Linc00261 suppresses growth and metastasis of non-small cell lung cancer via repressing epithelial-mesenchymal transition

J. LIAO[1], L.-P. DONG[2]

[1]Department of Thoracic Surgery, Yantaishan Hospital, Yantai, China
[2]Department of Medical Oncology, The Second People's Hospital of Weifang, Weifang, China

Abstract. – OBJECTIVE: Long non-coding RNAs (lncRNAs) have been identified to participate in the development and progression of various types of cancers, including non-small cell lung cancer (NSCLC). However, the expression and function of linc00261 in NSCLC has not been studied yet. We aim to explore the role and potential of linc00261 in NSCLC tumorigenesis.

PATIENTS AND METHODS: The expression level of linc00261 in 71 paired of NSCLC tissues and matched normal tissues, was detected using quantitative Real-time polymerase chain reaction (qRT-PCR). Linc00261 expression in NSCLC cells was also measured. NSCLC cells were transfected with pcDNA3.1 or siRNA linc00261 to upregulate or downregulate linc00261 expression, respectively. MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay and colony formation assay were utilized for examining the proliferative ability of NSCLC cells. Wound-healing and transwell assays were performed for detecting metastatic ability of NSCLC cells. Protein levels of epithelial-mesenchymal transition markers were detected by Western blot. Furthermore, in vivo function of linc00261 was evaluated using the nude mice.

RESULTS: Linc00261 expressed significantly lower in NSCLC tissues and cell lines than that in the adjacent normal tissues or control cell line. Over-expression of linc00261 significantly inhibited proliferation, invasion and migration of NSCLC cells. On the contrast, knockdown of linc00261 promoted cell growth and metastasis of NSCLC cells. Furthermore, linc00261 inhibited the epithelial-mesenchymal transition of NSCLC via downregulating Snail. Linc00261 could slow down the growth of xenograft of NSCLC *in vivo*.

CONCLUSIONS: We demonstrated that linc00261 was lowly expressed in NSCLC tissues and cells. It inhibited cell proliferation and metastasis by downregulating Snail expression *via* EMT. This might provide a novel sight for the biological treatment for NSCLC.

Key Words
Linc00261, NSCLC, EMT, Snail.

Introduction

Lung cancer is pathologically divided into two subtypes: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts for the 80% of lung cancer cases[1]. In recent years, the incidence and mortality of NSCLC have increased year by year due to smoking and various environmental factors[2,3]. Although diagnostic and therapeutic approaches of NSCLC have been continuously improved, the overall five-year survival of NSCLC is still unsatisfactory[4]. Explorations on the progression and development of NSCLC at the molecular level could help improve the survival rate of NSCLC patients and reduce the mortality. The biological formation mechanism and regulation of non-coding RNA (ncRNA) have well concerned[5]. MicroRNAs have been shown to regulate the expression of target genes at the transcriptional or translational level, thus playing a very important role in cellular behaviors, such as cell growth, development, differentiation, proliferation, apoptosis and cell cycle[6]. Long non-coding RNA (LncRNA) is a non-coding RNA greater than 200 nucleotides in length. It has been found that lncRNAs are differentially expressed in various cancers and participate in the regulation of various molecular pathways, changing gene expressions and regulating cellular biological behaviors[5,7-9]. LncRNA SNHG1 regulated proliferation of colorectal cancer cells through interacting with miR-154-5p and EZH2. LncRNA DLEU1 regulates CDK1 expression through interacting with miR-490-3p, contributing to tumorigenesis and progression of ovarian carcinoma. LncRNA00607 suppressed hepatocellular carcinoma growth and metastasis *via* regulating nuclear factor-kappa B (NF-κB) p65/p53 signaling pathway, showing an oncogenic function[10-13]. However, the function of linc00261 in

Corresponding Author: Liping Dong, MM; e-mail: donglipingey@outlook.com

NSCLC has not been mentioned before. Here, we analyzed the expression of linc00261 in NSCLC tissues and cells. Functional experiments were conducted to elucidate the influence of linc00261 on cell proliferation, invasion and migration. Also, we detected expressions of epithelial-mesenchymal transition (EMT) markers. Our study provides new directions in NSCLC treatment.

Patients and Methods

Clinical Tissues

This study was approved by Yantaishan Hospital Ethics Committee. Informed consent was obtained before sample collection. A total of 71 pairs of NSCLC tissues and adjacent normal tissues were harvested from the Thoracic Surgery Department of Yantaishan Hospital from February 2015 to June 2016. None of the enrolled subjects underwent relevant chemotherapy, radiotherapy, biological therapy and drug-targeted therapy before surgery. Tissues were stored in liquid nitrogen for use.

Cells

Four NSCLC cell line (A549, H1650, PC-9, SPCA1) and the normal lung bronchial epithelial cell line BEAS-2B were provided by American Type Culture Collection (ATCC) (Manassas, VA, USA). Cells were cultured in Roswell Park Memorial Institute-1640 (RPMI-1640) (Gibco, Rockville, MD, USA) medium containing 10% fetal bovine serum (FBS) (Hyclone, South Logan, UT, USA). Cells were maintained in a constant temperature cell incubator at 37°C, 5% carbon dioxide, and saturated humidity.

Cell Transfection

SiRNA-Linc00261-1, siRNA-Linc00261-2, siRNA-Linc00261-3, and its negative control (siRNA-NC) were provided by Genepharma (Shanghai, China). pcDNA3.1-Linc00261 ant its control (pcDNA3.1-Empty) were synthesized by GeneWiz (Suchou, Jiangsu, China). Cells were seeded in a 12-well plate with 1×10^4 cells per well, and then cultured for 12 h. Cell transfection was performed using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). Transfection efficiency was detected by qRT-PCR at 48 h.

RNA Isolation and qRT-PCR

After extraction of total RNA from tissues and cells using TRIzol reagent (Invitrogen, Carlsbad, CA, USA), RNA concentration was measured using a NanoDrop1000 spectrophotometer (Thermo Scientific, Waltham, MA, USA). RNA was subjected to the ImPron.11 reverse transcription system (Roche, Basel, Switzerland) and the obtained cDNA was subjected to qRT-PCR in a 7900HT Real-time PCR system (Applied Biosystems, Foster City, CA, USA). The required primer sequences were as follows: Linc00261 forward primer: 5'- ACATTTGGTAGCCCGTGGAG-3', reverse primer: 5'- ACCACTACCCCAGCATTGTG-3'; GAPDH gene as internal reference, forward primer: 5'-TGGCACCCAGCACAATGAA-3', reverse primer: 3'- CTAAGTCATAGTCCGCCTAGAAGCA-5'. Relative expression level of linc00261 was calculated using the $2^{-\Delta\Delta Ct}$ formula.

MTT (3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyl Tetrazolium Bromide) Assay

Cell viability was measured by MTT method (Sigma-Aldrich, St. Louis, MO, USA). Cells at logarithmic growth phase were seeded in a 96-well cell culture plate at a concentration of 5.0×10^7/L, with 100 μL per well. After cell adherence, different concentrations of UA (5, 10, 20, 30 and 40 μmol/L) were added, with dimethylsulfoxide (DMSO) (Sigma-Aldrich, St. Louis, MO, USA) as the control group. After incubation for 24 h, 20 μL of MTT (2 g/L) were added to each well. Four hours later, the culture solution was aspirated and 150 μL of dimethylsulfoxide (DMSO) was added to each well. Absorbance of each well at a wavelength of 490 nm was measured using a microplate reader. The experiment was repeated for 3 times.

Colony Formation Assay

Transfected A549 or SPCA1 cells were prepared for single cell suspension. A total of 3000 cells per well were seeded in 6-well plates and cultured in 10% fetal bovine serum (FBS) medium for 2 weeks. After formation of macroscopically visible colony, cells were fixed in methanol and stained with crystal violet. Cell colonies containing more than 40 cells were counted. The experiment was repeated 3 times independently.

Wound-Healing Assay

Cells transfected with pcDNA3.1-Linc00261, pcDNA3.1-Empty, siRNA-Linc00261 or siRNA-NC were seeded in 6-well plates, cultured for 24 h. Three straight line was drawn using a 200 μL tip at the bottom of each well. After cell culture for 48 h, the scratch healing rate was calculated. The experiment was repeated 3 times in the standard state for recording the average value. Higher scratch healing rate indicated stronger migration ability.

Transwell Assay

Experiments were performed using 8 μm chambers (Millipore, Billerica, MA, USA). Cells transfected with pcDNA3.1-Linc00261, pcDNA3.1-Empty, siRNA-Linc00261 or siRNA-NC were planted on the top surface of the chamber with 2×10^4 cells, and cultured at 37°C for 24 h. The surface of the chamber was pre-coated with Matrigel (BD Sciences, Franklin Lakes, NJ, USA). Penetrating cells were stained with crystal violet solution. We randomly selected 10 fields in each sample to calculate the number of cells passing through the membrane (200×). The experiment was repeated 3 times.

Western Blot

After 24 h of cell culture, cells were collected and lysed using the radioimmunoprecipitation assay (RIPA) reagent (Beyotime, Nanjing, China). The protein was loaded to the 12% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) with 30 μg per well. After the electrophoresis, the protein was transferred to polyvinylidene difluoride (PVDF) membrane (Millipore, Billerica, MA, USA). The membrane was incubated with the primary antibody at a concentration of 1:1000 overnight. Next day, the membrane was incubated with secondary antibody at 1: 2000 at 37°C for 2 h. Electrochemiluminescence (ECL) kit (Millipore, Billerica, MA, USA) was used to measure the relative grayscale. The primary antibody used was: antibody for E-cadherin (1:1000), antibody for N-cadherin (1:1000), antibody for Vimentin (1:1000), antibody for Snail (1:1000) and antibody for glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (1:1000) as intern control.

In Vivo *Tumorigenesis Assay*

The effect of linc00261 on tumor growth was observed in xenograft formation in nude mice. Cells transfected with pcDNA3.1-Linc00261 or pcDNA3.1-Empty was adjusted to a density of 2×10^7/ml. 0.1 ml of the cell suspension was injected into the left forelimb of each nude mouse. Tumor growth in nude mice was observed weekly. Nude mice were sacrificed at 28 days. The tumor diameter (a) and vertical orthogonal diameter (b) of tumor-bearing mice in each group were measured. The tumor size [V(mm3)]=$a\times b^2/2$. After weighing tumor weight, tumor tissues were fixed with 4% paraformaldehyde.

Immunohistochemistry (IHC)

Immunohistochemistry was used to detect the expression of Snail in xenograft tissues of nude mice. Tumor tissues of nude mice were embedded using paraffin, and cut into 4 mm slides. The immunohistochemistry experimental procedure was performed according to the instructions of the immunohistochemical streptavidin peroxidase (SP) kit (Zhongshan Jinqiao, Beijing, China).

Statistical Analysis

Statistical analysis was performed using Graphpad 5.0 mapping software (La Jolla, CA, USA). The measurement data were expressed by the mean ± SD. Differences between the two groups were analyzed by *t*-test. $p<0.05$ was considered statistically significant.

Results

Linc00261 was Under-Expressed in NSCLC Tissues and Cell Lines

We detected the expression of linc00261 in 71 pairs of NSCLC tissues and matched normal tissues using qRT-PCR. Linc00261 was lowly expressed in tumor tissues than the normal group (Figure 1A), indicating that linc00261 acted as a tumor suppressor in NSCLC. Also, linc00261 level was lower in NSCLC cells than the normal BEAS-2B cells (Figure 1B). Next, transfection of pcDNA3.1-Linc00261 in SPCA1 cells markedly upregulated linc00261 level (Figure 1C). On the contrast, linc00261 expression in A549 cells was inhibited by transfection of siRNA-Linc00261. Transfection efficiency of siRNA-Linc00261-1 was the best among the three siRNAs and thus chosen for the following experiments (Figure 1D).

Over-Expression of linc00261 Inhibited Cell Proliferation and Cell Circle Progression of NSCLC Cells

Next, we evaluated the influence of linc00261 on the proliferation of NSCLC cells. MTT assay showed that transfection of pcDNA3.1-Linc00261 significantly decreased the cell proliferation of SPCA1 cells, while transfection of siRNA-Linc00261 increased the proliferation of A549 cells relative to controls (Figure 2A, 2B). Similarly, over-expression of linc00261 reduced the colony numbers of SPCA1 cells. Conversely, linc00261 knockdown elevated colony number of A549 cells than controls (Figure 2C, 2D). These suggested that linc00261 inhibited proliferation of NSCLC cells.

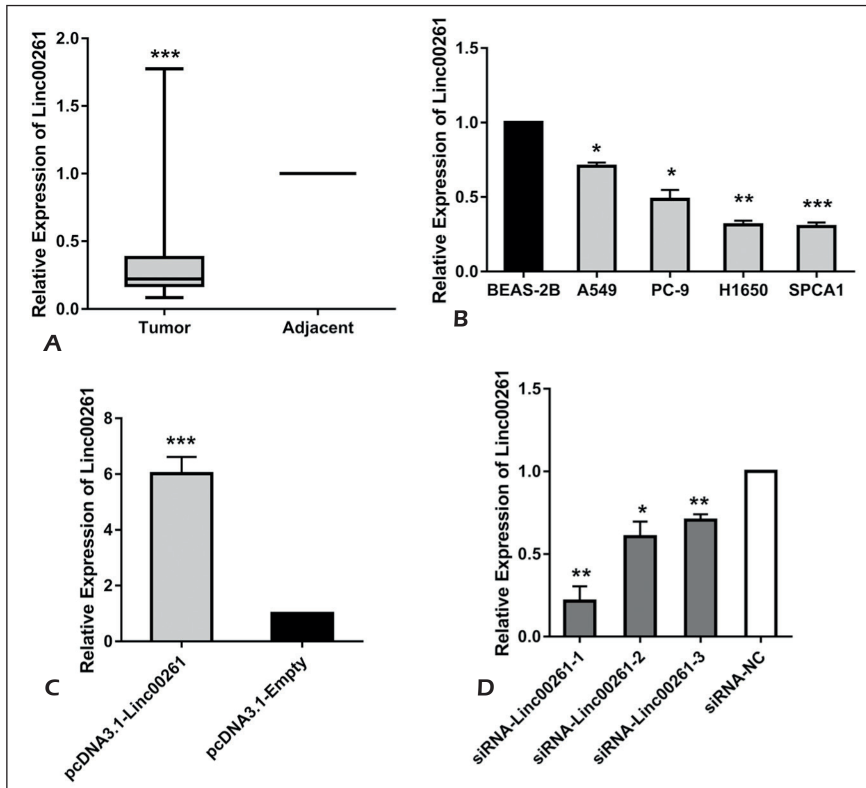

Figure 1. Linc00261 expression decreased in NSCLC tissues and cell lines. **A**, Analysis of the expression level of linc00261 in 71 pairs of NSCLC tissue samples and adjacent normal tissue samples. **B**, Analysis of linc00261 expression level in NSCLC cell lines (SPCA1, PC-9, H1650, A549) and human normal lung bronchial epithelial cell line BEAS-2B. **C**, Expression of linc00261 in SPCA1 cells transfected with pcDNA3.1-Linc0026. **D**, Expression of linc00261 in A549 cells transfected with siRNA-Linc00261. **p*<0.05, ***p*<0.01, ****p*<0.001.

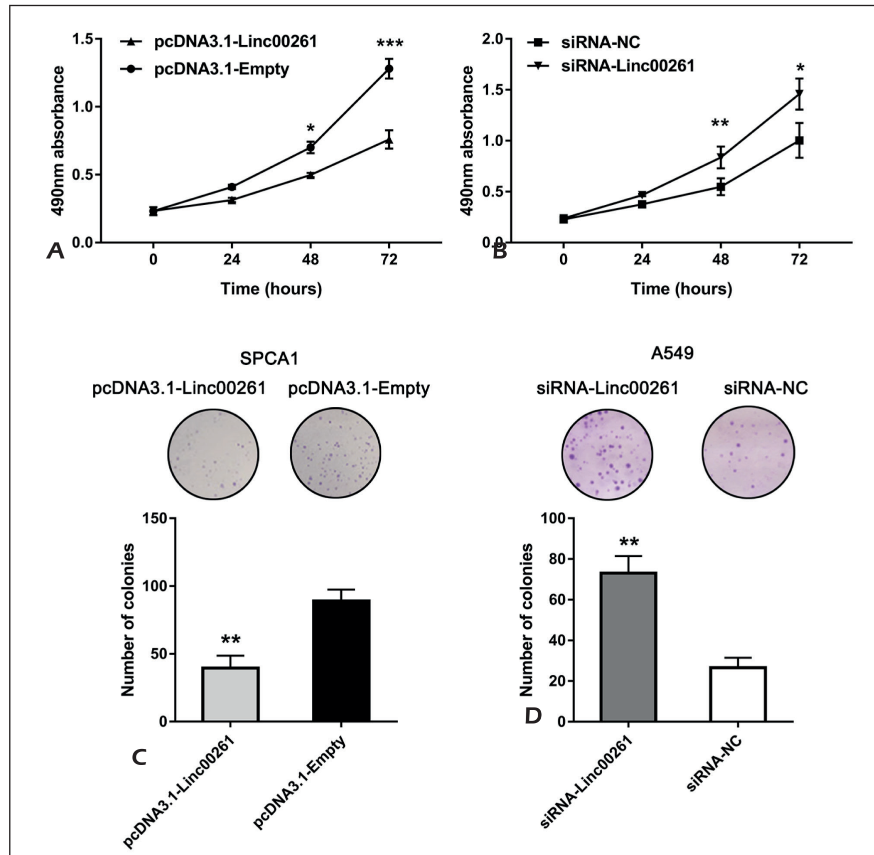

Figure 2. Linc00261 effected the proliferation of NSCLC cells. **A-B**, MTT assay was performed to determine the proliferation of SPCA1 (**A**) or A549 (**B**) cells transfected with pcDNA3.1-Linc00261 or siRNA-Linc00261 compared to each negative control. **C-D**, Colony formation analysis was performed to determine the cell growth of SPCA1 (**C**) or A549 (**D**) cells transfected with pcDNA3.1-Linc00261 or siRNA-Linc00261, respectively. **p*<0.05, ***p*<0.01, ****p*<0.001.

Linc00261 Influenced Cell Invasion and Migration in NSCLC Cells

The effect of linc00261 on cell metastasis was evaluated by wound healing and transwell assays. The reduced migration ability was showed in SPCA1 cells overexpressing linc00261 upregulated (Figure 3A). A549 cells transfected with siRNA-Linc00261 showed increased migration ability when comparing with the siRNA-NC group (Figure 3B). Transwell assay demonstrated that over-expression of linc00261 significantly decreased the invasion ability of SPCA1 cells, while knockdown of linc00261 promoted cell invasion of A549 cells (Figure 3C). These data indicated linc00261-reduced invasion and migration of NSCLC cells.

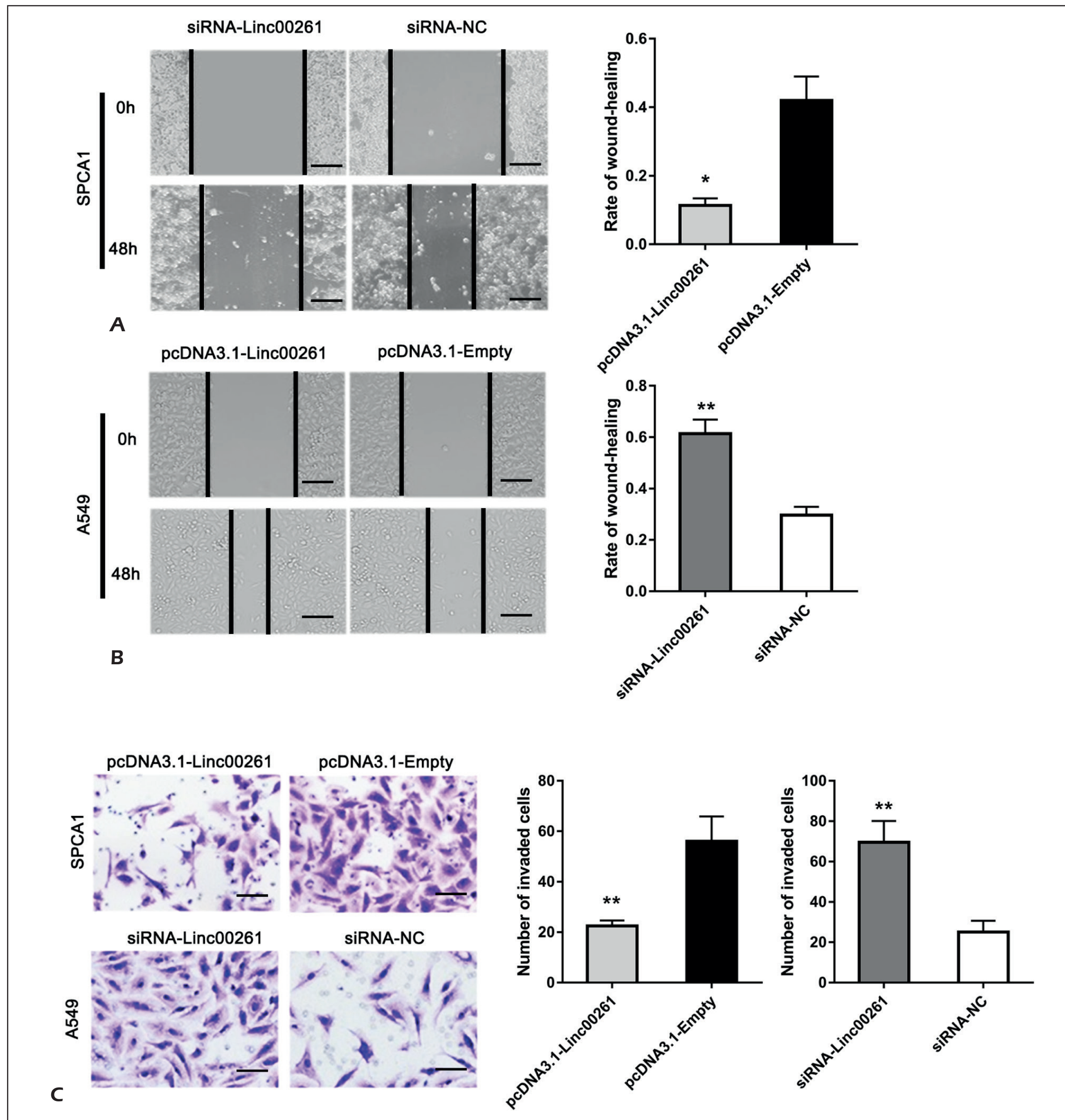

Figure 3. Linc00261 effected the invasion and migration of NSCLC cells. **A-B**, Wound-healing assay was used to detect the migration ability of SPCA1 cells or A549 cells transfected with pcDNA3.1-Linc00261 or siRNA-Linc00261. **C**, Transwell invasion assay was used to detect the invasion ability of SPCA1 cells or A549 cells transfected with pcDNA3.1-Linc00261 or siRNA-Linc00261 (200×). Data were presented as the mean ± SD of three independent experiments. **p*<0.05, ***p*<0.01, ****p*<0.001.

Linc00261 Regulated Epithelial-Mesenchymal Transition (EMT) of NSCLC Via Regulating Snail

EMT is an important progression in NSCLC, so we evaluated changes of EMT in the established cells. As shown in Figure 4A-4C, the epithelial marker E-cadherin was upregulated in SPCA1 cells transfected with pcDNA3.1-Linc00261, but decreased in A549 cells transfected with siRNA-Linc00261 transfected. Meanwhile, the mesenchymal marker N-cadherin and Vimentin were reduced by linc00261 overexpression. Conversely, linc00261 knockdown upregulated expressions of N-cadherin and Vimentin. These suggested that linc00261 inhibited the EMT of NSCLC. Also, we found that Snail, which functions as a regulator for EMT, was negatively regulated by linc00261. Furthermore, the expression of Snail in 71 NSCLC tissues was detected and showed a negative relationship with linc00261 expression (R^2=0.0.449, p<0.001) (Figure 4D). These demonstrated that linc00261 inhibited EMT of NSCLC *via* repressing Snail expression.

Up-Regulation of linc00261 Inhibited Tumor Growth of NSCLC in Vivo

As we have analyzed the function of Linc00261 *in vitro*, we next injected the experimental SPCA1 cells to nude mice to explore the function of Linc00261 *in vivo*. The volume and weight of xenografts in the pcDNA3.1-Linc00261 group were significantly lower than in the pcDNA3.1-Empty group (Figure 5A, 5B). The tumor growth curve was markedly slower in the up-regulation group (Figure 5C). The expression of linc00261 in the pcDNA3.1-Linc00261 group was also significantly reduced (Figure 5D). IHC showed the expression of Snail in the pcDNA3.1-Linc00261 treated group decreased than the control group (Figure 5E). These indicated that linc00261 overexpression inhibited tumor growth of NSCLC *in vivo*.

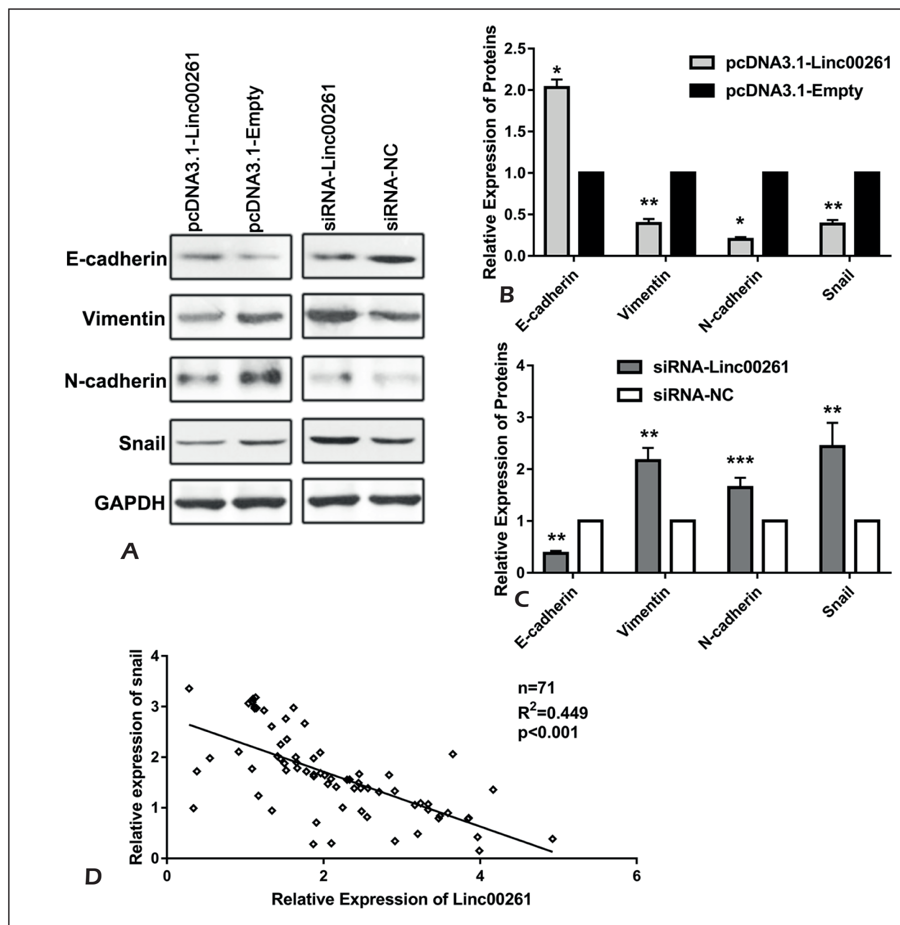

Figure 4. Linc00261 inhibited EMT of NSCLC via downregulating Snail. **A**, Expression of EMT markers in experimental cells. **B**-**C**, Relative level of protein. **D**, relationship between mRNA expressions of linc00261 and Snail in 71 NSCLC tissues. Data were presented as the mean ± SD of three independent experiments. *p<0.05, **p<0.01, ***p<0.001.

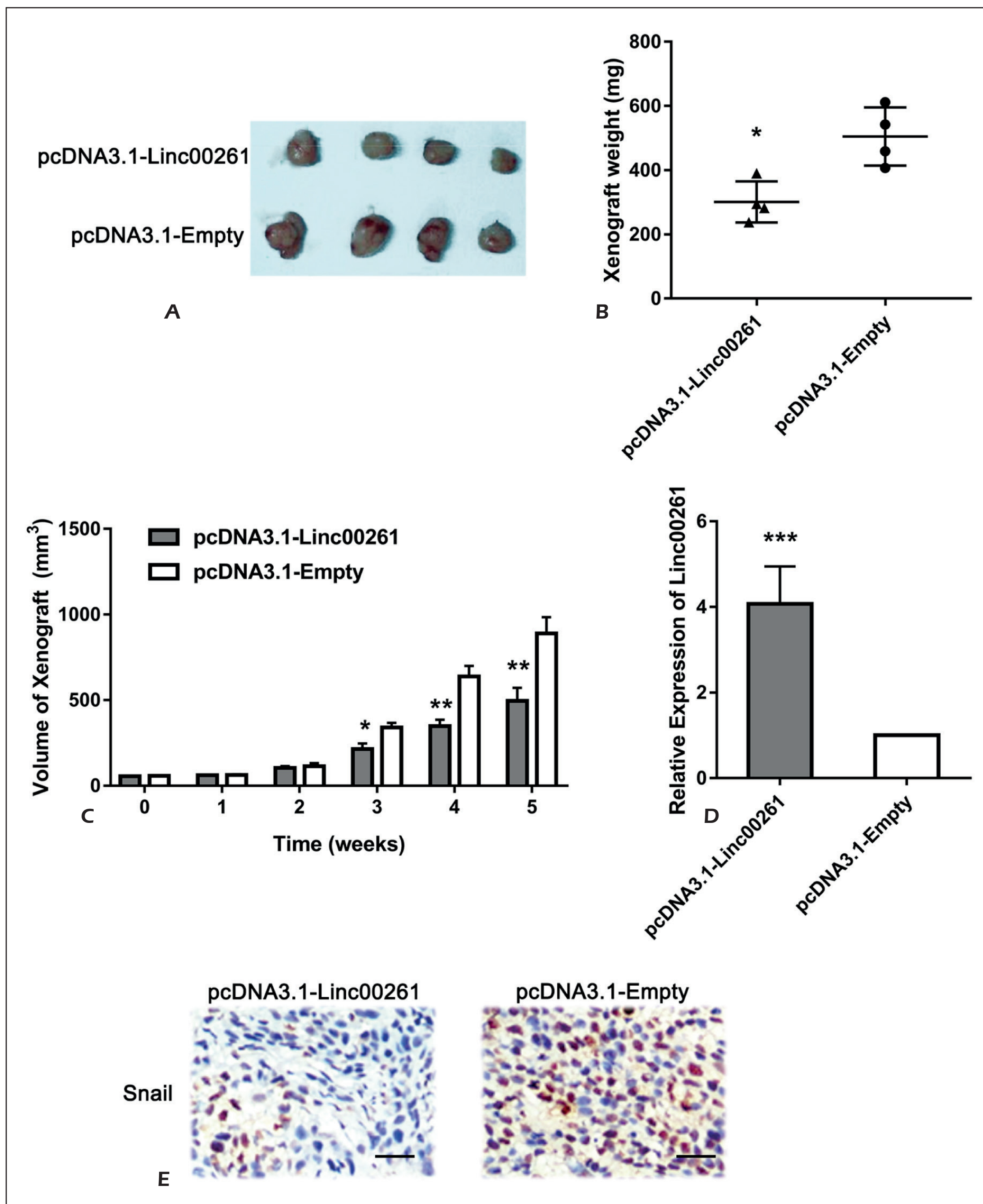

Figure 5. Linc00261 inhibited NSCLC cell growth *in vivo*. **A**, Xenografts of SPCA1 cells transfected with pcDNA3.1-Linc00261 or pcDNA3.1-Empty. **B**, Analysis of the weight of xenografts. **C**, Growth curve of xenografts. **D**, Expression of linc00261 in xenografts. E, IHC showed the expression of Snail protein in xenografts (400×). Data were represented as the mean ± SD of three replicates. *p<0.05, **p<0.01, ***p<0.001.

Discussion

The incidence and mortality of lung cancer grow the fastest among malignant tumors worldwide. According to the latest statistics from the American Cancer Society (ACS), lung cancer-related deaths account for about 28% of cancer-caused deaths[2,3]. Active researches on the pathogenesis of lung cancer, especially NSCLC, and studies on finding potential molecular targets are of great significance for the clinical diagnosis and treatment of NSCLC[14,15]. LncRNA has become a hotspot in the field of oncology study recently. More and more studies have shown that lncRNA is closely related to tumors[16-18]. In lung cancer, various lncRNAs have been confirmed to be involved in the process of proliferation, apoptosis, autophagy, invasion and metastasis of lung cancer cells. LncRNA EPEL promotes lung cancer proliferation by interacting with E2F activation. Linc01510 is highly expressed in NSCLC, indicating poor prognosis and promoting its malignant progression. In addition, autophagy of NSCLC cells is inhibited by lncRNA NBAT1 through downregulating ATG7 expression. Furthermore, lncRNA FAL1 increases cell growth, metastasis and EMT of NSCLC *via* PTEN/AKT axis[19-21]. Linc00261 has been identified as a tumor suppressor in few cancers. In human esophageal cancer, gastric cancer, human choriocarcinoma, pancreatic cancer, endometrial carcinoma and hepatocellular carcinoma, linc00261 inhibited cell proliferation and metastasis *via* several downstream molecules[22-27]. Here, we detected the expression of Linc00261 in NSCLC tissues and cell lines for the first time, and found a significantly decrease of linc00261 expression in the cancer group. Furthermore, abnormal expression of linc00261 showed that linc00261 overexpression inhibited cell proliferation, invasion and migration of SPCA1 cells. Linc00261 knockdown, conversely, promoted cell growth and metastasis of A549 cells. These validated linc00261 as a tumor suppressor in NSCLC, which are consistent to its function in other cancer diseases. Epithelial-mesenchymal transition (EMT) is a common biological mechanism that plays an extremely important role in tumor metastasis[28]. Many studies have shown that EMT and its related regulatory proteins, including Snail, are involved in the progression of NSCLC[29, 30]. Therefore, this study examined the expression of the major epithelial-mesenchymal transition markers and its regulator protein Snail. We found that E-cadherin, N-cadherin, Vimentin expressions were regulated by linc00261. The epithelial markers E-cadherin were upregulated, while mesenchymal marker N-cadherin and Vimentin were downregulated after linc00261 over-expression. Snail expression was negatively regulated by linc00261. It is suggested that linc00261 may promote epithelial-mesenchymal transition by regulating Snail expression, thereby enhancing metastatic ability of NSCLC. Furthermore, we verified the function of linc00261 *in vivo*. Over-expression of linc00261 remarkably inhibited xenograft growth in nude mice. Snail expression in the xenograft of pcDNA3.1-Linc00261 group significantly decreased compared to the control group, consisting of the *in vitro* function of linc00261.

Conclusions

We showed that linc00261 was lowly expressed in NSCLC tissues and cells. It inhibited cell proliferation, invasion and migration of NSCLC through downregulating Snail *via* EMT. Our study provides experimental basis for clinical treatment of NSCLC.

Conflict of Interests
The authors declared no conflict of interest.

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