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Long noncoding RNA LINC01426 promotes glioma progression through PI3K/AKT signaling pathway and serves as a prognostic biomarker

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Abstract. – OBJECTIVE: Growing evidence indicated that long intergenic non-protein coding RNA 1426 (LINC01426) played important roles in tumor initiation and progression. However, little was known about the expression pattern and biological function of LINC01426 in glioma. Here, we aimed to determine its expression pattern, clinicopathological significance, and biological roles in glioma.

PATIENTS AND METHODS: The Cancer Genome Atlas (TCGA) data was used to screen abnormally expressed lncRNAs in glioma. Reverse Transcription-Polymerase Chain Reaction (RT-PCR) was performed to detect the expression of LINC01426 in both glioma tissues and cell lines. Then, the associations between LINC01426 expression levels and various clinicopathologic characteristics and the clinical prognosis of patients with glioma were analyzed. The loss-of-function assay was performed to explore the effect of LINC01426 on glioma proliferation, metastasis, and apoptosis. Western blotting was performed to assess the protein expression levels.

RESULTS: We identified a differentially expressed novel oncogenic lncRNA termed as LINC01426 by TCGA. Subsequent RT-PCT indicated that LINC01426 expression was significantly up-regulated in both glioma tissues and cell lines. Increased LINC01426 expression was negatively correlated with WHO grade and KPS score. Furthermore, LINC01426 could serve as an independent predictor for overall survival in glioma. In vitro assay revealed that knockdown of LINC01426 suppressed glioma cells proliferation, migration and invasion, and induced apoptosis. Mechanistic investigation showed that LINC01426 exhibited its tumor promoter role by modulating PI3K/Akt signaling pathway in glioma.

CONCLUSIONS: The present study indicated that LINC01426 functioned as a tumor promoter and it might be a potential biomarker and therapeutic target in glioma.

Key Words:
lncRNA, LINC01426, Prognosis, PI3K/AKT, Metastasis.

Introduction

Glioma is one of the common primary brain tumors in the central nervous system, accounting for about 80% of all malignant brain tumors and 30% of all central nervous system tumors[1,2]. The most malignant form of glioma (Grade IV astrocytomas) is known as glioblastoma multiforme (GBM), which is the most common and lethal type of adult gliomas[3]. The biological characteristics of GBM primarily include high mortality and recurrence rates[4]. Despite the progress achieved in treating this form of cancer such as subsequent radiation, chemotherapeutic modalities, and other surgical techniques, the median survival is only 12-15 months for patients with GBM[5,6]. Accordingly, the leading cause of dismal outcomes in GMB is tumor metastasis[7]. Thus, it is critical to identify metastasis-related targeting for this disease. However, the potential mechanism underlying GMB metastasis remains largely unclear. Long noncoding RNAs (lncRNAs) are a major type of ncRNAs with more than 200 nucleotides[8]. Although more than 3000 human lincRNAs have been identified, less than 1% of them have been characterized. Growing evidence[9,10] indicated that lncRNAs are critical in various biological events, including cell differentiation, cell cycle, and apoptosis. Recent studies[11,12] indicated that the changes in lncRNAs expression levels have been observed in many cancers, and modulated various pathways involved in survival, prolif-

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eration, invasion, and apoptosis. For instance, lncRNA GAPLINC, a highly expressed lncRNA in gastric cancer, was reported to promote gastric cancer cell proliferation by acting as a molecular sponge of miR-378 to modulate MAPK1 expression[13]. LncRNA BLACAT1 was found to be up-regulated in colorectal cancer and associated with poor prognosis, and its knockdown suppressed colorectal cancer cell proliferation *in vitro* and *in vivo* by epigenetically silencing of p15[14]. Also, in glioma, several lncRNAs, such as lncRNA CRNDE[15], lncRNA MALAT1[16], and lncRNA TUSC7[17], were confirmed to be involved in the progression and development of glioma. Nonetheless, a large number of lncRNAs are probably still undiscovered and their biological functions still remain unclear. The long intergenic non-protein coding RNA 1426 (LINC01426), also known as LincRNA-uc002yug.2, is located on chromosome 12. Several groups have reported that LINC01426 is aberrantly expressed in esophageal cancer[18], lung adenocarcinoma[19], and colorectal cancer[20], suggesting that LINC01426 may be used as a biomarker for the diagnosis of these cancers. However, whether LINC01426 was abnormally expressed, and its biological function in glioma has not been investigated. In this study, we firstly found that LINC01426 was highly expressed in glioma patients and associated with poor prognosis. Loss-function experiments indicated that knockdown of LINC01426 suppressed glioma cells proliferation, migration, and invasion through PI3K/AKT signaling pathway. These investigations may facilitate a better understanding of LINC01426 in glioma.

Patients and Methods

Patients and Clinical Samples

Surgically resected paired human glioma tissue samples and corresponding adjacent normal brain tissues were collected from primary glioma patients from Jining No. 1 People's Hospital between 2009 and 2013. The histological grade of all glioma tissue samples was classified by experienced pathologists using WHO criteria. All enrolled patients did not receive any perioperative radiotherapy or chemotherapy. All glioma tissues were first preserved in liquid nitrogen and stored at -80°C for further use. The study was approved by the Ethical Committee of Jining No. 1 People's Hospital and the informed consent was obtained from all patients. The clinicopathological characteristics of these patients with glioma are summarized in Table I.

Cell Lines and Cell Culture

Human PG1, A172, LN229, U251, LN118, and H4 GBM cell lines were obtained from the Chinese Academy of Sciences Cell Bank (Xuhui, Shanghai, China) and normal human astrocytes

Table I. Relationship between the expression of LINC01426 and clinicopathological parameters in glioma.

Parameter	No. of cases	LINC01426 expression		*p*-value
		Low	High	
Age				0.273
< 50	46	21	25	
≥ 50	40	23	17	
Gender				0.679
Male	47	25	22	
Female	39	19	20	
Extent of resection				0.388
< 98%	43	20	23	
≥ 98%	43	24	19	
Tumor size				0.135
< 5 cm	50	29	21	
≥ 5 cm	36	15	21	
WHO grade				0.005
I-II	48	31	17	
III-IV	38	13	25	
KPS score				0.001
< 80	48	32	16	
≥ 80	38	12	26	

(NHAs) were purchased from the ScienCell Research Laboratories (ScienCell, Carlsbad, CA, USA). The cells were grown in Dulbecco's Modified Eagle's Medium (DMEM; Invitrogen, Carlsbad, CA, USA) supplemented with 10% of fetal bovine serum (FBS; HyClone, Logan, Utah, USA) and antibiotics (100 U of penicillin/mL and 100 μg/mL of streptomycin) at 37°C with 5% CO_2.

Cell Transfection and Regents

The specific small interfering RNAs (siRNA) including siRNA control (NC), LINC01426 siRNA1 (si-lncRNA1), and LINC01426 siRNA2 (si-lncRNA2) were synthesized by Ribobio Co, Ltd (Guangzhou, Guangdong, China). Lipofectamine 2000 reagents (Invitrogen Co., Carlsbad, CA, USA) were used for cell transfection according to the manufacturer's protocol. Briefly, U251 and LN299 cells (2×10^5 cells per well) were plated in a 6-well plate (Thermo Fisher Scientific, Waltham, MA, USA) and incubated for an appropriate time before use in experiments. Until the cell confluence reached about 70%, the mixture of siRNA duplex (20 μM; 12 μl) and Lipofectamine 2000 regents (10 μl) were prepared, and then added into the grown cells and incubated at 37°C with 5% CO_2 for 4-5 h. Subsequently, the medium was changed with fresh DMEM medium (Invitrogen, Carlsbad, CA, USA) supplemented with 10% of fetal bovine serum and antibiotics (100 U of penicillin/mL and 100 μg of streptomycin/mL) at 37°C with 5% CO_2.

Quantitative Reverse Transcription-Polymerase Chain Reaction (qRT-PCR)

The total RNA of the tissue samples and cell lines was extracted using the TRIeasy Total RNA Extraction Reagent (Yeasen, Xuhui, Shanghai, China) according to the manufacturer's protocols. Then, 10 ng of total RNA was reverse transcribed into cDNA using FastKing One Step RT-PCR Master Mix kit (TIANGEN, Haidian, Beijing, China). The cDNA was used for subsequent qRT-PCR reactions (TaKaRa, Dalian, Liaoning, China) according to the manufacturer's instructions. QRT-PCR was performed using the SYBR Select Master Mix (Applied Biosystems, Foster City, CA, USA) on an ABI 7900 system (Applied Biosystems, Foster City, CA, USA). The results were normalized to the expression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH). The $2^{-\Delta\Delta Ct}$ method was used to calculate the relative fold changes. The sequences of the PCR primers are as following: LINC01426 sense 5'-TCCCGAAGTGCATAGGCAAG-3'; reverse 5'-CCTGAACAAGTTGGGGAGGA-3'; GAPDH sense 5'-TCACCAGGGCTGCTTTTAAC-3'; reverse 5'-GACAAGCTTCCCGTTCTCAG-3'.

Western Blot Analysis

Whole-cell extracts were prepared with the radio-immunoprecipitation assay (RIPA; Beyotime, Pudong, Shanghai, China) with a protease inhibitor (Thermo Fisher Scientific, Waltham, MA, USA). An equal amount of protein was separated on sodium dodecyl sulphate-polyacrylamide gel (SDS-PAGE) and transferred to polyvinylidene difluoride (PVDF) membrane. The blots were blocked with 5% non-fat milk (Beyotime, Pudong, Shanghai, China) in Tris-Buffered Saline and Tween-20 (TBST-20; Beyotime, Pudong, Shanghai, China). Then, the membranes were incubated with primary antibodies: Anti-Caspase-3 antibody, Anti-Caspase-9 antibody, Anti-E-Cadherin antibody, Anti-Vimentin antibody, Anti-N-Cadherin antibody, Anti-p-PI3K antibody, Anti-PI3K antibody, Anti-p-AKT antibody, Anti-AKT antibody, Anti-GAPDH antibody. After washing with TBST, the membranes were incubated with secondary antibodies for 1 h at room temperature. The specific band was visualized using an enhanced chemiluminescent (ECL) detection system (Pierce ECL Substrate; Thermo Fisher Scientific, Waltham, MA, USA) and imaged using a BioSpectrum Gel Imaging System (Bio-Rad, Hercules, CA, USA).

Cell Proliferation Assay

The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (Yeasen, Xuhui, Shanghai, China) was utilized to assess the cell proliferation. In brief, U251 or LN299 cells (1×10^3 cells per well) were plated in 96-well plates (Thermo Fisher Scientific, Waltham, MA, USA). After transfecting with the siRNAs (NC, si-lncRNA1 or si-lncRNA2), the cell culture medium was replaced and 20 μl MTT solution (0.5 mg/ml) was added into each well. Following incubation at 37°C for 0 h, 24 h, 48 h, 72 h, and 96 h, the medium containing MTT solution was discarded, and 100 μl dimethyl sulfoxide (DMSO; Beyotime, Pudong, Shanghai, China) was added into each well. After incubated at 37°C with 5% CO_2 for 10 min, the plates were recorded at a wavelength of 490 nm using a plate reader (Infinite M200; Tecan, Pudong, Shanghai, China).

Clonogenic Assay

For colony formation assay, U251 or LN299 cells (500 cells per well) were placed in 6-well plates (Nunc, Roskilde, Denmark) and cultured in medium supplemented 10% FBS, changing the medium every 4 days. After about two weeks, visible cell colonies were fixed with 4% paraformaldehyde (Beyotime, Shanghai, China) for 15 min and stained with 0.1% crystal violet (Yeasen, Xuhui, Shanghai, China) for 1 h. Subsequently, the plates were washed three times with phosphate buffer saline and counted using a microscope (Nikon, Chiyoda-Ku, Tokyo, Japan).

Flow Cytometry Analysis of Apoptosis

For the cell apoptosis analyses, an Annexin-V-FITC apoptosis detection kit (BD, Franklin Lakes, NJ, USA) was utilized. In short, U251 or LN299 cells transfected with siRNAs (NC, si-lncRNA1 or si-lncRNA2) were harvested at 48 hours after transfection. Then, cold PBS-washed cells were resuspended in binding buffer and stained with Annexin V-fluorescein isothiocyanate (FITC) and propidium iodide (PI) for 15 min at the room temperature. The apoptosis cells were analyzed by FACS Calibur flow cytometer (BD Biosciences, San Jose, CA, USA).

Transwell Assays

For transwell migration assays or invasion assays, U251 or LN299 cells (100 µl; 5×10^4 cells) were seeded on uncoated (for migration assays) or Matrigel (BD Bioscience, Franklin Lakes, NJ, USA) coated (for invasion assays) upper chambers (8 µm pore size; Corning, Cambridge, MA) respectively. The lower chamber was filled with 500 µl medium supplemented with 10% FBS while there was no FBS in the medium of the upper chamber. After incubation for 16 h, the upper surface of the membrane was wiped using a cotton swab to remove non-invasive cells. Subsequently, 4% paraformaldehyde (Beyotime, Xuhui, Shanghai, China) were applied to fix the cells on the lower surface of the membrane and the cells were stained with 0.1% crystal violet (Yeasen, Pudong, Shanghai, China). Then, a microscope (Nikon, Chiyoda-Ku, Tokyo, Japan) was utilized to capture the images.

Statistical Analysis

Statistical analysis was performed with SPSS Statistics software version 17 (SPSS Inc., Chicago, IL, USA). All experiments were repeated in triplicate, and the results were expressed as the means ± SEM. Comparison between two groups was evaluated using an unpaired two-tailed *t*-test. Association of LINC01426 expression with clinical parameters was analyzed by x^2-test. The Kaplan-Meier method was used to calculate the survival curve, and the statistical significance was determined by the log-rank test. Cox's multivariate regression model was performed to identify independent prognostic factors of overall survival. Differences were considered to be statistically significant when $p < 0.05$.

Results

Upregulation of LINC01426 is Correlated With Poor Prognosis

To explore the expression of LINC01426 in glioma, we first analyze the data of lncRNAs of glioma and normal brain tissue from the cancer genome atlas (TCGA) database by a bioinformatics tool "GEPIA"[21]. As shown in Figure 1A, the results showed that LINC01426 expression was significantly up-regulated in glioma tissues compared with normal brain tissues. Furthermore, the data from TCGA indicated that the patients with high LINC01426 expression had shorter survival time than those with low LINC01426 expression (Figure 1B). Then, we further explore the expression of LINC01426 in glioma tissues and cell lines from our hospital. As shown in Figure 1C, overexpression of LINC01426 was observed in glioma tissues compared with matched normal brain tissues ($p < 0.01$). Moreover, we also confirmed that LINC01426 expression was significantly up-regulated in glioma cell lines (PG1, U251, U118, LN229, A172, U87MG, and H4) compared with that in normal human astrocytes (NHA) cells (Figure 1D). Taken together, our findings indicated that LINC01426 expression was up-regulated in glioma and involved in the progression of glioma.

Then, we further analyzed the association between LINC01426 expression and clinical variables of glioma. All tumor samples were classified into low LINC01426 expression group and the high LINC01426 expression group according to the median LINC01426 expression level of all glioma samples. As shown in Table I, we observed that high expression of LINC01426 was significantly associated with WHO grade ($p = 0.005$) and KPS score ($p = 0.001$). However, LINC01426 expression was not correlated with age, gender, extent of resection, and tumor size

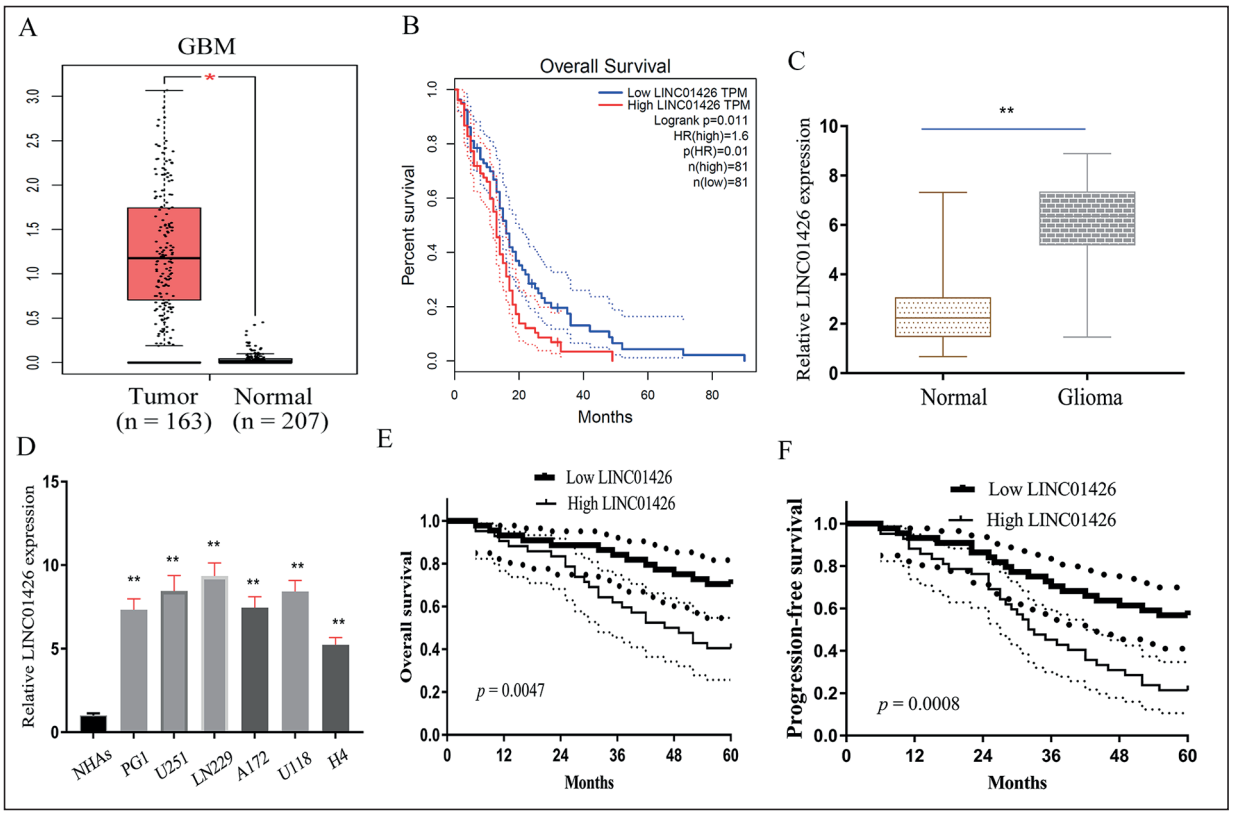

Figure 1. Expression levels of LINC01426 in glioma and its clinical significance. ***A,*** Screening out LINC01426 by bioinformatics tools "GEPIA". Data from TCGA of lncRNAs of glioma were analyzed by bioinformatics tools "GEPIA". glioma (n = 163), normal bladder tissue (n = 207). ***B,*** Kaplan-Meier survival estimates of the correlations between LINC01426 expression and overall survival of 162 glioma patients from TCGA data. ***C,*** The expression of LINC01426 in glioma tissues and matched normal tissues by RT-PCR. ***D,*** The expression of LINC01426 in glioma cell lines and Normal human astrocytes (NHAs) by RT-PCR. ***E,*** and ***F,*** Kaplan-Meier method with the log-rank test was used to analyze the overall survival and disease-free survival curves of patients in high and low LINC01426 expression groups. $^{**}p < 0.01$, $^{*}p < 0.05$.

($p > 0.05$). We analyzed the impact of LINC01426 expression on disease outcomes in glioma patients using Kaplan-Meier survival analysis. As shown in Figure 1E and 1F, we found that patients with high level of LINC01426 expression had poorer overall survival and disease-free survival. Finally, the multivariate analyses identified LINC01426 expression as an independent prognostic factor for both overall survival and disease-free survival (Table II).

Table II. Multivariate analysis of parameters associated with overall survival and progression-free survival of glioma patients.

Parameter	Overall survival			Progression-free survival		
	HR	95% CI	*p*	HR	95% CI	*p*
Age	1.424	0.561-1.955	0.362	–	–	–
Gender	1.755	0.671-2.544	0.121	–	–	–
Extent of resection	1.658	0.843-2.331	0.182	–	–	–
Tumor size	2.132	0.787-2.653	0.091	–	–	–
WHO grade	3.132	1.225-4.235	0.014	3.674	1.427-5.452	0.007
KPS score	3.326	1.327-5.557	0.005	4.368	1.672-7.458	0.001
LINC01426 expression	2.895	1.216-5.123	0.016	3.769	1.321-6.325	0.008

Knockdown of LINC01426 Decreases U251 and LN299 Cells Proliferation and Induces Cells Apoptosis

We next assessed the effects of LINC01426 on the proliferation and apoptosis of GBM cancer cells. After transfection with LINC01426 siRNAs (si-lncRNA1 or si-lncRNA2), the results of qRT-PCR assay showed that the expression levels of LINC01426 in both U251 and LN299 cells decreased significantly (Figure 2A). The impact of LINC01426 knockdown on the proliferation of U251 and LN299 cells was further evaluated using MTT assay. As presented in Figure 2B and 2C, the data suggested that suppression of LINC01426 resulted in a markedly decreased proliferation of the U251 and LN299 cells compared to the respective NC group. Similarly, results of the colony formation assays demonstrated that a reduction of LINC01426 expression also greatly inhibited the colony forming capabilities of U251 and LN299 cells (Figure 2D). In addition, the flow cytometry assay was conducted to investi-

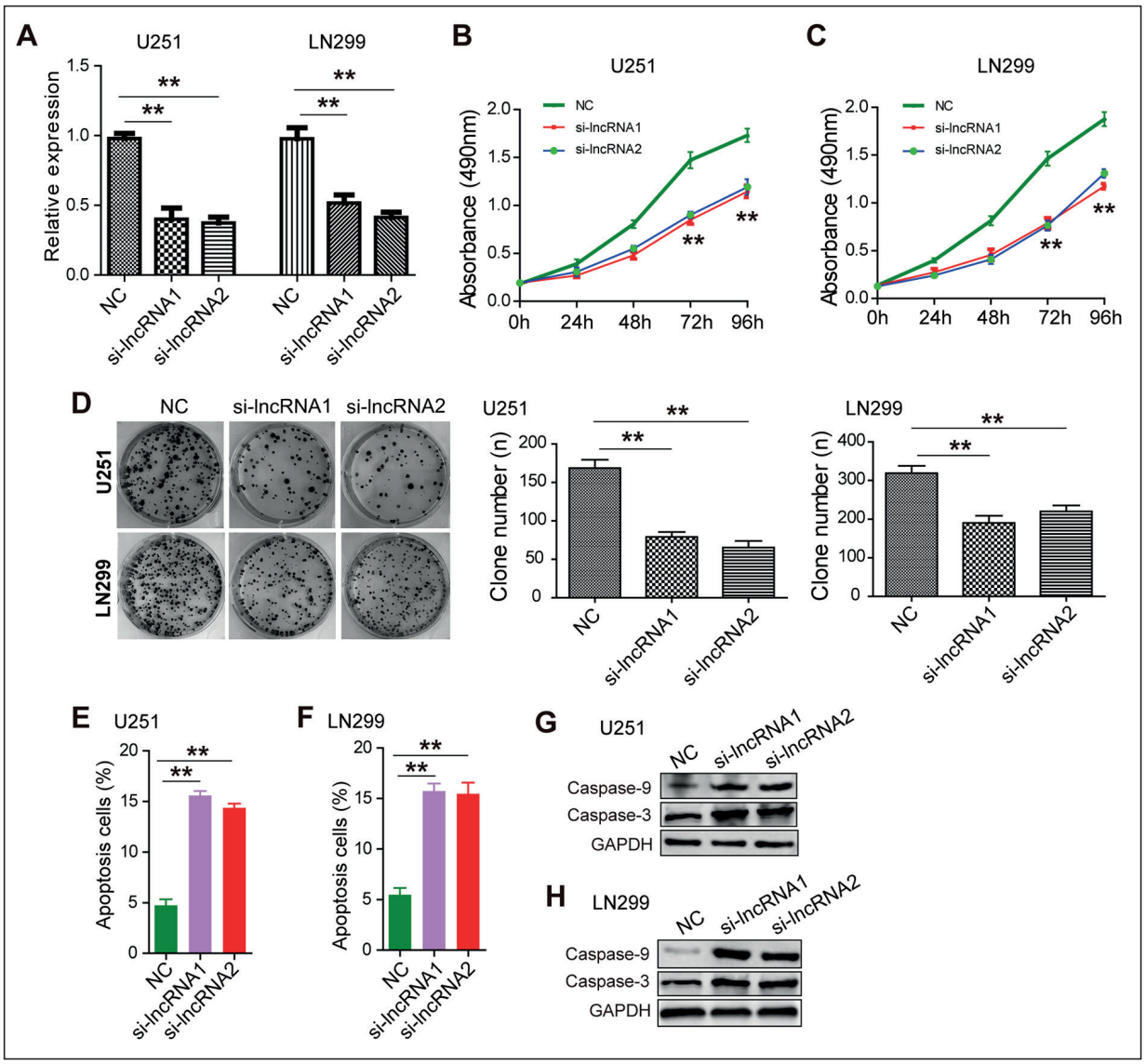

Figure 2. LINC01426 regulated glioma cells proliferation and apoptosis. ***A,*** Relative mRNA expression levels of LINC01426 in U251 and LN299 cells. ***B,*** and ***C,*** MTT assay indicated that LINC01426 knockdown inhibited the proliferation of U251 and LN299 cells. ***D,*** Knockdown of LINC01426 inhibited colony formation ability of U251 and LN299 cells. ***E*** and ***F,*** Flow cytometry analysis of U251 and LN299 cells apoptosis. ***G,*** and ***B,*** The protein levels of caspase 3 and caspase 9 detected by Western-blot assays in U251 and LN299 cells. The values were means ± SEM. *$p < 0.05$, **$p < 0.01$.

gate the functions of LINC01426 knockdown on the apoptosis of GBM cells. The results showed that silence of LINC01426 increased apoptosis dramatically in both U251 and LN299 cells (Figure 2E and F). Consistently, Western blot assay revealed that the protein levels of caspase 3 and caspase 9 increased after LINC01426 knockdown in U251 and LN299 cells (Figure 2G and 2H). Taken together, the results of the present study indicated that knockdown of LINC01426 inhibited the proliferation of GBM cells and induced cells apoptosis.

Silence of LINC01426 Inhibits the Migration and Invasion of U251 and LN299 Cells

To investigate whether LINC01426 affected the metastatic abilities of GBM cells, transwell migration assays, and invasion assays were carried out in the present study. The transwell migration assays showed that LINC01426 suppression significantly impaired the migration ability of U251 and LN299 cells than the control group (Figure 3A). Similarly, the transwell invasion assay revealed that decreased expression of LINC01426 markedly suppressed U251 and LN299 cells invasion capacities compared with the control group (Figure 3B). Besides, the Western blot assay was further utilized to detect the protein levels of epithelial-mesenchymal transition (EMT) related markers including vimentin, N-cadherin and E-cadherin in U251 and LN299 cells. The results revealed a decrease in vimentin and N-cadherin expression in LINC01426 siRNAs transfected cells compared with the controls, while the protein levels of E-cadherin were up-regulated in LINC01426 knockdown U251 and LN299 cells (Figure 3C and D). Overall, our data indicated that LINC01426 could increase metastatic potential of GBM cells through promoting the EMT ability.

Depletion of LINC01426 Suppresses the PI3K/Akt Signaling in GBM Cells

Upon finding that knockdown of LINC01426 inhibited the development and progression of GBM cells, we next investigated the possible mechanisms behind these functions. Hence, the alteration of the PI3K/Akt signaling pathway which had diverse functions in tumor progression was detected by Western-blot assay in U251 and LN299 cells. The data suggested that the protein levels of phosphorylated PI3K (p-PI3K) as well as phosphorylated AKT (p-AKT) decreased significantly in LINC01426 siRNAs transfected U251 cells, while the expressions of PI3K and AKT had no significance between LINC01426 knockdown U251 cells and the control cells (Figure 4A). Similarly, the significantly suppressed expressions of p-PI3K and p-AKT were also observed in LINC01426 siRNAs transfected LN299 cells (Figure 4B). To sum up, our data indicated that knockdown of LINC01426 attenuated the development and progression of GBM cells via inhibiting the activity of PI3K-AKT signaling.

Discussion

Glioma remains one deadly disease for many affected patients. The identification of molecular markers that are predictive patient outcome has the potential to improve the ability to manage patients[22,23]. Growing evidence[24,25] indicates lncRNAs as potential prognostic and diagnostic biomarker for glioma patients. In this study, we firstly performed TCGA analysis and the results indicated that the expression of LINC01426 was significantly suppressed in glioma tissues compared with normal brain tissues. Kaplan-Meier method by analyzing TCGA showed that glioma patients in high LINC01426 expression group had significantly shorter 5-year overall survival time than those in low LINC01426 expression group. Furthermore, by analyzing the clinical data from our patients, we also confirmed that increased LINC01426 expression in glioma samples and its correlation with advanced WHO grade, KPS score, shorter overall survival, and shorter disease-free survival. More notably, the multivariable analysis suggested that increased LINC01426 expression was an independent prognostic factor of overall survival and disease-free survival in glioma patients. Taken together, LINC01426 was up-regulated in glioma tissues and it could be an independent prognostic indicator for glioma patients. LINC01426, a newly identified tumor-related lncRNA, has been demonstrated to be involved in the progression of several tumors. Wu et al[17] reported that LINC01426 expression was significantly up-regulated in esophageal cancer and associated with poor prognosis of esophageal cancer patients. However, the biological function of LINC01426 in cancers remains largely unclear. In this study, we performed MTT and clone formation assay to explore the effect of LINC01426 on GBM cells, finding that knockdown of LINC01426

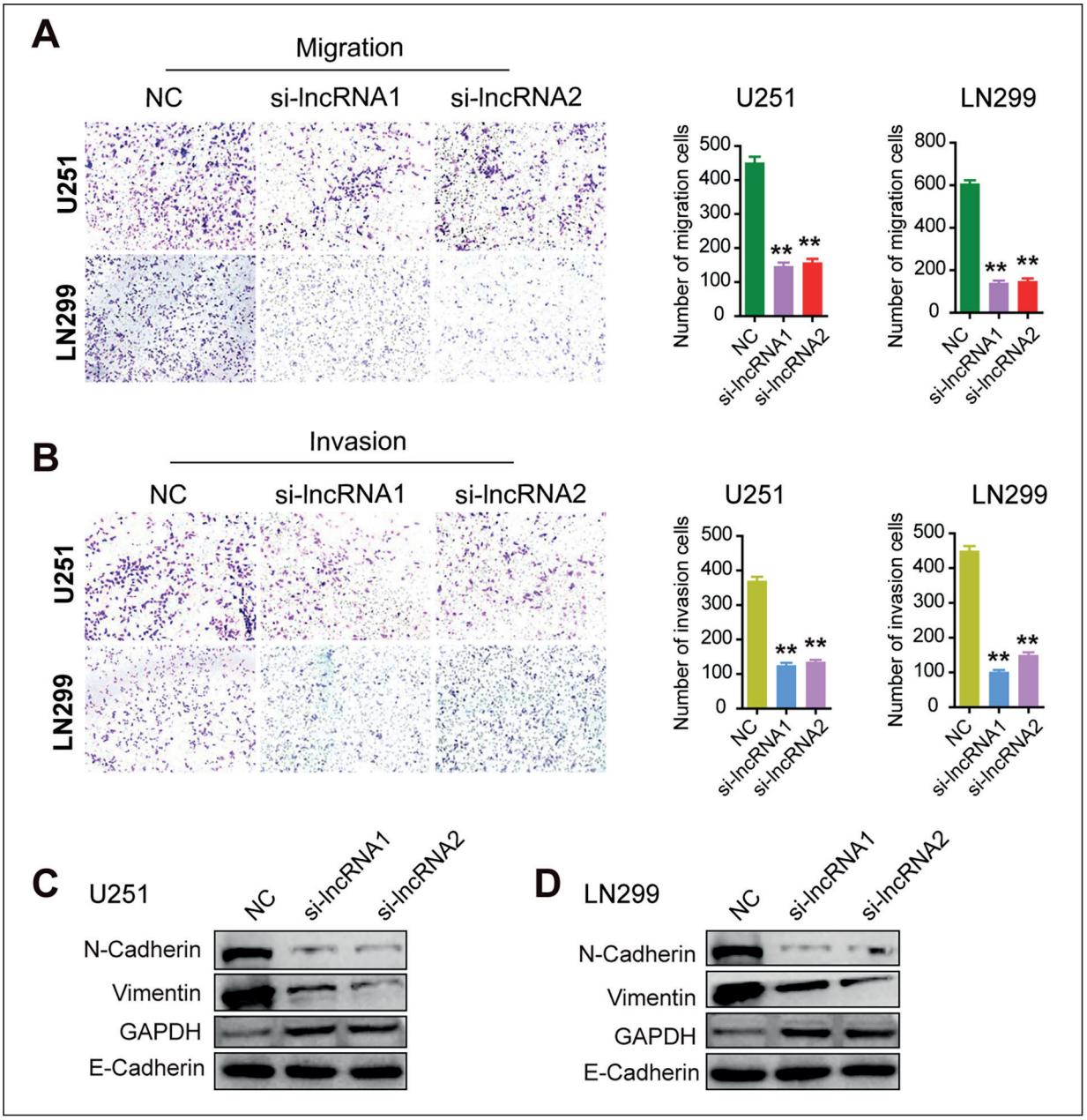

Figure 3. Effects of LINC01426 on migration and invasion of U251 and LN299 cells. ***A,*** Representative images and quantification analysis of the transwell migration assays of U251 and LN299 cells transfected with either NC or LINC01426 siRNAs. ***B,*** Transwell invasion assays were used to detect the invasive capabilities of U251 and LN299 cells. ***C*** and ***D,*** Protein expression levels of N-cadherin, vimentin, and E-cadherin in U251 and LN299 cells were detected by Western blot analysis. The values were means ± SEM. *$p < 0.05$, **$p < 0.01$.

significantly suppressed proliferation and colony forming capabilities of U251 and LN299 cells. Then, flow cytometry assay indicated that silence of LINC01426 increased apoptosis dramatically in both U251 and LN299 cells by modulating caspase 3 and caspase 9 expression. Our results indicated that LINC01426 play a positive regulator in GBM cells proliferation. Then, we performed migration and invasion assay and found that LINC01426 promoted U251 and LN299 cell EMT, migration and invasion, which was consistent with clinical test that high LINC01426 expression was closely associated with WHO grade. Taken together, our findings suggested LINC01426 served as a tumor promoter in the progression of glioma.

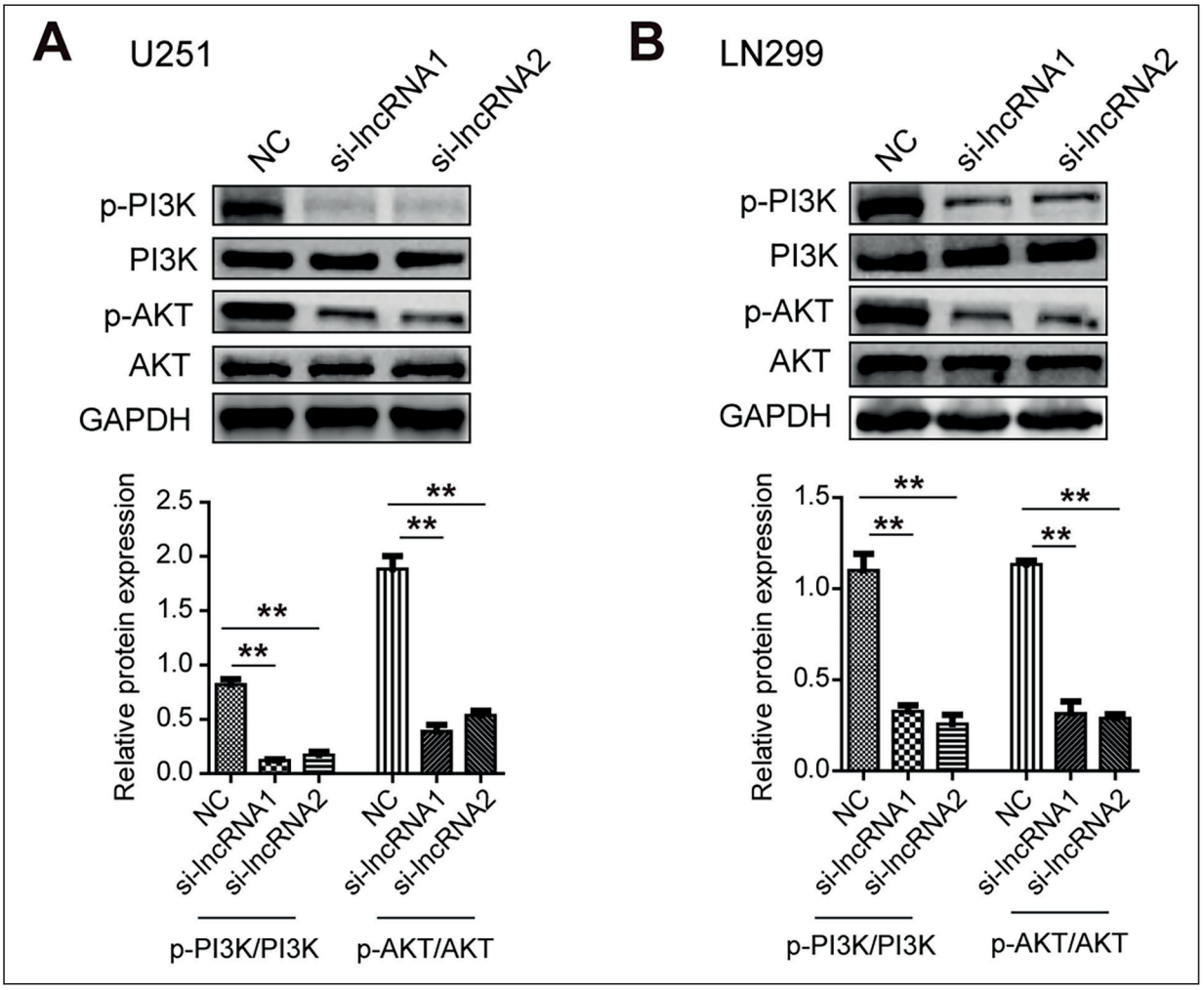

Figure 4. Effects of LINC01426 on PI3K/AKT signaling in glioblastoma. ***A,*** The protein expression levels and optical density analysis of p-PI3K, PI3K, p-AKT, and AKT in U251 cells detected by Western blot assay. ***B,*** The protein expression levels and optical density analysis of p-PI3K, PI3K, p-AKT, and AKT in LN299 cells detected by Western blot assay. The values were means ± SEM. *$p < 0.05$, **$p < 0.01$.

The PI3K/Akt signaling pathway is activated by many types of cellular stimuli and regulates fundamental cellular functions such as translation, proliferation, growth, apoptosis, and cell differentiation[26,27]. The PI3K/Akt signaling pathway can be considered as a master regulator for cancer[28]. The role of the PI3K/AKT signaling in cancer pathogenesis has been thoroughly investigated in recent years, and several drugs targeting the pathway are under development[29,30]. Several studies[31-33] reported that lncRNAs exerted their carcinogenic or anti-carcinogenic role by modulating PI3K/AKT in several tumors. These findings encouraged us to explore the association between LINC01426 and PI3K/AKT in glioma. We performed Western blot to detect the expression of PI3K/AK-related proteins and found that the effects of LINC01426 underexpression in glioma were mediated through the AKT/p-AKT signaling pathway, which indicated that LINC01426 promoted glioma cells proliferation, migration, invasion, and EMT by modulating AKT/p-AKT signaling pathway. However, the detailed mechanism by which LINC01426 modulate AKT/p-AKT needs to be further explored.

Conclusions

We showed that LINC01426 was significantly up-regulated in glioma and that the increased expression of this miRNA may be independent-

ly associated with shorter overall survival and disease-free survival. Moreover, LINC01426 acts as a tumor promoter gene in glioma and can suppress glioma cell migration and invasion by modulating AKT/p-AKT. Therefore, these findings will contribute to our understanding of how LINC01426 regulates the pathogenesis of glioma, and support a promising therapeutic agent for glioma treatment.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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