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# LncRNA SNHG15 promotes the proliferation of nasopharyngeal carcinoma *via* sponging miR-141-3p to upregulate KLF9

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**Abstract. – OBJECTIVE: Long non-coding RNAs (lncRNAs) have been identified to exert an oncogenic or anti-tumor function in malignant tumors. LncRNA SNHG15 is verified to be an oncogene in hepatocellular carcinoma, colorectal cancer, and prostate cancer. In this paper, we mainly investigate the potential influence of SNHG15 on the progression of nasopharyngeal carcinoma (NPC).**

**PATIENTS AND METHODS: SNHG15 levels in NPC tissues and cell lines were detected by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR). Correlation between SNHG15 level and prognosis of NPC patients was evaluated by the Kaplan-Meier method. Regulatory effects of SNHG15 on proliferative, colony formation abilities, and apoptosis of SUNE1 and CNE1 cells were assessed through a series of functional experiments. Potential miRNAs binding SNHG15 and the downstream gene of the microRNA (miRNA) were predicted by bioinformatics method, which was confirmed by Dual-Luciferase reporter gene assay and Western blot.**

**RESULTS: SNHG15 was upregulated in NPC tissues and cells. High level of SNHG15 indicated worse survival in NPC patients. Knockdown of SNHG15 markedly suppressed proliferative ability and induced apoptosis in SUNE1 and CNE1 cells. It is verified that miR-141-3p was the direct target binding SNHG15, and KLF9 was the downstream gene of miR-141-3p. SNHG15 was demonstrated to be a ceRNA to upregulate KLF9 by competitively binding miR-141-3p.**

**CONCLUSIONS: SNHG15 is upregulated in NPC tissues, and this aggravates the progression of NPC by absorbing miR-141-3p to upregulate KLF9.**

*Key Words:*
Nasopharyngeal carcinoma, SNHG15, Proliferation, MiR-141-3p, KLF9.

## Introduction

Nasopharyngeal carcinoma (NPC) is a highly prevalent malignancy throughout the world, which is originated in the head and neck[1]. Southeastern China and Southeast Asia are the risk areas of NPC[2]. Pathogenic factors of NPC are diverse, including EB virus infection, genetic factors, and smoking[3]. Radiotherapy is preferred to early-stage NPC, and radiotherapy combined chemotherapy is usually applied in advanced NPC patients[4]. Nevertheless, resistance of chemotherapy or radiotherapy markedly restricts the therapeutic efficacy[5]. It is urgent to uncover novel targets that could effectively improve the clinical outcomes of NPC.

Long non-coding RNAs (lncRNAs) are non-coding RNAs spanning over 200 nucleotides long[6]. Accumulating evidence has identified critical functions of lncRNAs in the regulation of gene expressions, epigenetics, chromatin structure, nuclear translocation, etc. They are important regulators in human diseases as well[7,8]. Maternal imprinting gene 19 (H19) is the first discovered lncRNA, which is upregulated in hepatocellular carcinoma and prostate cancer, serving as an oncogene[9,10].

MicroRNAs (miRNAs) are short-chain, non-coding RNAs with 22-25 nt long; they are able to degrade and inhibit translation of target mRNAs by binding 3′-untranslated region (3′-UTR) mRNAs[11]. Some studies[12] have proposed diagnostic and prognostic potentials of miRNAs in malignant tumors. So, miR-185 contributes to suppress proliferative ability and trigger apoptosis and autophagy in NPC cells by regulating HOXC6 and transforming growth factor-β1/mammalian target of rapamycin (TGF-β1/mTOR) pathway[13]. MiR-21 is a tumor-associated miRNA regulated by a specific lncRNA[14].

Previous studies[15-17] have demonstrated the oncogenic role of SNHG15 in many types of tumors, which stimulates the malignant growth and metastasis of tumor cells. This study mainly explores the potential influence of SNHG15 on the malignant progression of NPC.



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## Patients and Methods

### Sample Collection

A total of 50 NPC tissues and 28 normal nasopharyngeal epithelial tissues were collected and confirmed by pathology. All samples were stored at –80°C. Patients and their families in this study have been fully informed. This investigation was approved by the Ethics Committee of West China Hospital.

### Cell Culture

Human immortalized nasopharyngeal epithelial cell line (NP69) and NPC cell lines (SUNE1, CNE1, CNE2, and HONE1) were cultured in Roswell Park Memorial Institute-1640 (RPMI-1640; HyClone, South Logan, UT, USA) containing 10% fetal bovine serum (FBS; HyClone, South Logan, UT, USA), and 1% penicillin-streptomycin in a 5% $CO_2$ incubator at 37°C. Medium was regularly replaced. Cell passage was conducted at 80-90% confluence.

### Cell Transfection

SNHG15 siRNAs were provided by GenePharma (Shanghai, China). Cells were inoculated in 6-well plates and cultured to 60-70% confluence. Cell transfection was conducted using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). Six hours later, the fresh medium was replaced.

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

Cells were lysed to harvest RNAs using TRIzol method (Invitrogen, Carlsbad, CA, USA). The extracted RNAs were reversely transcribed following the instructions of PrimeScript RT reagent Kit (TaKaRa, Otsu, Shiga, Japan). RNA concentration and purity were determined using a spectrometer, and qualified RNA was applied for qRT-PCR using the SYBR Premix Ex Taq TM kit (TaKaRa, Otsu, Shiga, Japan). Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and U6 were used as internal references. Relative level was calculated using the $2^{-\Delta\Delta CT}$ method. Primer sequences were listed: SNHG15 Forward: 5′-GCTGAGGTGACGGTCTCAAA-3′; Reverse: 5′-GCCTCCCAGTTTCATGGACA-3′; MiR-141-3p Forward: 5′-CCTCGTCTTGAGCTGAGAGC-3′; Reverse: 5′-AGGGCTCCCTGAAGGTTACT-3′: KLF9 Forward: 5′-GCCGCCTACATGGACTTCG-3′; Reverse: 5′-GGATGGGTCGGTACTTGTTCA-3′; U6 Forward: 5′-GCTGAGGTGACGGTCTCAAA-3′; Reverse: 5′-GCCTCCCAGTTTCATGGACA-3′; GAPDH Forward: 5′-CGGAGTCAACGGATTTGGTCGTAT-3′; Reverse: 5′-AGCCTTCTCCATGGTGGTGAAGAC-3′.

### Cell Counting Kit-8 (CCK-8) Assay

Cells were seeded into 96-well plates. At the appointed time points, 10 μL of CCK-8 solution (Dojindo Laboratories, Kumamoto, Japan) was added in each well. The absorbance at 450 nm of each sample was measured by a microplate reader (Bio-Rad, Hercules, CA, USA).

### Colony Formation Assay

Cells inoculated in 6-well plates were cultured for 2 weeks, washed using FBS, and fixed in 4% polyformaldehyde. Cells were then dyed in 0.05% violet crystal for 15 min. Visible colonies containing over 50 cells were captured and calculated.

### Flow Cytometry

Cells were washed with phosphate-buffered saline (PBS) twice, digested and prepared to cell suspension with $1\times10^5$/mL. Cells were incubated in 1 mL of pre-cold 70% ethanol at 4°C overnight. On the other day, cells were washed with PBS twice and incubated with 100 μL of RNaseA at 37°C, in the dark for 30-min water bath. Subsequently, cells were dyed with 500 μL of propidium iodide (PI) at 4°C, in the dark for 15 min. At last, apoptotic rate was determined at 488 nm wavelength.

### Subcellular Distribution Determination

Cells were washed in PBS twice at 4°C, lysed on ice for 20 min, and centrifuged at 3000 r/min for 15 min. The supernatant was cytoplasmic fractions. Subsequently, the precipitant was repeatedly washed and centrifuged for three times. After incubation on ice for 20 min, the precipitant was subjected to vortex agitation and 15-min centrifugation at 12500 rpm/min. Finally, we got the supernatant, which was the nuclear fraction.

### Dual-Luciferase Reporter Gene Assay

Binding sequences between miR-141-3p with SNHG15 or KLF9 were predicted by bioinformatics method. Luciferase vectors were constructed based on the binding sequences by GenePharma

(Shanghai, China). Cells were co-transfected with wild-type/mutant-type vectors and miR-141-3p mimics/NC for 24 h, followed by luciferase activity determination.

### Western Blot

Cellular protein was extracted for determining protein concentration. Protein sample was loaded on sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE), transferred to polyvinylidene difluoride (PVDF) membrane (Millipore, Billerica, MA, USA) and blocked in 5% skim milk for 1 h. Membranes were reacted with primary and secondary antibodies. After washing with 1×Tris-Buffered Saline and Tween-20 (TBST) for 1 min, the chemiluminescent substrate kit was used for exposure of the protein band.

### Statistical Analysis

Statistical Product and Service Solutions (SPSS) 16.0 (SPSS Inc. Chicago, IL, USA) and GraphPad prism 5.0 (GraphPad Software Inc., San Diego, CA, USA) were used for data analysis. Data were expressed as mean ± standard deviation ($\bar{x} \pm$ SD). Data between two groups were compared using the *t*-test. Pearson correlation test was conducted to assess the expression relationship between two genes. Survival analysis was conducted by introducing Kaplan-Meier method. $p<0.05$ considered the difference was statistically significant.

## Results

### SNHG15 Was Upregulated in NPC Tissues and Cell Lines

Compared with 28 normal controls, SNHG15 was upregulated in 50 NPC tissues (Figure 1A). In particular, SNHG15 level remained higher in NPC patients with stage III and IV than those with stage I and II (Figure 1B). In addition, survival analysis based on SNHG15 was conducted by introducing Kaplan-Meier method. It is shown that NPC patients expressing high

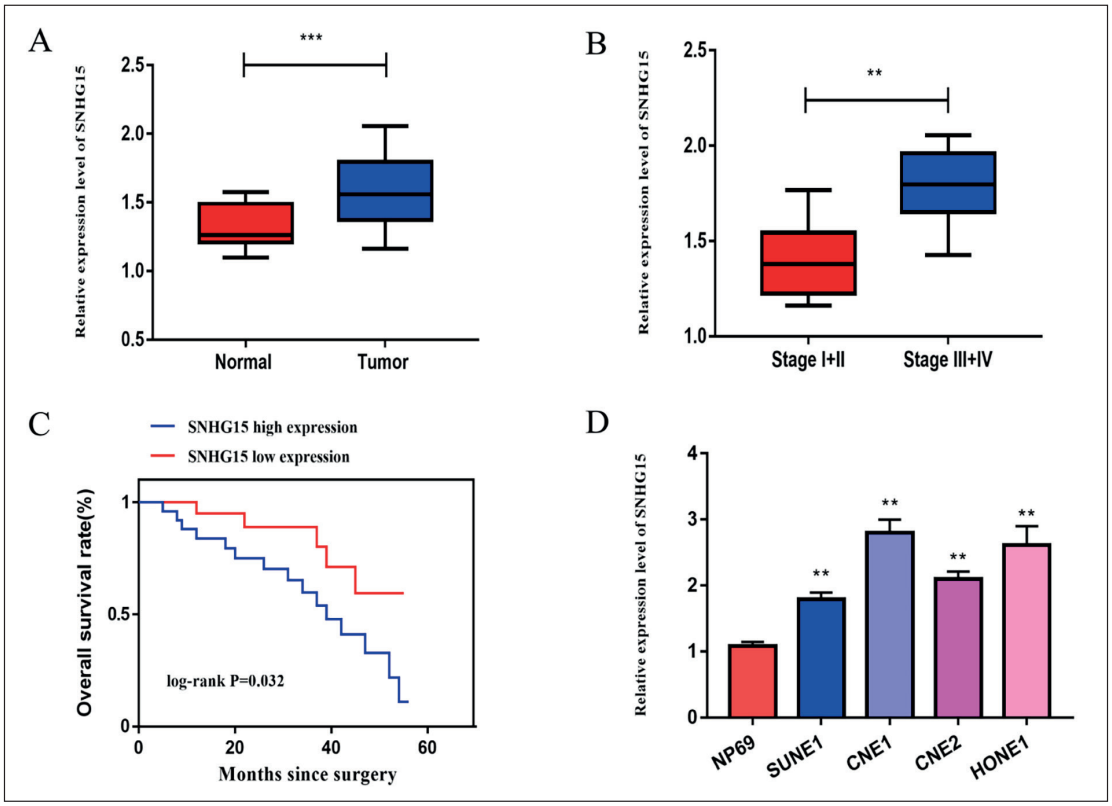


**Figure 1.** SNHG15 was upregulated in NPC tissues and cell lines. **A,** SNHG15 levels in normal tissues and NPC tissues. **B,** SNHG15 levels in NPC patients with stage I-II or stage III-IV. **C,** Overall survival in NPC patients expressing high or low level of SNHG15. **D,** SNHG15 level in human immortalized nasopharyngeal epithelial cell line (NP69) and NPC cell lines (SUNE1, CNE1, CNE2, and HONE1). *$p<0.05$, **$p<0.01$, ***$p<0.001$.

level of SNHG15 suffered worse prognosis ($p$=0.032) (Figure 1C). Consistently, *in vitro* level of SNHG15 was highly expressed in NPC cell lines (Figure 1D). It is suggested that SNHG15 exerted an oncogenic role during the progression of NPC.

### Knockdown of SNHG15 Suppressed Proliferative Ability in NPC

In the following experiments, SUNE1 and CNE1 cells were selected. First of all, transfection efficacy of two SNHG15 siRNAs (siRNA-1 and siRNA-2) was verified in NPC cells. QRT-PCR data illustrated that transfection of either one could effectively downregulate SNHG15, and the former one showed the better efficacy (Figure 2A). Subsequently, CCK-8 assay revealed the attenuated viability in SUNE1 and CNE1 cells transfected with SNHG15 siRNA-1 (Figure 2B). Colony formation assay identically showed that knockdown of SNHG15 inhibited clonality in NPC cells (Figure 2C). Moreover, apoptotic rate in NPC cells was elevated after knockdown of SNHG15 (Figure 2D). The above data demonstrated that SNHG15 could promote proliferative ability and inhibit apoptosis in NPC.

### SNHG15 Sponged MiR-141-3p

Subcellular distribution of a lncRNA determines its possible biological functions. Here, SNHG15 was found to be mainly distributed in cytoplasm, indicating its potential regulation at post-transcriptional level (Figure 3A). Through bioinformatics method, binding sequences in the promoter regions of miR-141-3p and SNHG15 were depicted (Figure 3B). Dual-Luciferase reporter gene assay uncovered the declined luciferase activity after co-transfection of SNHG15 WT vector and miR-141-3p mimics (Figure 3C). Hence, the binding relationship between SNHG15 and miR-141-3p has been verified. Compared with normal controls, miR-141-3p was lowly expressed in NPC tissues (Figure 3D). Spearman correlation test revealed a negative correlation between expression levels of SNHG15 and miR-141-3p in NPC tissues (R=-0.7925, $p$<0.001) (Figure 3E).

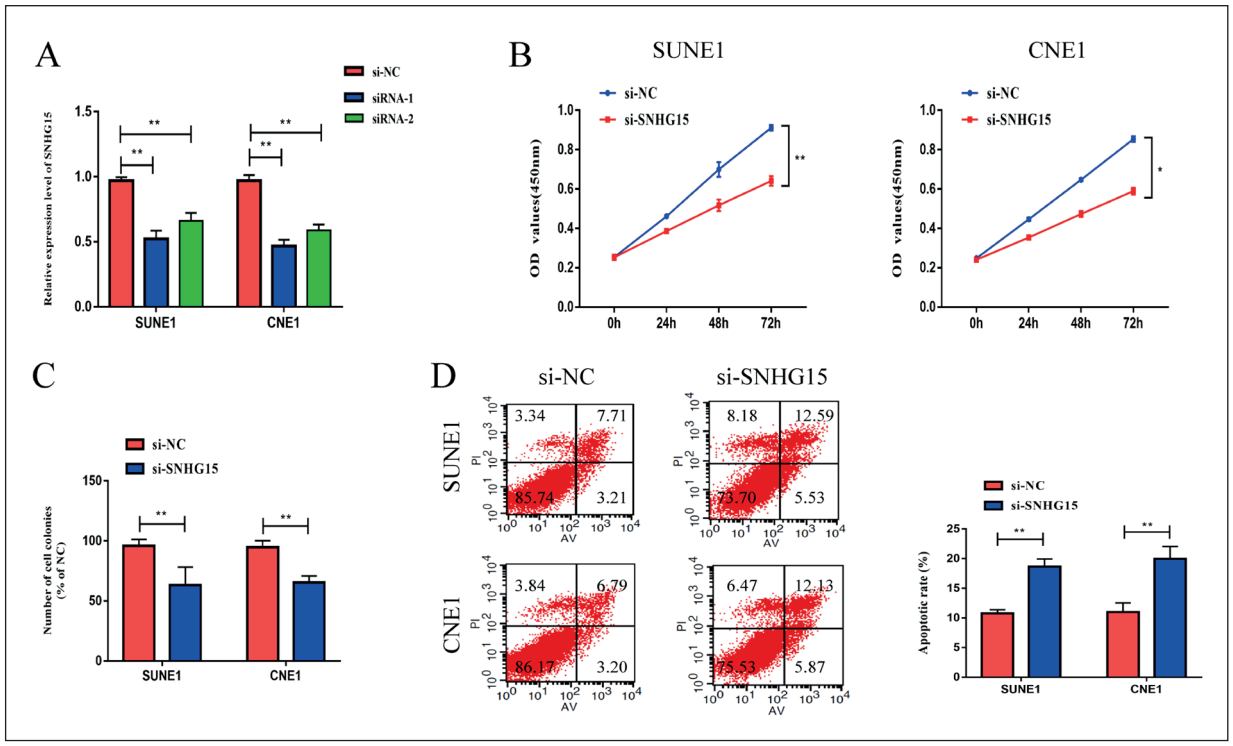


**Figure 2.** Knockdown of SNHG15 suppressed proliferative ability in NPC. **A,** Transfection efficacy of SNHG15 siRNA-1 and SNHG15 siRNA-2 in SUNE1 and CNE1 cells. **B,** Viability in SUNE1 and CNE1 cells transfected with si-NC or SNHG15 siRNA-1. **C,** Number of cell colonies in SUNE1 and CNE1 cells transfected with si-NC or SNHG15 siRNA-1. **D,** Apoptotic rate in SUNE1 and CNE1 cells transfected with si-NC or SNHG15 siRNA-1. *$p$<0.05, **$p$<0.01.

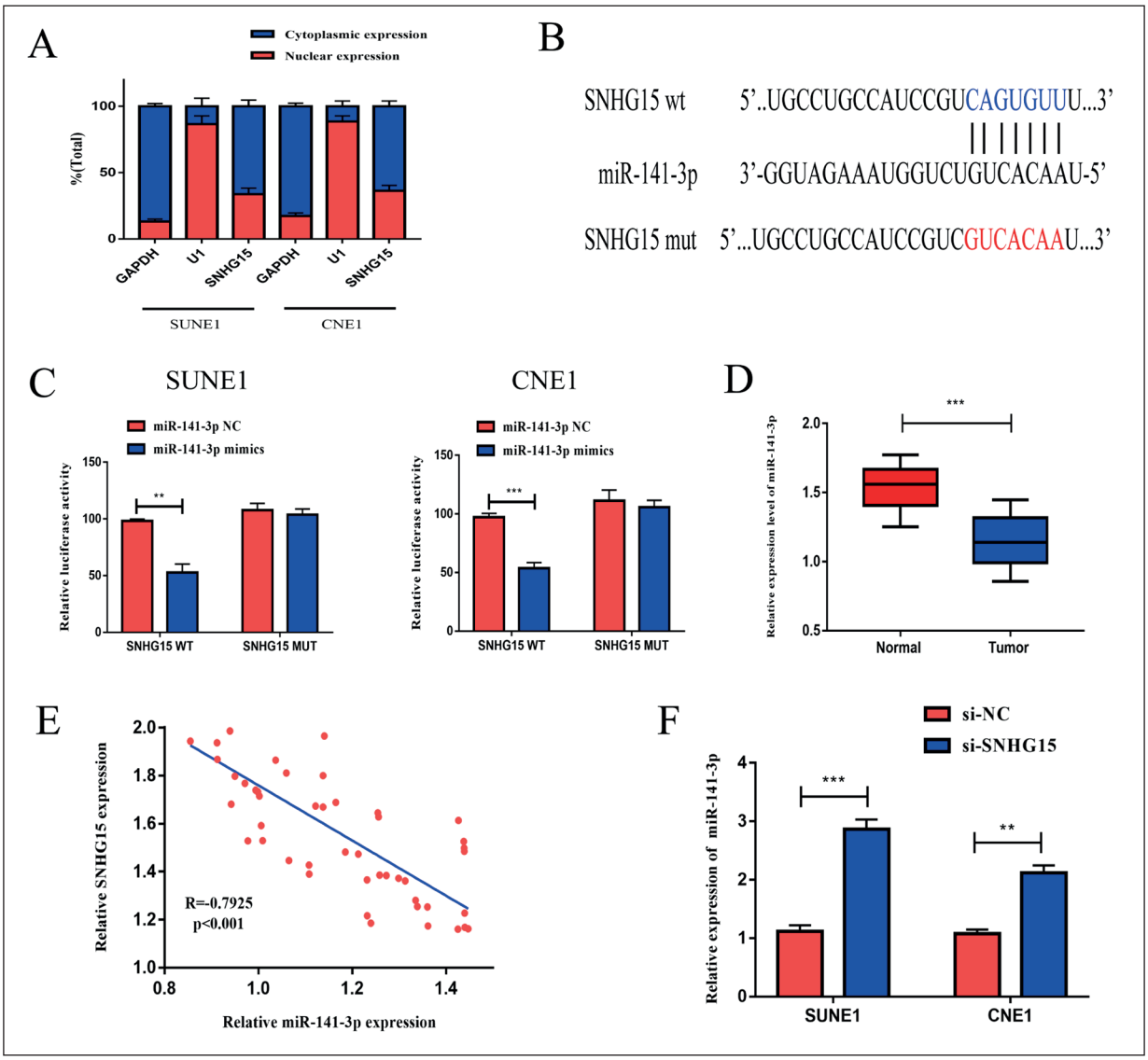


**Figure 3.** SNHG15 sponged miR-141-3p. **A,** Subcellular distribution of SNHG15 in SUNE1 and CNE1 cells. GAPDH and U1 were the internal reference of cytoplasmic fraction and nuclear fraction, respectively. **B,** Predicted binding sequences in the promoter regions of SNHG15 and miR-141-3p. **C,** Luciferase activity in SUNE1 and CNE1 cells co-transfected with SNHG15 WT/SNHG15 MUT and miR-141-3p mimics/NC. **D,** MiR-141-3p levels in normal tissues and NPC tissues. **E,** A negative correlation between expression levels of SNHG15 and miR-141-3p in NPC tissues. **F,** MiR-141-3p level in SUNE1 and CNE1 cells transfected with si-NC or SNHG15 siRNA-1. $^{**}p<0.01$, $^{***}p<0.001$.

Moreover, transfection of SNHG15 siRNA-1 markedly downregulated miR-141-3p in NPC cells (Figure 3F).

### *MiR-141-3p Directly Downregulated KLF9*

Potential downstream genes of miR-141-3p were predicted on TargetScan, and finally KLF9, the most optimal one was selected. Binding sequences between miR-141-3p and KLF9 were listed in Figure 4A. In a similar way, the binding relationship between miR-141-3p and KLF9 was verified by Dual-Luciferase reporter gene assay (Figure 4B). In NPC tissues, KLF9 was highly expressed (Figure 4C). Both mRNA and protein levels of KLF9 were downregulated in SUNE1 and CNE1 cells overexpressing miR-141-3p (Figure 4D, 4F). As a result, SNHG15/miR-141-3p/KLF9 regulatory loop has been observed to stimulate the malignant progression of NPC.

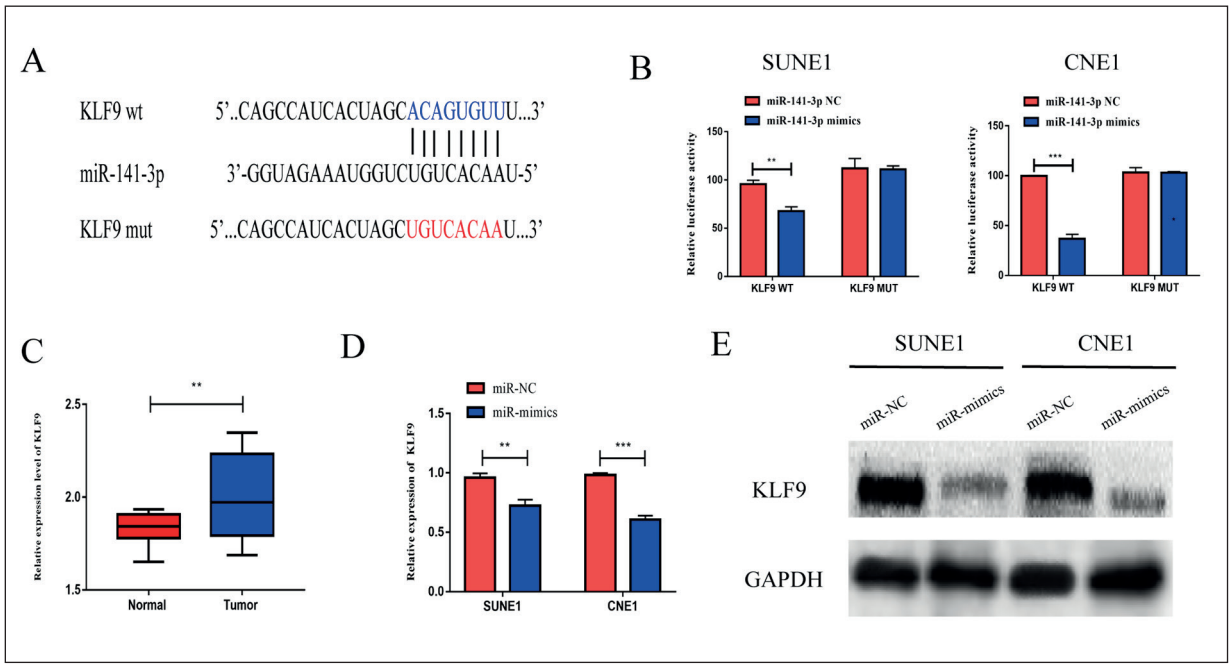


**Figure 4.** MiR-141-3p directly downregulated KLF9. **A,** Predicted binding sequences in the promoter regions of miR-141-3p and KLF9. **B,** Luciferase activity in SUNE1 and CNE1 cells co-transfected with KLF9 WT/KLF9 MUT and miR-141-3p mimics/NC. **C,** KLF9 levels in normal tissues and NPC tissues. **D,** The mRNA level of KLF9 in SUNE1 and CNE1 cells transfected with NC or miR-141-3p mimics. **E,** The protein level of KLF9 in SUNE1 and CNE1 cells transfected with NC or miR-141-3p mimics. **$p$<0.01, ***$p$<0.001.

## Discussion

There are about 80,000 newly onset cases and 50,000 death cases of NPC annually[18]. Sensitive hallmarks contribute to effective and accurate diagnosis of NPC in the early stage, thus improving the clinical outcome of affected patients[19,20]. However, drug resistance is a major obstacle that restricts therapeutic efficacy of malignant tumors. As a result, clarifying mechanisms of pathogenesis and etiology of NPC is of significance[21].

LncRNAs used to be considered as non-functional transcripts. Later, it has been verified that lncRNAs are critical regulators in life activities and tumor progression[22]. They are widely involved in every aspect of tumor cell behaviors[23]. So, lncRNA RP1 enhances proliferative and migratory abilities of breast cancer cells *via* inactivating the p27kip1 pathway[24]. Proliferative and metastatic abilities of colorectal cancer cells are enhanced through the interaction between lncRNA ZFAS1 and miR-484[25]. As a newly discovered lncRNA, SNHG15 is upregulated in gastric cancer tissues and closely linked to invasive depth, TNM staging, lymphatic metastasis, and poor prognosis of gastric cancer patients[26].

Dysregulated miRNAs could lead to carcinogenesis[27]. LncRNA-miRNA interaction has been proposed, which is extensively involved in pathological conditions[28]. By downregulating KLF9, miR-141-3p promotes the malignant progression of prostate cancer[29]. In glioma and breast cancer, miR-141-3p acts on p27/Kip1, CDK6, PR, and Stat5a by regulating the activity of transcription factor 5, serving as a tumor-suppressor gene[30-32].

KLF9 is a transcription factor related to differentiation, which belongs to the Sp1 C2H2 zinc finger family. KLF9 widely participates in nerves system development, differentiation, proliferation, and apoptosis of B cells. Zucker et al[33] suggested that KLF9 is the downstream gene of the anti-oxidant transcription factor Nrf2, which is closely associated with oxidative stress. In addition, KLF9 affects the progression of glioma by regulating ROS production.

In this paper, SNHG15 was markedly upregulated in NPC tissues and cell lines. Kaplan-Meier curves revealed worse survival in NPC patients expressing high level of SNHG15. Subsequently, *in vitro* experiments detected that SNHG15 could promote proliferative ability and inhibit apoptosis in NPC cells. Recently, ceR-

NA theory proposed that lncRNA could absorb miRNAs to further upregulate the downstream genes, thus affecting disease progression. Here, subcellular distribution analysis uncovered that SNHG15 was mainly located in cytoplasm, suggesting the possibility of SNHG15 as a ceRNA. Subsequently, the regulatory loop SNHG15/miR-141-3p/KLF9 was identified to aggravate the malignant progression of NPC. In the future, *in vivo* experiments are required to further validate our findings.

## Conclusions

To sum up, SNHG15 is upregulated in NPC tissues, which absorb miR-141-3p to upregulate KLF9. SNHG15/miR-141-3p/KLF9 regulatory loop aggravates the progression of NPC, and it could be utilized as potential therapeutic targets for NPC.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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