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LncRNA SNHG14 promotes the development of cervical cancer and predicts poor prognosis

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Abstract. – OBJECTIVE: The aim of this study was to explore the role of long non-coding RNA (LncRNA) small nucleolar RNA host gene 14 (SNHG14) in cervical cancer, and to further understand the possible underlying mechanism.

PATIENTS AND METHODS: Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) was performed to detect the expression of SNHG14 in cervical cancer. The relationship between SNHG14 expression with clinic-pathological features and pro[illegible] pati[illegible] aly[illegible] Counting Kit-[illegible] (CCK-8), 5-Ethyny[illegible] 2'-deox[illegible]uridine (E[illegible]U) and flow cytometry were u[illegible]ed to ev[illegible]uate the [illegible]rolifer[illegible] atio[illegible] and apoptosis o[illegible]ells. At [illegible] time, th[illegible] cha[illegible]ges in the expre[illegible]sion of [illegible]poptos[illegible]-relat[illegible] pro[illegible]ins after SNHG14 [illegible]nockdo[illegible]n were d[illegible]tect[illegible]d.

RESULTS: Compared with normal cervical tissues, the expression of SNHG14 was significantly higher in cervical cancer tissues. The prognosis of patients with higher expression of SNHG14 was worse than those with a lower level. The relationship between the expression of SNHG14 and clinicopathological features of patients with cervical cancer was further analyzed. The results demonstrated that a higher expression level of SNHG14 indicated later tumor stage and higher incidence of lymph node metastasis. Compared with normal cervical epithelial cell line End1/E6E7, the level of SNHG14 in cervical cancer cell lines (including SW756, SiHa and HeLa) was markedly up-regulated. Among them, SW756 and SiHa cells exhibited the highest level of SNHG14. After knocking down SNHG14, the viability and proliferation ability of SW756 and SiHa cells were remarkably decreased, while cell apoptosis was increased. Subsequently, we investigated the possible underlying mechanism. The results found that the knockdown of SNHG14 enhanced the activation of caspases-3, and increased the protein expression of Bax, JAK2 and STAT3, whereas decreased the expression of Bal-2 and Bid.

CONCLUSIONS: LncRNA SNHG14 was highly expressed in cervical tumor tissues or cells, which could promote the progression of cervical cancer. Furthermore, SNHG14 might be associated with the activation of the JAK-STAT pathway.

Key Words
Cervical cancer, LncRNA SNHG14, JAK-STAT, Cell apoptosis.

Introduction

Cervical cancer (CC) is one of the most common fe[illegible]e ca[illegible]cers wo[illegible]rwide, [illegible]pecially in China[1]. According to in[illegible]complete [illegible]statistics of [illegible]e W[illegible]ld Health Organiz[illegible]tion, th[illegible] [illegible]out 0,00[illegible] new cervical can[illegible]r patien[illegible] every year ov[illegible] th[illegible] world, [illegible]ith a y[illegible]unger t[illegible]nd of incidence[4,5]. At the same time, nearly 270,000 people die from cervical cancer annually, ranking third among all cancers[6,7]. The main risk factors for clinically induced cervical cancer include persistent infection of high-risk human papillomavirus (HPV)[8,9], such as HPV 16, 18, 31 and 33. However, increasing evidence has indicated that HPV infection alone is not sufficient to induce malignant transformation of normal cervical cells[4,10]. Therefore, the molecular mechanism of cervical cancer remains to be elucidated. Furthermore, more tumor-specific molecular markers are needed to be confirmed.

Long non-coding RNAs (LncRNAs) are a type of ncRNAs with more than 200 nucleotides in length. They are involved in the regulation of gene expression by affecting transcriptional regulation, post-transcriptional regulation, chromatin modification and gene imprinting[11-13]. Researchers[14-17] have demonstrated that lncRNAs are closely related to the occurrence and progression of malignant tumors, especially non-small cell lung cancer, colorectal cancer and breast cancer. Gibb et al[18] have shown that lncRNAs participate in various processes of cellular life activities, including cell growth, proliferation, cell cycle regulation,

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differentiation and apoptosis. It is hypothesized[19] that lncRNAs may become important molecules for accurate pre-diagnosis and targeted specific treatment of cancer. Therefore, the biological function and clinical significance of lncRNAs may play a critical role in genetic and phenotypic regulation of diseases including cancer.

Research has indicated that lncRNA is closely associated with the occurrence of cervical cancer. The technique of long-segment gene expression relationship sequence was used to detect 16 cases of different grades of intraepithelial neoplasia. A total of 1056 lncRNAs have been found to express in human cervical tissues. Meanwhile, the differential expression of lncRNAs has been determined in CIN to explore whether they contribute to the development of cervical cancer[20]. Sun et al[21] have found that the down-regulation of MALAT1 by shRNA in cervical tumor cells inhibits cell invasiveness and metastasis. However, the absence of H19 gene imprinting function lea to increased H level i cervica tissues. Th may eventually romote PV infec on and eve ancer[22]. n our w vestiga ed e role of LncRN small n cleolar NA h ge 14 (SNHG14) in ervical cancer and nitia ly explored the underlying mechanism.

Patients and Methods

Sample Collection

30 tumor tissues and adjacent normal tissues were collected from patients with cervical cancer in the Yantai Yuhuangding Hospital between October 2015 and October 2017. Collected tissue specimens were quickly placed in sterile and non-enzymatic cryopreservation tubes, which were then transferred to liquid nitrogen for storage. All tissues were confirmed by pathology. None of the patients received anti-tumor treatment such as chemotherapy or radiotherapy before surgery. There were no significant differences in age, tumor location and pathological tissue classification of subjects. The investigation was approved by the Ethics Committee of the Yantai Yuhuangding Hospital. The informed consent was obtained from each subject before the study.

Cell Culture and Transfection

Normal endo-cervical epithelial cell line (End1/E6E7) and cervical cancer cell lines (SW756, SiHa, HeLa) were cultured in high glucose Dulbecco's Modified Eagle's Medium (DMEM) medium (Gibco, Grand Island, NY, USA) containing 10% fetal bovine serum (FBS; Gibco, Grand Island, NY, USA) in an incubator at 37°C. The culture medium was changed every other day. SNHG14-siRNA and NC dry powder were centrifuged and dissolved in the corresponding amount of diethyl pyrocarbonate (DEPC) water (Beyotime, Shanghai, China) according to the synthesis report of Shanghai Jima Pharmaceutical Technology Co., Ltd. (Shanghai, China). Subsequently, they were mixed, prepared into a working solution with a final concentration of 20 μmol/L and stored at -20°C. 24 hours after inoculation, cell transfection was carried out according to the instructions of Lipofectamine TM2000 (Invitrogen, Carlsbad, CA, USA) when the adherent cells reached about 50%. After 6 hours, the medium was changed. The cells were incubated for another 48 h for subsequent experiments.

RNA Extraction and Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR)

1 mL of TRIzol (Invitrogen, CA, USA) was added to extract total RNA in tissues or cells. RNA was then carefully extracted according to the experimental procedures. The concentration of RNA was determined by ultra-micro UV spectrophotometer. When the A260/A280 of RNA solution was 1.8 to 2.1, the purity was acceptable. 1 μg of total RNA was taken, and Reverse Transcription was performed according to the instructions of the reverse transcription kit to obtain complementary deoxyribose nucleic acid (cDNA). Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) reaction solution was prepared according to the instructions of SYBR fluorescence quantitative premixing kit (TaKaRa, Otsu, Shiga, Japan), with a total system of 10 μL. Specific PCR reaction conditions were: pre-denaturation at 95°C for 30 s, 95°C for 5 s, and 60°C for 31 s, for a total of 40 cycles. The experiment was repeated three times. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was taken as an internal reference. Primer sequences used in this study were as follows: SNHG14: F: GGGTGTTTACGTAGACCAGAACC, R: CTTCCAAAAGCCTTCTGCCTTAG GAPDH F: CGCTCTCTGCTCCTCCTGTTC, R: ATCCGTTGACTCCGACCTTCAC.

Cell Counting Kit-8 (CCK-8) Assay

48 hours after transfection, the cells were seeded into 96-well plates at a density of 2 × 10^3/100

μL. Cell Counting Kit-8 detection (CCK-8; Dojindo, Kumamoto, Japan) was performed at 0 h, 24 h, 48 h, and 72 h, respectively. The serum-free medium was added to replace the complete medium, and 10 μL of CCK-8 solution was added to each well. Subsequently, the cells were incubated at 37°C in a 5% CO_2 incubator for another 2 h. Finally, optical density (OD) value at the wavelength of 450 nm was detected by a microplate reader.

5-Ethynyl-2'- Deoxyuridine (EdU) Assay

48 h after transfection, EdU staining was performed according to the instructions of Guangdong Ruibo EdU reagent (Guangzhou, China). Briefly, 300 μL of EdU (50 μl/L) was added to each well, followed by incubation for 2 h. Afterward, 300 μL of 1 x Apollo staining reaction was added and incubated for 30 min. Then, 300 μL of 1 x Hoechst 33342 reaction solution was used to decolorize at room temperature in the dark. Subsequently, the cells were observed and photographed using CX23 fluorescence microscopy (40x). 4 different fields of view were randomly selected for each sample. EdU cell proliferation rate = number of cells with new proliferating DNA labeled with EdU/total number of cells with nuclei labeled with Hoechst 33342 x 100%.

Flow Cytometry

48 h after transfection, cell apoptosis was observed by Annexin V-FITC (fluorescein isothiocyanate)/Propidium Iodide (PI) double staining (Thermo Fisher Scientific, Waltham, MA, USA). Cells in each group were collected, adjusted to the density of 5×10^5 cells/mL and washed with Phosphate-Buffered Saline (PBS; Gibco, Grand Island, NY, USA). After the cells were re-suspended in 500 μL of binding buffer, 5 μL of Annexin V-FITC and 10 μL of PI were added at 18-28°C in the dark. Subsequently, the mixture was centrifuged for 15 min and analyzed using a flow cytometer. The experiment was repeated three times.

Western Blot Assay

The cells were washed twice with PBS 48 h after transfection, followed by lysis with protein lysate. Then, the cells were fully lysed by ultrasound on the ice and the supernatant was centrifuged. The concentration of extracted protein was determined by the bicinchoninic acid (BCA) method (Pierce, Rockford, IL, USA). After being separated by sodium dodecyl sulphate (SDS) gel electrophoresis, the proteins were transferred onto polyvinylidene difluoride (PVDF) membranes (Roche, Basel, Switzerland) *via* wet transfer method. After blocking with 5% skim milk for 1 hour, the membranes were incubated with primary antibodies at 4°C overnight. On the next day, the membranes were washed with Tris-Buffered Saline and Tween 20 (TBST) 3 times and incubated with the corresponding secondary antibody at room temperature for 2 h. Finally, immunoreactive proteins were developed with the enhanced chemiluminescence (ECL) method (Thermo Fisher Scientific, Waltham, MA, USA).

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 17.0 software (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis. Measurement data were expressed as mean ± standard deviation ($\bar{x}\pm s$) and analyzed using the *t*-test. The χ^2-test was used for count data. The Kaplan Meier method was applied for survival analysis, and the difference was evaluated by time series test (Log-rank test). $p<0.05$ was considered statistically significant.

Results

SNHG14 Was Highly Expressed in Cervical Tumor Tissues

In this experiment, the expression of SNHG14 in cervical cancer tissues was significantly higher than that of normal tissues (Figure 1A). Based on the expression level of SNHG14 in 30 cases of cervical tumor tissues, the patients were divided into high expression group and low expression group (Figure 1B). Survival analysis of the two groups indicated that the survival rate of patients in the high SNHG14 expression group was significantly lower than that of the low expression group. This suggested that the higher expression of SNHG14 indicated worse prognosis of patients (Figure 1C). We then analyzed the relationship between the expression of SNHG14 and clinic-pathological features. The results found that the expression of SNHG14 in patients with tumor size ≥4 cm was markedly higher than those with tumor size <4 cm (Figure 1D). Meanwhile, the expression of SNHG14 in patients with FiGO III-IV was remarkably higher than those with FIGO I-II (Figure 1E). The expression of SNHG14 in the LM (lymphatic metastasis) group was higher than that of the NLM (lymph metastasis) group

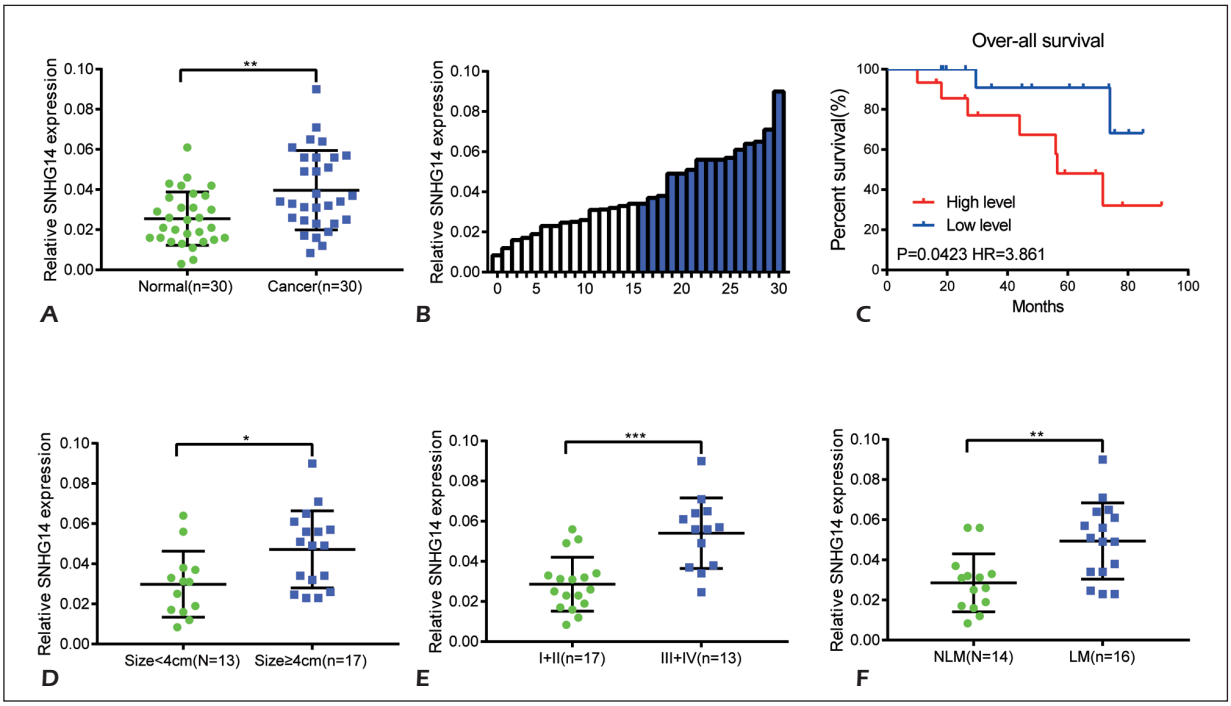

Figure 1. LncRNA SNHG14 was highly expressed in cervical cancer. **A**, The expression of SNHG14 in 30 normal cervical tissues was significantly lower than that of cervical cancer tissues. **B**, According to the median expression of SNHG14 in 30 cervical cancer tissues, they were divided into two groups. **C**, Survival analysis showed that the survival rate of patients in the SNHG14 high expression group was markedly lower than that of the low expression group. **D**, The expression level of SNHG14 in patients with tumor size ≥4 cm was remarkably higher than those with tumor size <4 cm. **E**, The expression level of SNHG14 in FIGO I-II group was lower than that of FIGO III-IV group. **F**, The expression level of SNHG14 in patients with LM (lymphatic metastasis) was higher than those with LM (lymphoid metastasis).

(Figure 1F). However, the SNHG14 level was not associated with age and presence/absence of stromal metastasis (Table I). The above results suggested that the higher SNHG14 level predicted larger tumor size, later stage and a higher incidence of lymph node metastasis.

Table I. Relationship between expression of SNHG14 and clinicopathological features in cervical cancer patients (n=30).

Clinicopathologic features	Total	SNHG14 expression		*p*-value
		Low (n=15)	High (n=15)	
Age (years)				0.8203
<45	8	3	5	
≥45	22	12	10	
Tumor size				0.0106*
< 4 cm	15	11	4	
≥4 cm	15	4	11	
FIGO stage				0.0281*
I-II	14	10	4	
III-IV	16	5	11	
Stromal metastasis				0.7125
Yes	17	8	9	
No	13	7	6	
Lymph node metastasis				0.0253*
Yes	12	9	3	
No	18	6	12	

*$p<0.05$

SNHG14 Promoted Proliferation of Cervical Cancer Cells

Similar to the population results, compared with normal cervical epithelial cells End1/E6E7, SNHG14 expression was significantly up-regulated in cervical cancer cell lines (including SW756, SiHa and HeLa). Among them, SW756 and SiHa exhibited the highest level of SW756. Therefore, they were selected for subsequent experiments (Figure 2A). By transfecting interfering sequence si-SNHG14, we successfully knocked down SNHG14 in SiHa and HeLa cells (Figure 2B-2C). Among them, si-SNHG14-1 had the most significant inhibitory effect, which was then used in subsequent experiments. Cell function experiments found that the activity of SiHa and HeLa cells was markedly decreased after the knockdown of SNHG14 (Figure 2D-2E). EdU re-

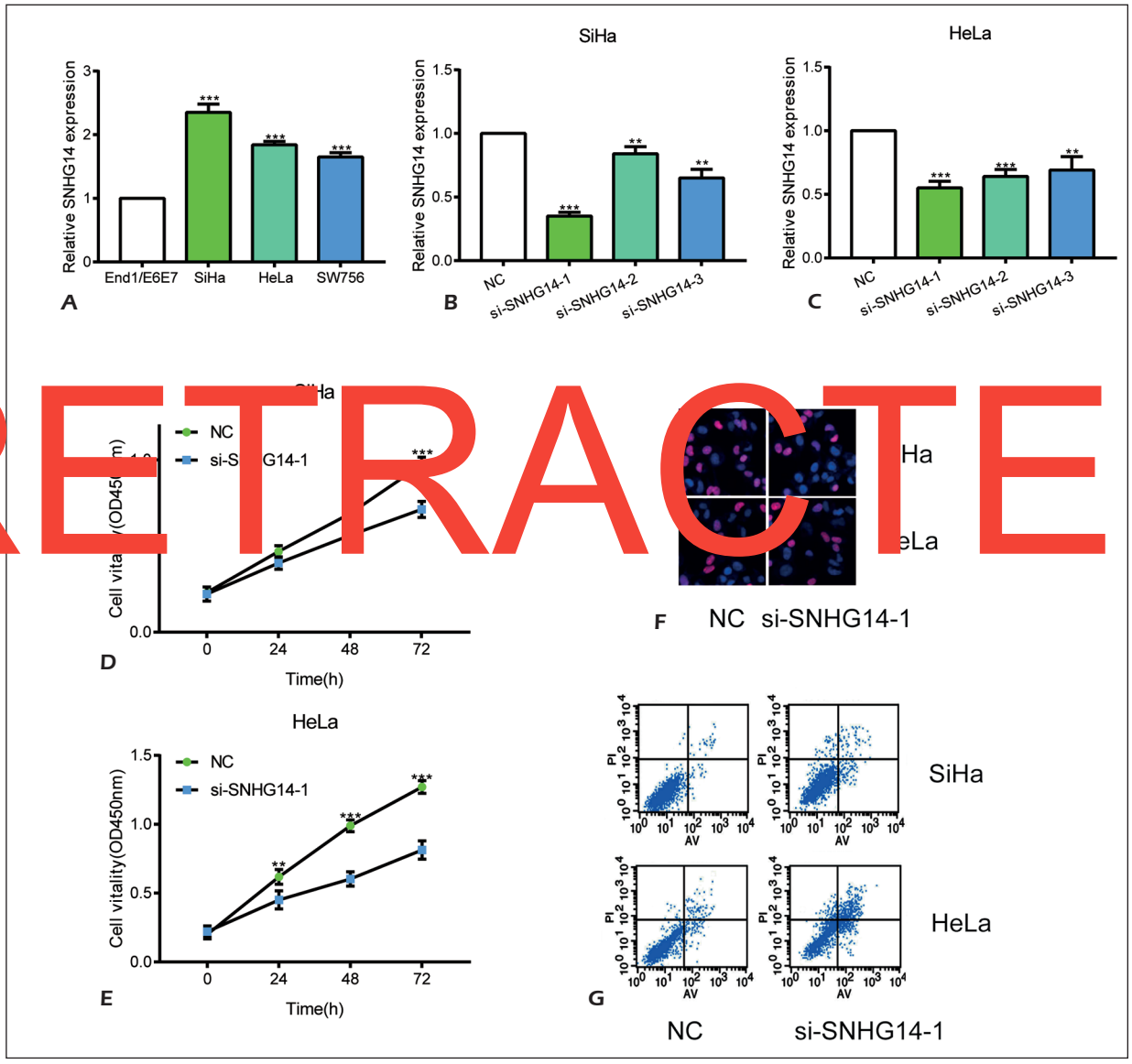

Figure 2. LncRNA SNHG14 promoted proliferation of cervical cancer cells. **A**, Compared with normal endo-cervical epithelial cell line (End1/E6E7), the expression level of SNHG14 was significantly increased in cervical cancer cells (SW756, SiHa, HeLa). **B**-**C**, After transfecting SNHG14 interference sequence, the expression of SNHG14 in SiHa and HeLa cells was markedly decreased. **D**-**E**, After knocking down SNHG14, the viability of SiHa and HeLa cells was remarkably reduced. **F**, After knocking down SNHG14, EdU experiments showed that the proliferation ability of SiHa and HeLa cells was significantly decreased. **G**, After inhibition of SNHG14 expression, the apoptosis of SiHa, HeLa cells was increased.

sults also demonstrated the inhibitory effect of SNHG14 on cell proliferation (Figure 2F). Flow cytometry revealed that the apoptosis of SiHa and HeLa cells increased remarkably after SNHG14 down-regulation (Figure 2G). The above experimental results suggested that after knocking down SNHG14, the proliferation ability of cervical cancer cells was decreased, whereas the apoptosis was increased.

Mechanism of SNHG14 Inhibition in Promoting Apoptosis of Cervical Cancer Cells

The mitochondrial pathway is the regulatory center of apoptosis[23]. Cytochrome C released into the cytoplasm activates Caspase-3, thereby inducing cell apoptosis. Proto-oncogenes or tumor suppressor genes, such as Bal-2 and Bax, regulate cell apoptosis by preventing or inducing the release of mitochondrial cytochromes[24]. Next, we examined the changes of apoptotic proteins in cells after inhibiting SNHG14. Meanwhile, we explored the mechanism of SNHG14 inhibition in pro[illegible] cells. We[illegible]ern blot results s[illegible]owed tha[illegible] after kno[illegible]kdown of [illegible]NHG14, the ac[illegible]vation [illegible]-3 wa[illegible] significantly enhanc[illegible]d. More[illegible]ver, [illegible] prote[illegible] expressions of Bax, [illegible]JAK2 a[illegible]d p-STA[illegible]3 w[illegible]re increased, whereas Bcl-2 and [illegible]id were markedly decreased (Figure 3A-3D).

Discussion

More and more studies have shown that lncRNA is involved in the development of malignant tumors. For example, it plays an important role in cervical cancer. Chen et al[25] have found that the level of BC200 is significantly up-regulated in cervical tumor tissues. This is the first lncRNA discovered to be associated with cervical cancer. Multiple studies have indicated that SNHG14 is abnormally expressed in tumors. Meanwhile, it plays a vital role in tumor-promoting genes in lung cancer[26] and gastric cancer[27] and acts as a tumor suppressor gene in gliomas[28]. However, its role in cervical cancer remains unclear. In this work, we aimed to explore the exact role of SNHG14 in cervical cancer.

We first found that SNHG14 expression was significantly up-regulated in cervical cancer tissues. Meanwhile, a higher expression indicated a larger tumor size, later stage, the greater possibility of lymph node metastasis, and worse prognosis. Sub[illegible]quent[illegible] cellular experim[illegible]nts were initially p[illegible]rformed and the p[illegible]ssible m[illegible]chanism was explor[illegible]d. The expression l[illegible]vel of SN[illegible]G14 in cervical t[illegible]mor cells was fou[illegible]d marke[illegible]y increased. A[illegible]er k[illegible]ocking [illegible]own SN[illegible]G14, th[illegible] proliferation ab[illegible]ity of c[illegible]rvical tumor cells decreased, while

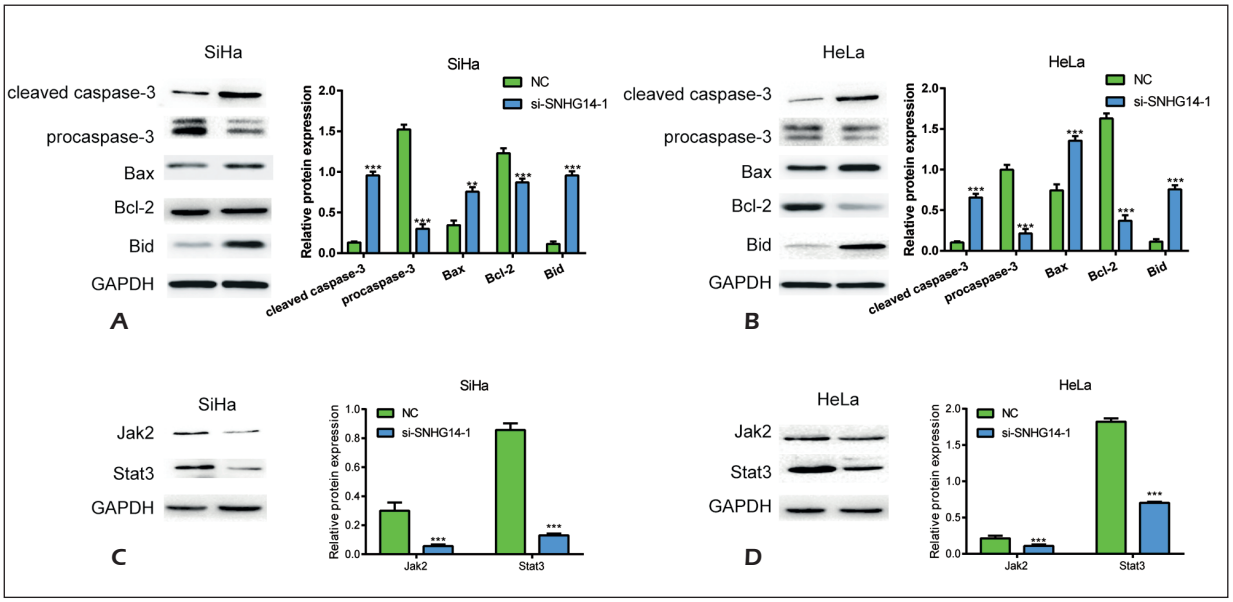

Figure 3. Mechanism of SNHG14 inhibition in promoting apoptosis of cervical cancer cells. **A-B**, After knockdown of SNHG14, Western blotting was used to detect the activation and division of caspases induced by SNHG14, and the expression of Bax, Bal-2 and Bid in SiHa and HeLa cells. **C-D**, After knocking down SNHG14, the JAK-STAT pathway was inhibited.

cell apoptosis increased. It was suggested that SNHG14 might promote the development of cervical cancer by promoting the JAK-STAT signaling pathway, inhibiting the activation of Caspases-3 and the expression of apoptotic proteins.

The JAK2/STAT3 signaling pathway is an important signal transduction pathway in cells. It is a common pathway for signal transduction of various cytokines and growth factors. Meanwhile, it plays a vital role in pathophysiological processes, such as embryonic development, hematopoietic cell formation, cell proliferation, differentiation, apoptosis, immunity and tumorigenesis. The expression of phosphorylated JAK2 (P-JAK2) and phosphorylated STAT3 (P-STAT3) is activated in tumor tissues of patients with cervical cancer. However, non-phosphorylated JAK2 and STAT3 are only expressed in normal tissues[29-31]. The process of apoptosis involves a series of molecular regulatory mechanisms, which are mainly regulated by intracellular apoptotic proteins. Caspase-3, located downstream of the apoptotic [illegible] is one of the most important apoptosis performers in the Caspase family. Moreover, it is the most critical factor in the apoptotic cascade. Apoptosis is caused by Caspase-mediated signaling pathway, which makes it essential for the transmission of apoptotic signals[32]. Bcl-2 and Bax, acting as apoptosis-related proteins, antagonize each other. If the proportion of bcl-2 is increased, it will inhibit cell apoptosis. On the contrary, if the proportion of Bax is increased, it will promote cell apoptosis[33]. Bid is another pro-apoptotic protein in the Bcl-2 family of proteins[34]. In our research, we found that after knocking down SNHG14, the expressions of pro-apoptotic proteins were significantly elevated, while the expression of the apoptosis-inhibiting protein was notably reduced.

Conclusions

We found that SNHG14 was highly expressed in cervical tumor tissues and cells. Furthermore, it promoted the progression of cervical cancer *via* activating the JAK-STAT signaling pathway.

Conflict of Interest

The authors declared no conflict of interest.

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