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Up-regulation of long non-coding RNA SNHG1 contributes to proliferation and metastasis in laryngeal squamous cell carcinoma

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Abstract. – OBJECTIVE: To investigate the expression of human long non-coding ribonucleic acid (RNA) small nucleolar RNA host gene 1 (SNHG1) in laryngeal carcinoma tissues, and to study the effect of SNHG1 on biological functions of laryngeal carcinoma HEp-2 cells.

PATIENTS AND METHODS: The expression levels of SNHG1 in 20 pairs of laryngeal carcinoma tissues and para-carcinoma tissues were detected via Real-time fluorescence quantitative polymerase chain reaction (PCR). Laryngeal carcinoma cells were transfected with small interfering (si)-SNHG1 transiently using the RNA interference technique. The effects of si-SNHG1 on proliferation, apoptosis, invasion, and migration of laryngeal carcinoma HEp-2 cells were detected via cell counting kit-8 (CCK-8), colony formation assay, flow cytometry, and wound healing and Transwell assay, respectively.

RESULTS: Results of PCR showed that the expression of SNHG1 in carcinoma tissues was increased compared with that in para-carcinoma tissues. Results of CCK-8 and colony formation assay revealed that SNHG1 knockdown could significantly inhibit the proliferation of laryngeal carcinoma HEp-2 cells. Flow cytometry showed that transfection with si-SNHG1 could promote the apoptosis of HEp-2 cells. Moreover, results of wound healing and Transwell assay showed that SNHG1 knockdown could inhibit invasion and migration of HEp-2 cells through inhibiting the epithelial-mesenchymal transition (EMT) process and expressions of matrix metalloproteinase-2 (MMP-2) and MMP-9 in cells.

CONCLUSIONS: The expression of SNHG1 in laryngeal carcinoma tissues is significantly higher than that in para-carcinoma tissue. Patients with high expression of SNHG1 have a poor prognosis. SNHG1 knockdown in HEp-2 cells can inhibit cell proliferation, invasion, and metastasis, and can promote apoptosis.

Key Words:
Laryngeal carcinoma, Proliferation, Apoptosis, lncRNA SNHG1.

Introduction

Laryngeal carcinoma accounts for about 25% of malignant tumors in head and neck. About 95% laryngeal carcinomas are laryngeal squamous cell carcinoma, and cervical lymph node metastasis occurs easily. In recent years, the incidence rate of laryngeal carcinoma has been gradually increased[1-3]. Surgery combined with chemoradiotherapy is dominated in the treatment of laryngeal carcinoma[4]. Due to the large scope of surgical resection, swallowing, breathing and phonic functions of patients with middle and advanced laryngeal carcinoma will be affected to some extent, the treatment effect, and prognosis and life quality of patients are still not satisfactory, and its 5-year survival rate is about 64.2%[5,6]. Therefore, deeply studying the relevant molecular mechanisms of the occurrence and development of laryngeal carcinoma is of great significance in developing efficient and reasonable diagnosis and treatment plan of laryngeal carcinoma, increasing the survival rate and improving the life quality of patients with laryngeal carcinoma.

Long non-coding ribonucleic acid (lncRNA) generally refers to the non-coding RNA with more than 200 nt in length, without complete open reading frame and participating in protein encoding[7]. Studies[8,9] have shown that the expression level of lncRNA is different in different tissues and cells, and it can be expressed abnor-

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mally in many human tumor tissues. Studies[10-12] have also revealed that small nucleolar RNA host gene 1 (SNHG1) is highly expressed in tissues of lung cancer, liver cancer, colon cancer, prostate cancer, etc., which plays a role as oncogene. However, there have been no studies on differential expression and related functions of SNHG1 in laryngeal carcinoma. So, this study aims to explore the role of SNHG1 in laryngeal carcinoma and its mechanism.

Patients and Methods

Laryngeal Carcinoma Tissue Samples

A total of 20 patients diagnosed with laryngeal squamous cell carcinoma and receiving operative treatment in the Otolaryngology Department of our hospital from March 2013 to October 2015 were collected. Patients received no chemoradiotherapy before surgery and signed the informed consent before specimen taking. This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Shantou University Medical College. During surgery, primary lesions of laryngeal carcinoma were cut, and tumor specimens with good cell activity at the edge of mass were taken. At the same time, para-carcinoma tissues more than 2 cm away from the tumor tissues and pathologically diagnosed as no infiltration of carcinoma cells after surgery were taken, and quickly cryopreserved in liquid nitrogen for standby application.

Materials

Anti-B-cell lymphoma-2 (Bcl-2), anti-Bcl-2 associated X protein (Bax), anti-Caspase-9, anti-poly-ADP-ribose polymerase (PARP), anti-E-cadherin, anti-Snail, anti-Vimentin, anti-matrix metalloproteinase-2 (MMP-2), anti-MMP-9 and anti-actin antibodies were purchased from Cell Signaling Technology, Inc. (Danvers, MA, USA). Annexin V/propidium iodide (PI) staining kits were purchased from Nanjing KeyGen Biotech Co., Ltd. (Nanjing, China). Methyl thiazolyl tetrazolium (MTT) kits were bought from Beyotime (Shanghai, China). Quantitative reverse transcription polymerase chain reaction (qRT-PCR) kits SYBR Green were bought from Roche (Basel, Switzerland), USA. Small interfering (si)-NC and si-SNHG1 were synthesized by Nanjing Genscript Biotech Co., Ltd. (Nanjing, China), and other experimental reagents were purchased from Sigma-Aldrich (St. Louis, MO, USA).

Cell Culture

HEp-2 cells were purchased from Shanghai Cell Bank, Chinese Academy of Sciences (Shanghai, China). Cells were incubated using Dulbecco's modified Eagle medium (DMEM) containing 10% fetal bovine serum (FBS), 1% penicillin-streptomycin double-antibody solution and 1% non-essential amino acids in an incubator with 5% CO_2 at 37°C. The cell growth was observed every day, and the solution was replaced once every 2 d. When about 80% cells were fused, cells were subcultured at a ratio of 1:1, and cells in the logarithmic growth phase were taken for all experiments.

Laryngeal Carcinoma Specimen Collection

A total of 20 pairs of laryngeal carcinoma tissues and para-carcinoma normal tissues were collected from patients receiving surgical resection in our hospital. Patients received no chemoradiotherapy and other treatments before surgery. The specimens collected were all confirmed pathologically and stored in liquid nitrogen within 5 min after resection, to avoid RNA degradation affecting the experimental results.

qRT-PCR

The total messenger RNA (mRNA) was extracted from cells using TRIzol and reversely transcribed into complementary deoxyribonucleic acid (cDNA). The conditions of reverse transcription reaction are as follows: 25°C for 10 min, 50°C for 30 min and 85°C for 5 min, and detection using the fluorescence quantitative PCR kit. Primer sequences of SNHG1 are as follows: forward primer: 5'-CCTAAAGCCACGCTTCTTG-3', reverse primer: 5'-TGCAGGCTGGAGATCCTACT-3'. Primer sequences of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (internal reference) are as follows: forward primer: 5'-GGTCTCCTCTGACTTCAACA-3', reverse primer: 5'-AGCCAAATTCGTTGTCATAC-3'. Conditions of fluorescence quantitative PCR are as follows: 95°C for 5 min, 95°C for 15 s, 60°C for 1 min, a total of 40 cycles. The solubility curve temperature was set at 60-95°C, and three repeated wells were set for each specimen.

Detection of Cell Proliferation

HEp-2 cells were transfected with si-NC and si-SNHG1. After 48 h of transfection, cells were collected and the concentration of cell suspension was adjusted. Then, the cells were added into

a 96-well plate, making the cell density in the si-NC group and si-SNHG1 group 4000 cells/well. Cells were cultured in an incubator with 5% CO_2 at 37°C. The cell proliferation in each group was detected using MTT kits at 24 h, 48 h, and 72 h. The optical density (OD) value was read at a wavelength of 450 nm using a microplate reader, and the cell growth curve was drawn. Three repeated wells were set for each group, and the experiment was repeated independently for 3 times. At the same time, the cell proliferation in both groups was detected *via* cell colony formation assay. After 48 h of transfection of HEp-2 cells, cells were collected, inoculated into a 6-well plate (400 cells/well), and cultured in the incubator with 5% CO_2 at 37°C for another 14 d. After 14 d of culture, cells were washed with phosphate-buffered saline (PBS), fixed with 10% formaldehyde, stained with Giemsa and photographed. The cell colony containing more than 50 cells indicated one clone. The experiment was repeated for 3 times.

Apoptosis Detection

HEp-2 cells were transfected with si-NC and si-SNHG1, collected at 48 h after transfection, and washed with PBS twice. 500 μL 1×binding buffer was added to resuspend the cells, and the cell suspension was added with 5 μL Annexin V-fluorescein isothiocyanate (FITC) reagent, followed by incubation in a dark place at room temperature for 15 min. Then, 10 μL PI reagent was added and gently mixed, followed by incubation in a dark place at room temperature for 5 min, and submission for detection within 1 h. The experiment was repeated for 3 times.

Wound Healing Assay

Cells were inoculated into the 6-well plate. When 90%-100% cells were fused, wounds were made uniformly and slowly using a 10 μL spearhead perpendicular to the bottom of the 6-well plate (3 wounds/well), and the width of each wound should be uniform during the operation. Then, cells were washed with PBS for 3 times to clear away the floating cells, and serum-free Dulbecco's modified Eagle Medium (DMEM) was added to inhibit cell proliferation and division, followed by incubation. At 0 h and 24 h after wounding and culture, the migration distance of cells in the wound area was observed under a microscope, and several different fields of view were randomly selected for photography. The experiment was repeated for 3 times.

Transwell Migration and Invasion Assays

After different treatments, cells in both groups were collected, counted, and resuspended in the serum-free DMEM. 100 μL cell suspension was added into the upper chamber, while 500 μL complete medium containing 10% FBS was added into the lower chamber, followed by incubation for 24 h. After fixation and staining, five fields of view were randomly selected for photography under an inverted microscope. In invasion assay, what was different from migration assay was that the Transwell chamber was paved with a layer of Matrigel. Cells were incubated in the incubator for 30 min and inoculated. The remaining operations were the same as those in the migration assay. Three repeated wells were set for each group, and the experiment was repeated for 3 times.

Western Blotting

HEp-2 cells were transfected with si-NC and si-SNHG1 and collected at 48 h after transfection. After cells were washed with pre-cooled PBS, they were fully lysed with radioimmunoprecipitation assay (RIPA) cell lysis solution. After centrifugation, the supernatant was taken and quantified. Then, 20 μg total protein was taken and mixed with 5×sodium dodecyl sulfate (SDS) protein loading buffer, followed by denaturation at 100°C for 5 min, and loading in SDS-polyacrylamide gel electrophoresis (PAGE). Moreover, the gel and activated polyvinylidene difluoride (PVDF) were placed on the membrane transfer frame for membrane transfer for 2 h. The PVDF membrane was taken and sealed with 5% skim milk powder for 1 h. The corresponding primary antibodies were added for incubation at 4°C overnight. The membrane was washed with Tris-Buffered Saline with Tween-20 (TBST), and added with the corresponding horseradish peroxidase (HRP)-labeled secondary antibodies for incubation at room temperature for 1 h. After washing with TBST and color development, the gray value was analyzed using Image J software, and the relative expression level of the target protein was presented as target protein/actin. The experiment was repeated for 3 times.

Cell Transfection

HEp-2 cells in the logarithmic growth phase were taken, digested and cultured in the 6-well plate. When about 60% cells were fused, 500 μL transfection medium already prepared, opti-MEM, containing Lipofectamine2000 and siRNA was added into each well. Cells in experiment

group and control group were transfected with si-SNHG1 and si-NC, respectively, shaken evenly and incubated in the incubator for 6 h. Then, the original medium was discarded, and 2 mL complete medium was added into each well, followed by incubation for another 48 h for standby application. Sequence of si-SNHG1: 5'-CAGCAGTTGAGGGTTTGCTGTGTAT-3'; sequence of si-NC: 5'-UUCUCCGAACGUGUCACGUTT-3'.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 10.0 software (Chicago, IL, USA) was used for statistical analysis. The *t*-test was used for enumeration data. The survival rate was calculated using Kaplan-Meier method, and the survival curve was drawn. The survival rate was compared using Log-rank test, and $\alpha = 0.05$ indicated the significance level.

Results

SNHG1 Was Highly Expressed in Laryngeal Carcinoma Tissues and Correlated with Poor Prognosis

Results of qRT-PCR showed that the expression of SNHG1 in laryngeal carcinoma tissues was significantly higher than that in para-carcinoma tissues. The difference was statistically significant ($p < 0.05$) (Figure 1A), suggesting that SNHG1 promotes the occurrence and development of laryngeal carcinoma to some extent; in other words, it plays a role as an oncogene in laryngeal carcinoma. With the average SNHG1 expression level (2.63 relative to GAPDH) in 20 patients with laryngeal carcinomas as a criterion, laryngeal carcinoma patients were divided into low SNHG1 expression group and high SNHG1 expression group. The correlations of SNHG1 expression level in laryngeal carcinoma tissues with clinicopathological data were further analyzed. It was found that the SNHG1 expression level was related to the pathological staging and lymph node status. The SNHG1 expression level in patients with advanced laryngeal carcinoma was higher than that in patients with early laryngeal carcinoma ($p = 0.014$) (Table I), and the SNHG1 expression level in patients with positive lymph node metastasis was higher than that in patients with negative lymph node metastasis ($p = 0.037$) (Table I). There were no significant correlations of SNHG1 expression with age, smoking and pathological grading (Table I, $p > 0.05$). Furthermore, it was found in Kaplan-Meier survival analysis that the prognosis of patients in low SNHG1 expression group was significantly superior to that of patients in high SNHG1 expression group, and both disease-free survival (DFS) and overall survival (OS) in low SNHG1 expression group were longer (Figure 1B and C). Results showed that the median DFS was 42 months in high SNHG1 expression group, and 79 months in low SNHG1 expression group ($p = 0.022$). The median survival time was about 57 months in high SNHG1 expression group and about 79 months in low SNHG1 expression group ($p = 0.007$).

Down-regulation of SNHG1 Expression Inhibited HEp-2 Cell Proliferation In Vitro

To further investigate the role of SNHG1 in HEp-2 cells and its mechanism, SNHG1 was knocked down *in vitro*. The inhibition efficien-

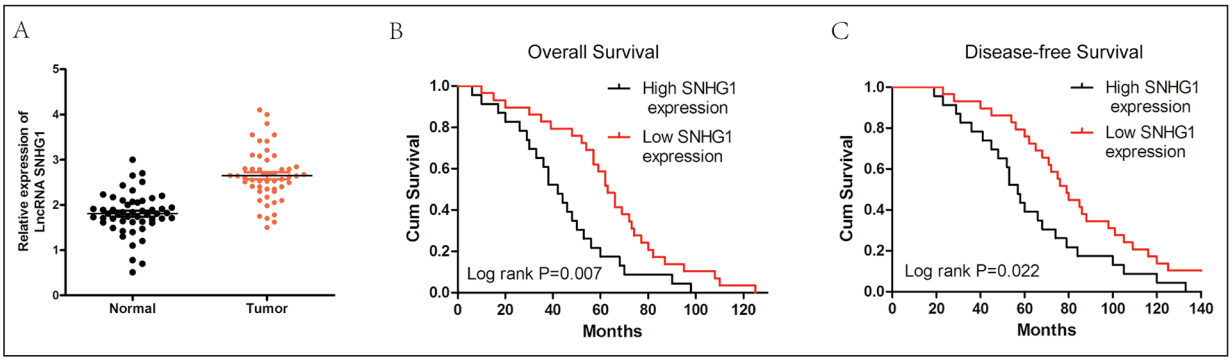

Figure 1. Relative SNHG1 expression in laryngeal carcinoma tissues and its clinical significance. ***A,*** Relative expression of SNHG1 in laryngeal carcinoma tissues (n = 52) and adjacent non-cancerous tissues (n = 52) was examined by qPCR and normalized to GAPDH expression. ***B, C,*** Kaplan-Meier overall survival and disease-free survival curves according to SNHG1 expression levels. (*$p < 0.05$).

Table I. Correlation between SNHG1 expression and clinicopathological characteristics of laryngeal squamous cell cancer patients.

Characteristics	BANCR		*p* Chi-squared test *p*-value
	High No. cases (23)	Low No. cases (29)	
Age (years)			0.930
≤ 60	14	18	
> 60	9	11	
Smoking history			0.112
Smokers	13	10	
Never smokers	10	19	
TNM stage			0.014 *
I + II	8	20	
III	15	9	
Lymph node metastasis			0.037 *
Negative	11	22	
Positive	12	7	
Histological grade			0.278
I+ II	10	17	
III	13	12	

cy after transfection with si-SNHG1 for 48 h was verified *via* qRT-PCR. As shown in Figure 2D, si-SNHG1 was effective in inhibiting the SNHG1 expression in laryngeal carcinoma HEp-2 cells, and there was a statistically significant difference compared with that in the negative control group ($p < 0.05$), so si-SNHG1 was selected for transfection in subsequent experiments. Next, MTT and colony formation assays were performed to verify the effect of SNHG1 on HEp-2 cell proliferation *in vitro*. HEp-2 cells interfered with si-SNHG1 and si-NC were cultured for 24 h, 48 h, and 72 h, respectively, followed by MTT assay. Results showed that the growth rate of HEp-2 cells was significantly inhibited after knockdown of SNHG1 (Figure 2A). Results of colony formation assay revealed that the number of colony formation in the SNHG1 knockdown group was significantly reduced compared with that in control group (Figure 2C), suggesting that down-regulation of SNHG1 expression can significantly inhibit the colony formation.

Down-regulation of SNHG1 Expression Promoted HEp-2 Cell Apoptosis

To investigate the mechanism of SNHG1 knockdown in inhibiting HEp-2 cell proliferation, the effect of SNHG1 knockdown on apoptosis was examined. Results of flow cytometry showed that the total apoptosis rate in the knockdown group was significantly increased compared with that in control group (Figure 2B). Results of Western blotting, consistent with the above results, revealed that the expressions of Bax, cleaved Caspase-9, and cleaved PARP were significantly up-regulated after the SNHG1 knockdown, but the expression level of Bcl-2 was down-regulated (Figure 2E). The above results suggest that inhibiting SNHG1 expression can significantly increase the Bax/Bcl-2 ratio, increase the expressions of cleaved Caspase-9 and cleaved PARP, initiate the mitochondrial apoptosis pathway, and promote the cell apoptosis, thus inhibiting the tumor.

Down-regulation of SNHG1 Expression Inhibited HEp-2 Cell Migration and Invasion

Invasion and metastasis are important features of the tumor. Therefore, the effects of SNHG1 on migration and invasion of laryngeal carcinoma cells were further analyzed. First, wound healing assay was used to detect the cell migration capacities in control group and SNHG1 knockdown group. Results showed that the migration distance of cells in the SNHG1 knockdown group was shorter than that in control group after 24 h ($p < 0.05$, Figure 3A and B). Next, transwell migration assay was performed, and results were consistent with those in wound healing assay. After the knockdown, the number of cells passing through the filter membrane in the lower chamber was reduced, and the difference was statistically significant ($p < 0.05$, Figure 3C and D).

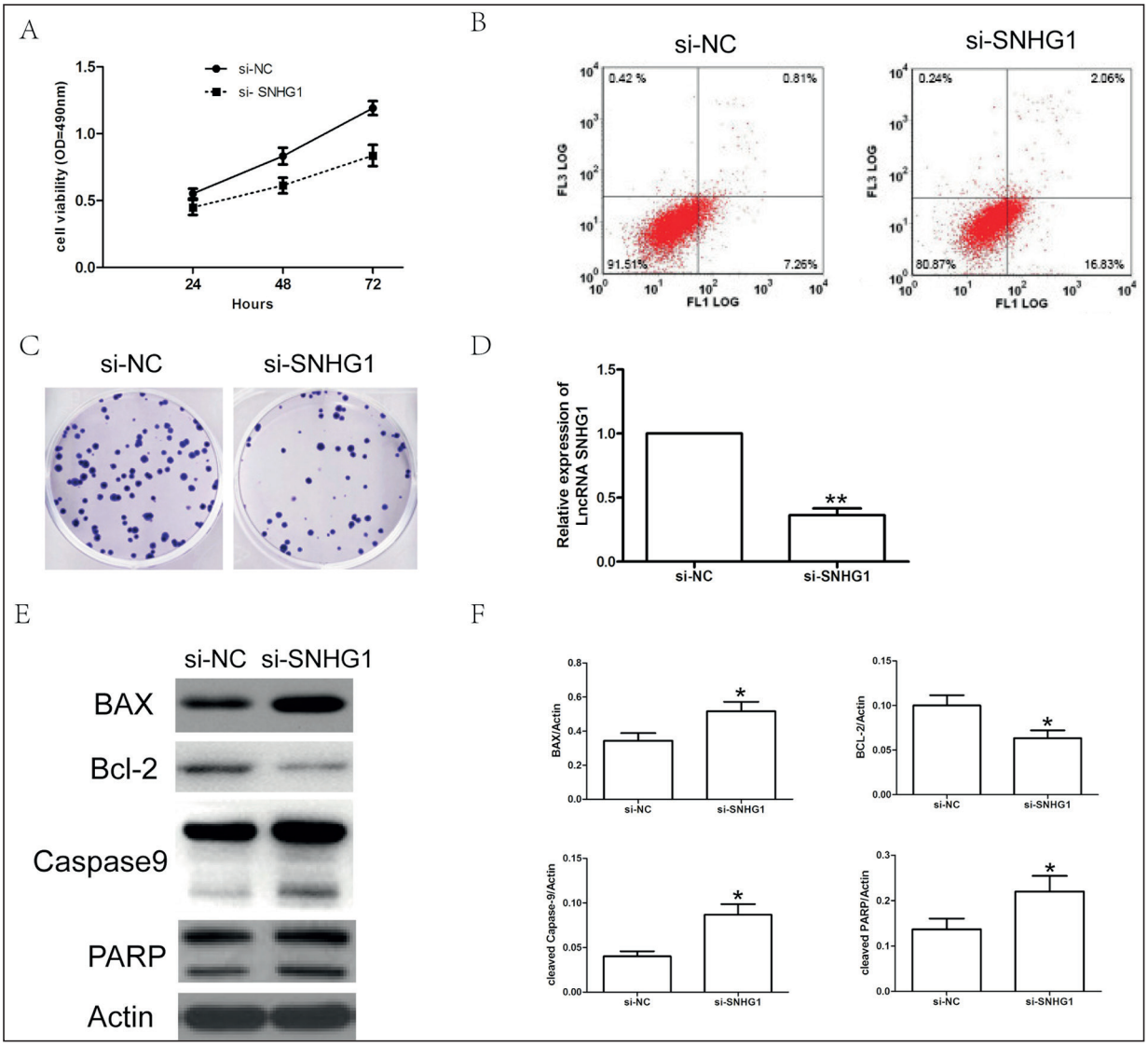

Figure 2. Effects of SNHG1 on HEp-2 cells proliferation and apoptosis *in vitro*. ***A,*** MTT assays were performed to determine the proliferation of si-SNHG1 and si-NC transfected HEp-2 cells. ***B,*** Flow cytometry was conducted to determine the apoptosis of si-SNHG1 transfected HEp-2 cells. ***C,*** Colony-forming assays were conducted to determine the proliferation of si-SNHG1 and si-NC transfected HEp-2 cells. ***D,*** Effective knockdown of SNHG1 in HEp-2 cells 48 h after siRNA treatment. ***E,*** The proteins levels of BAX, Bcl-2, cleaved-caspase9 and PARP were determined by Western blotting in si-SNHG1 transfected HEp-2 cells. (*$p < 0.05$, **$p < 0.01$).

Knockdown of SNHG1 Expression Inhibited Epithelial-Mesenchymal Transition (EMT) Process and Expressions of MMP-2 and MMP-9 in HEp-2 Cells

To further investigate the mechanism of SNHG1 knockdown in inhibiting the migration and invasion capacities of HEp-2 cells, the expressions of related molecules were further detected *via* Western blotting. As shown in Figure 4, E-cadherin expression was significantly up-regulated after the SNHG1 knockdown, but Snail and Vimentin expressions were down-regulated. It was further found that SNHG1 knockdown could also down-regulate the expressions of MMP-2 and MMP-9 in HEp-2 cells. The above results indicate that SNHG1 knockdown can inhibit cell migration through inhibiting the EMT process and expressions of MMPs in HEp-2 cells.

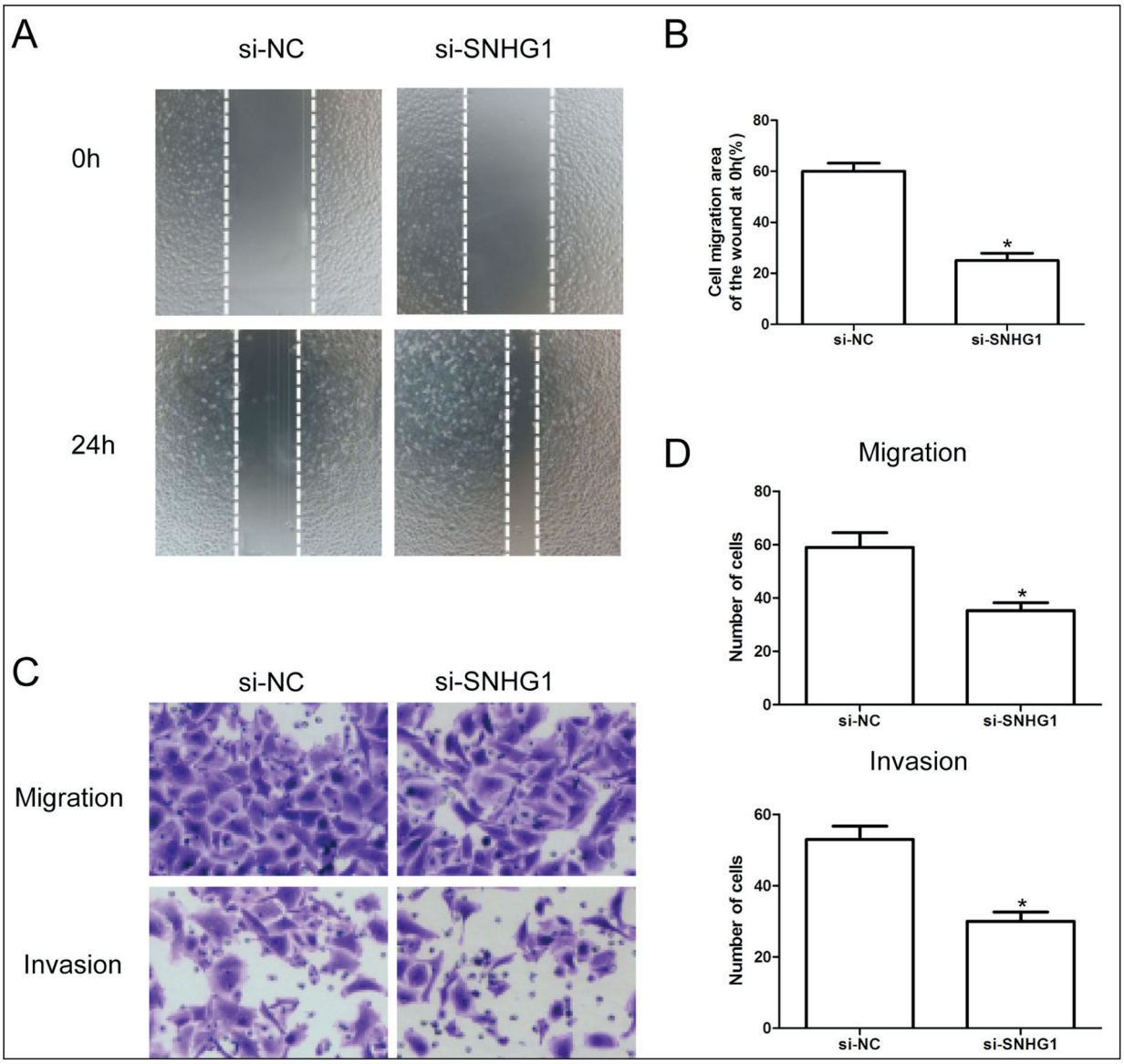

Figure 3. Effects of SNHG1 on HEp-2 cells migration and invasion *in vitro*. ***A, B,*** HEp-2 cells were treated with si-SNHG1 and si-NC, and the effects on cell migration were determined with cell scratch test. ***C, D,*** The effects on cell migration and invasion were determined with cell transwell test. (*$p < 0.05$, **$p < 0.01$)

Discussion

LncRNA is closely related to cell proliferation, apoptosis, aging, death, and other processes, and it is found that there are many lncRNAs associated with tumor occurrence, development, diagnosis, and prognosis[13-15]. SNHG1 is highly expressed in tissues of a variety of tumors, such as non-small cell lung cancer, liver cancer, and prostate cancer, and plays a role as oncogene[11,16,17]. Zhang et al[11] found that liver cancer patients with high SNHG1 expression have more poorly-differentiated tumor tissues, relatively higher tumor node metastasis (TNM) staging and shorter survival time than those with low SNHG1 expression. A research[17] on relevant mechanism has shown that SNHG1 can inhibit apoptosis, and activate Wnt/β-catenin signaling pathway, thereby promoting proliferation and metastasis of tumor cells. Based on previous studies, the role of SNHG1 in laryngeal carcinoma and its mechanism were explored in our work.

First, the difference in SNHG1 expression in laryngeal carcinoma tissues and corresponding para-carcinoma tissues was verified *via* fluores-

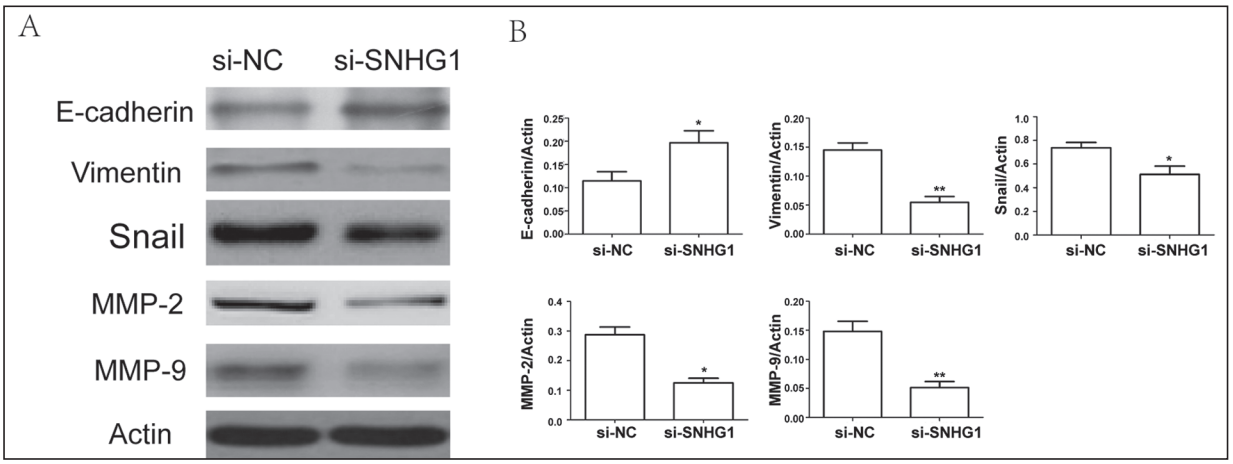

Figure 4. Effects of SNHG1 on the proteins expression related to migration and invasion of HEp-2 cells. ***A, B,*** The expression levels of target proteins (E-cadherin, Vimentin, Snail, MMP-2 and MMP-9) measured by Western blotting in HEp-2 cells transfected with si-SNHG1 or si-NC. ***C,*** Data shown are representative of 3 independent experiments. (*$p < 0.05$, **$p < 0.01$).

cence quantitative PCR. It was found that the expression level of SNHG1 in laryngeal carcinoma tissues was significantly higher than that in corresponding para-carcinoma tissues, which was consistent with results of previous studies, suggesting that SNHG1 is highly expressed in laryngeal carcinoma tissues, and plays a potential role as oncogene. To investigate the correlations of SNHG1 with tumor characteristics and prognosis of patients, the clinicopathological features, DFS, OS, and SNHG1 expression level in patients were further analyzed. Interestingly, lymph node metastasis occurred more easily, and the staging was also relatively higher in patients with high SNHG1 expression. Of note, there were significant differences in DFS and OS between patients in high SNHG1 expression group and those in low SNHG1 expression group. Results of this study showed that the median DFS was 42 months in high SNHG1 expression group, and 79 months in low SNHG1 expression group ($p = 0.022$). The median survival time was about 57 months in high SNHG1 expression group and about 79 months in low SNHG1 expression group ($p = 0.007$). In summary, SNHG1 is a factor of poor prognosis of patients with laryngeal carcinoma.

To explore the mechanism of SNHG1 in laryngeal carcinoma, SNHG1 in laryngeal carcinoma cells was knocked down, and its effects on cell proliferation, apoptosis, invasion, and metastasis were explored. Results revealed that down-regulation of SNHG1 expression could significantly inhibit the proliferation of laryngeal carcinoma cells. Anti-apoptosis is one of the characteristics of tumor cells[18], and previous studies[12,19] have shown that SNHG1 can promote cell proliferation, and inhibiting SNHG1 can promote tumor cell apoptosis. Similarly, we found that SNHG1 knockdown could significantly promote the apoptosis of laryngeal carcinoma cells. Results of Western blotting showed that SNHG1 knockdown could activate the mitochondrial apoptotic pathway and up-regulate the Bax/Bcl-2 ratio, thereby increasing the expressions of cleaved Caspase-9 and cleaved PARP, ultimately promoting cell apoptosis. Previous studies[19-21] have shown that SNHG1 can promote invasion and metastasis of a variety of tumors. Wang et al[20] revealed that SNHG1 can promote the EMT process of nasopharyngeal carcinoma cells, thereby promoting cell metastasis. However, clinical data in this work showed that the proportion of positive lymph node metastasis in patients with high SNHG1 expression was increased, indicating that SNHG1 is related to invasion and metastasis of laryngeal carcinoma cells. Furthermore, wound healing assay and transwell assay were performed for verification. Results showed that SNHG1 knockdown could inhibit the invasion and migration of HEp-2 cells *via* inhibiting the EMT process and the expressions of MMP-2 and MMP-9 in cells.

The above results indicate that SNHG1 is highly expressed in laryngeal carcinoma, and it is significantly correlated with lymph node metasta-

sis, TNM staging, and prognosis of patients with laryngeal carcinoma. Knockdown of SNHG1 can inhibit proliferation, invasion, and metastasis, and promote apoptosis of laryngeal carcinoma.

Conclusions

We showed that lncRNA SNHG1 plays a role as an oncogene in the occurrence and development of laryngeal carcinoma, and it is expected to become a molecular target for the diagnosis, prognosis, evaluation and even treatment of laryngeal carcinoma.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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