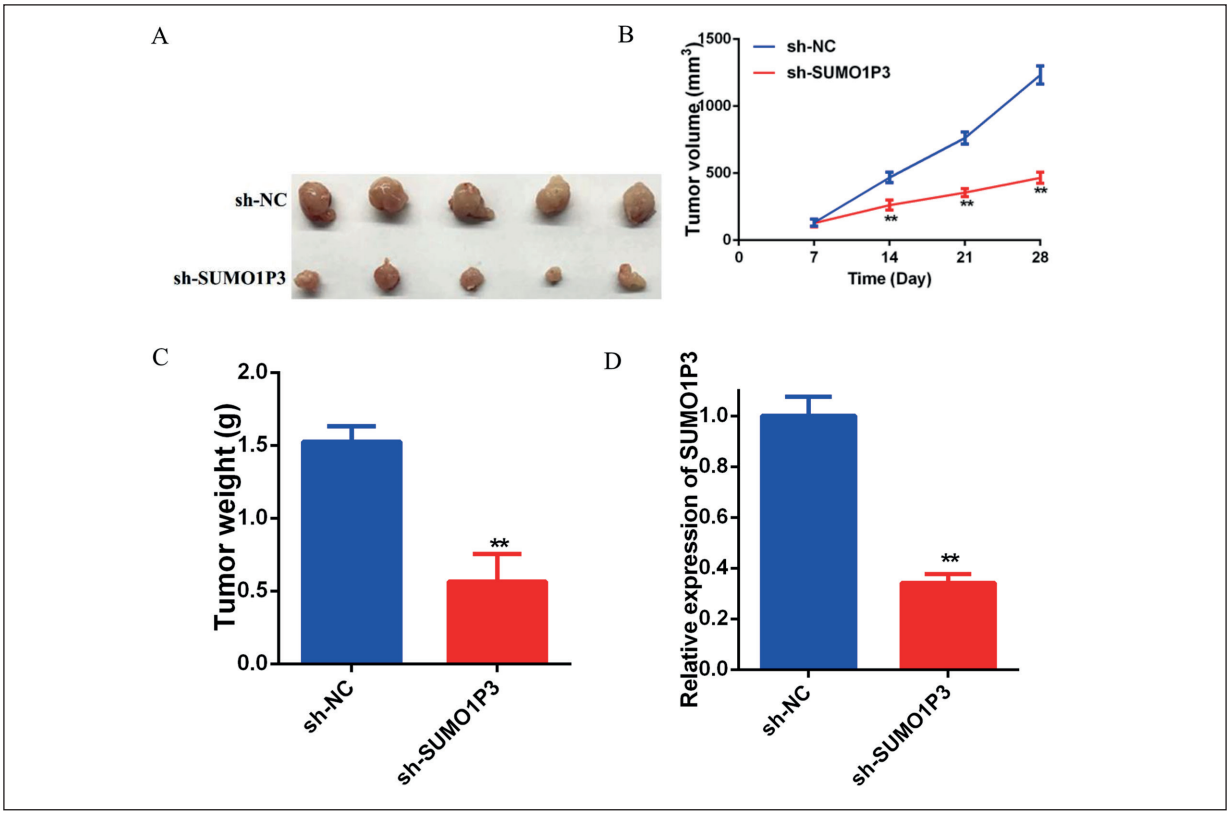

Figure 4. SUMO1P3 promotes growth of glioma cells *in vivo*. **A,** Tumors collected from nude mice were excised. **B,** The tumor volumes were calculated every week after injection. **C,** The tumor weight of nude mice was suppressed in SUMO1P3 shRNA group compared with the negative group. **D,** Expression levels of SUMO1P3 in tumors. $^{**}p < 0.01$.

motility, invasiveness, and drug resistance are enhanced[19,20]. E-cadherin has widely been accepted as a canonical epithelial marker and a crucial inhibitor of the motility and invasion of cancer cells[21]. In addition, N-cadherin can enhance the invasion and metastasis of numerous types

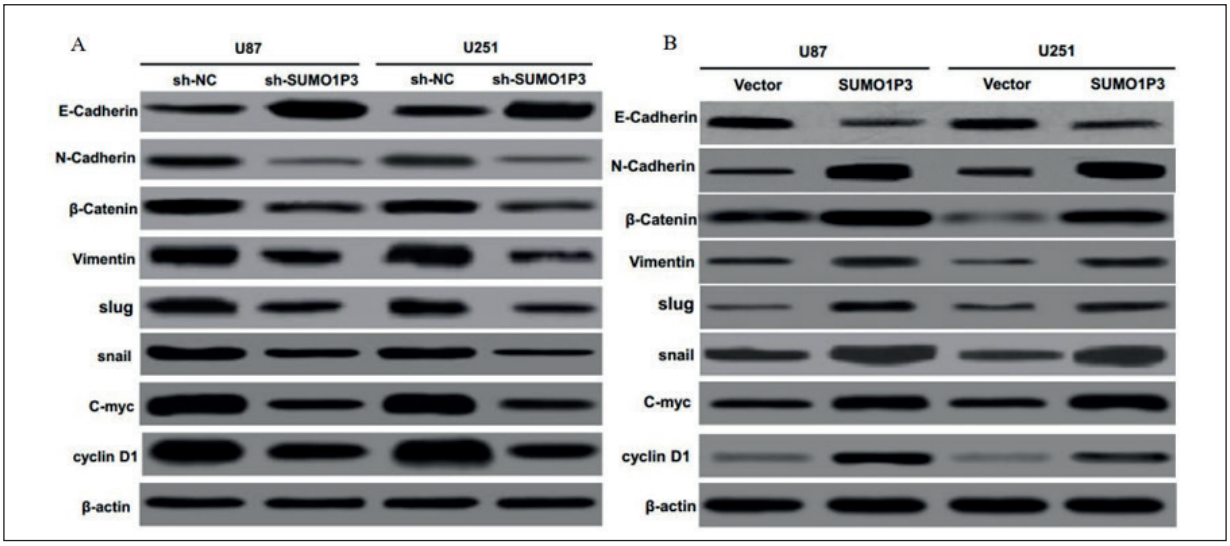

Figure 5. Influence of SUMO1P3 knockdown on the expression levels of proteins associated with the epithelial-mesenchymal transition and the Wnt/β-catenin signaling pathway.

of human malignancy[22]. Furthermore, vimentin, β-catenin, slug, and snail are widely accepted indicators for EMT[15]. The current data demonstrated that knockdown of SUMO1P3 increased the expression level of E-cadherin and reduced the expression levels of N-Cadherin Vimentin, β-catenin, slug, and snail, which suggests that SUMO1P3 promotes the EMT process in the development of glioma.

Considering its substantial effect on the EMT, drug resistance and the maintenance of cancer stem cells during glioma development, the Wnt/β-catenin signaling pathway has been acknowledged as a promising therapeutic target for glioma[23,24]. A number of studies have reported that certain lncRNAs exert vital roles in human cancer via the Wnt/β-catenin pathway; however, lncRNAs that can regulate the Wnt/β-catenin signaling pathway and EMT are infrequently investigated[25]. Tian et al[15] reported that SUMO1P3 can promote cell proliferation, migration, and invasion in pancreatic cancer *via* the EMT. The current western blot analysis results demonstrated that SUMO1P3 knockdown significantly inhibited the β-catenin expression and also suppressed the expression of C-myc and cyclin D1, which are important downstream genes of the Wnt/β-catenin signaling pathway. These data suggest that SUMO1P3 can activate the Wnt/β-catenin pathway in glioma cells.

Conclusions

The present study revealed that SUMO1P3 promotes glioma cell proliferation, migration, and invasion, and is associated with the EMT and Wnt/β-catenin signaling pathway. In summary, we demonstrated that SUMO1P3 may serve as a useful prognostic indicator for patients with glioma, and targeting SUMO1P3 and the Wnt/β-catenin signaling pathway may be a novel therapeutic strategy for glioma.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Availability of Data and Materials

The datasets used and/or analyzed during the current research are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The present investigation was approved by the Ethics and Research Committees of the First Affiliated Hospital of Gannan Medical University, and performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was collected from all subjects.

Authors' Contribution

JiL, JuL and JC designed the study. JiL and JuL performed experiments and analyzed the data. SY, GD, WL, RZ and CQ collected and analyzed clinical samples and was also a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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