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Downregulation of lncRNA SNHG7 inhibits proliferation and invasion of nasopharyngeal carcinoma cells through repressing ROCK1

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Abstract. – OBJECTIVE: Recent studies have revealed the important role of long noncoding RNAs (lncRNAs) in the progression of tumorigenesis. This study aimed to identify the [illegible]logical function of lncRNA small nucleol[illegible] host gene 7 (SNHG7) in the progression of [illegible]o-pharyngeal carcinoma (NPC).

PATIENTS AND METHODS: LncRNA SN[illegible] expressions in NPC cell lines and 50 pair[illegible] NPC tissue samples were dete[illegible] Real-tim[illegible] quantitative polymerase cha[illegible]eac[illegible] (RT-qP-CR). Transwell assay, wou[illegible]ealing [illegible]say and proliferation assay were [illegible]ducted[illegible]ate the in vitro function o[illegible]SN[illegible] nograft model was [illegible]blish[illegible] determining the *in vivo* effect[illegible]NHG7 on [illegible] formation and metastasis[illegible]C. The und[illegible]g mechanism of SN[illegible]in[illegible]iating the p[illegible]gression of NPC was e[illegible]plored [illegible]qPCR and Western blot.

RES[illegible]: SNHG7 expres[illegible]was remarkably down[illegible]ulated [illegible]NPC tissue[illegible] compared with tha[illegible]djace[illegible]ormal samples. Knockdown of SNH[illegible]tt[illegible]ted p[illegible]feration, invasion and migrati[illegible]NPC c[illegible] Moreover, tumor size [illegible]he n[illegible]r o[illegible]tastatic nodules were re-du[illegible] in n[illegible]ministrated with NPC cells tra[illegible]ected wi[illegible]n-SNHG7. Knockdown of SN-HG[illegible]regulated ROCK1 at mRNA and pro-[illegible]ides, the expression of ROCK1 in [illegible]mor tissues was positively correlated to SN-[illegible]7 expression.

[illegible]NCLUSIONS: Knockdown of SNHG7 inhibits [illegible]gration, invasion and proliferation of NPC cells through downregulating ROCK1, which may offer a new therapeutic intervention for NPC patients.

[illegible]Words:
[illegible]n noncodi[illegible]RNA, SNHG7, Nasopharyngeal car[illegible] ROC[illegible]

Introduction

Nasopharyngeal carcinoma (NPC) is one of the most common head and neck epithelial cancers with high morbidity in Southern China and Southeast Asia[1]. With the advances made in intensity-modulated radiotherapy and combined chemoradiotherapy, the prognosis for patients with local and regional NPC has been significantly improved. However, metastatic rate remains high in NPC patients, which is the leading cause of treatment failure and cancer-related death in NPC, with a median survival about 12 months[2,3]. Therefore, clarifying the molecular mechanisms underlying NPC is urgently required to promote the development of effective individualized therapy and improve the clinical outcomes of NPC patients. With the development of high-throughput sequencing and microarrays, researchers have discovered that more than 90% of mammalian genome can be transcribed into noncoding RNAs (ncRNAs). Long noncoding RNAs (lncRNAs), one subgroup of ncRNAs in over 200 nt long, are important clusters of transcripts with little protein-coding potential. Recently, evidence proved that lncRNAs are important regulators in many biological behaviors, including carcinogenesis. For example, lncRNA TP73AS1 dramatically

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promotes cell apoptosis and depresses cell proliferation in colorectal cancer by functioning as a competing endogenous RNA sponging miR103 to modulate the expression of PTEN (gene of phosphate and tension homology deleted on chromosome ten)[5]. Long non-coding RNA ZFAS1 promotes nasopharyngeal carcinoma through activating Wnt/beta-catenin pathway[6]. In addition, lncRNA CDKN2BAS promotes cell growth and migration in hepatocellular carcinoma through miR-153-5p/ARHGAP18 signaling pathway[7]. However, the potential role of lncRNA small nucleolar RNA host gene 7 (SNHG7) in the development of NPC remains unexplored. In the present study, expression level of lncRNA SNHG7 was remarkably upregulated in NPC samples. Moreover, functional experiments revealed that knockdown of SNHG7 depressed cell proliferation, invasion and migration in NPC. Furthermore, we discovered that lncRNA SNHG7 exerted its role in the progression of NPC by upregulating ROCK1.

Patients and Methods

Tissue Specimens

Paired NPC tissues and adjacent non-[tumor] tissues (≥ 5 cm away from the tumor edge) were surgically resected from 50 NPC patients undergoing surgery from February 2[0]... December 2018 in the Affiliated Hospital of Qingdao University. The Ethics Committee of the Affiliated Hospital of Qingdao University approved the study protocol, and all participants provided written informed consents.

Cell Lines

Human NPC cell lines CNE2, CNE1, 5-8F and 6-18B and immortalized normal nasopharyngeal epithelial cell line NP69 were offered by the Chinese Academy of Science (Shanghai, China). Cells were cultured in Roswell Park Memorial Institute 1640 (RPMI-1640) (HyClone, South Logan, UT, USA) containing 10% fetal bovine serum (FBS) (Gibco, Rockville, MD, USA) and 1% penicillin (epidermal growth factor was applied for culturing NP69 cells). Cells were maintained in an incubator with 5% CO_2 at 37°C.

Cell Transfection

Lentivirus expressing short-hairpin RNA (shRNA) directed against SNHG7 was provided by GenePharma (Shanghai, China). Complementary deoxyribose nucleic acid (cDNA) encoding SNHG7 was amplified and inserted into pcDNA3.1 (Invitrogen, Carlsbad, CA, USA). Cell transfection was conducted with Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). Transfection efficacy at 48 h was detected by reverse transcription quantitative polymerase chain reaction (RT-qPCR).

RNA Extraction and RT-qPCR

Total RNA from tissues and cells was extracted using TRIzol reagent (Invitrogen, Carlsbad, CA, USA). Then, total RNA was reversely transcribed to complementary deoxyribonucleic acids (cDNA) through reverse transcription Kit (TaKaRa Biotechnology Co., Ltd., Dalian, China). Polymerase chain reaction cycling conditions were as follows: 3 min at 95°C, 5 s at 95°C and 35 s at 60°C, for 40 cycles. Following were the primers used for RT-qPCR of SNHG7, forward: 5′- GTGACTTCGCCTGGATGGA-3′ and reverse: 5′-GGCCTCTAGTGTACCTTTATTCC-3′; glyceraldehyde 3-phosphate dehydrogenase (GAPDH), forward: 5′-GAAATCATGGGGCAATGCTGG-3′ and reverse: 5′-TGATGGCATGGACTGTGGGTCAT-3′. $2^{-\Delta\Delta Ct}$ method was utilized for calculating relative expression.

Western Blot

Total proteins were extracted from cells *via* radioimmunoprecipitation assay (RIPA) buffer and quantified by bicinchoninic acid (BCA) protein quantification kit (Beyotime, Shanghai, China). The target proteins were separated by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE). Protein samples were loaded on the polyvinylidene difluoride (PVDF) membrane (Millipore, Billerica, MA, USA). Membranes were blocked in 5% skim milk and incubated with primary antibodies (rabbit anti-GAPDH and rabbit anti-ROCK1) and secondary antibodies. Finally, the Pierce (Rockford, IL, USA) enhanced chemiluminescence (ECL) was utilized for visualizing Western blotting substrate immunoreactive bands.

Cell Proliferation Assay

Cell proliferation was monitored every 24 h by cell counting kit-8 (CCK-8) assay. Spectrophotometer (Thermo Scientific, Waltham, MA, USA) was utilized to measure the absorbance at 450 nm.

Wound Healing Assay

Cells seeded into 6-well plates, were cultured in Roswell Park Memorial Institute 1640 (RPMI-1640) medium overnight. After scratched with

a plastic tip, cells were cultured in serum-free (RPMI-1640). Wound closure was viewed at the appointed time points. Each assay was independently repeated for three times.

Matrigel Assay

24 h after transfection, 2×10^5 cells suspended in 100 µL of serum-free Roswell Park Memorial Institute-1640 (RPMI-1640) were applied on the top chamber of an 8-µm culture inserts (Corning, Corning, NY, USA) pre-coated with 50 µg Matrigel (BD Biosciences, Franklin Lakes, NJ, USA). Roswell Park Memorial Institute-1640 (RPMI-1640) containing 20% fetal bovine serum (FBS) was added in the bottom chamber. 24 h later, these inserts were treated by methanol for 30 min and stained by hematoxylin for 20 min. An inverted microscope (×40) (Nikon, Tokyo, Japan) was utilized for counting penetrating cells in three random fields.

Xenograft Model

For the tumor formation assay, transfected 5-8F cells were subcutaneously injected into NOD/SCID mice (6 weeks old). Tumor diameters were detected every 5 days after inoculation. The volume was calculated as the formula (volume = length × width^2 × 1/2). The mice were sacrificed and tumors were extracted after 4 weeks. For tumor metastasis assay, transfected 5-8F cells were injected into tail vein of NOD/SCID mice (6 weeks old). The mice were sacrificed and the lung tissues were extracted after 4 weeks. The number of metastatic nodules in the lung was counted. The animal experiments were approved by the Animal Ethics Committee of Qingdao University (Qingdao, China).

Statistical Analysis

Statistical analysis was conducted by Statistical Product and Service Solutions (SPSS) 18.0 (SPSS Inc., Chicago, IL, USA). Chi-square test, Student *t*-test and Kaplan-Meier method were selected when appropriate. Data were presented as mean ± SD (Standard deviation). $p<0.05$ was considered statistically significant.

Results

Expression Level of SNHG7 in NPC Tissues and Cell Lines

First, RT-qPCR was conducted for detecting SNHG7 expression in 50 paired NPC tissues and adjacent tissues. The result indicated that SNHG7 was significantly upregulated in NPC tissue samples than adjacent tissues (Figure 1A). Compared with the expression in NP69, SNHG7 level was significantly higher in NPC cells (Figu-

Knockdown of SNHG7 Repressed Cell Proliferation in Vitro

According to SNHG7 expression in cancer cells, 5-8F cells were selected for conducting SNHG7 knockdown model. The SNHG7 shR-

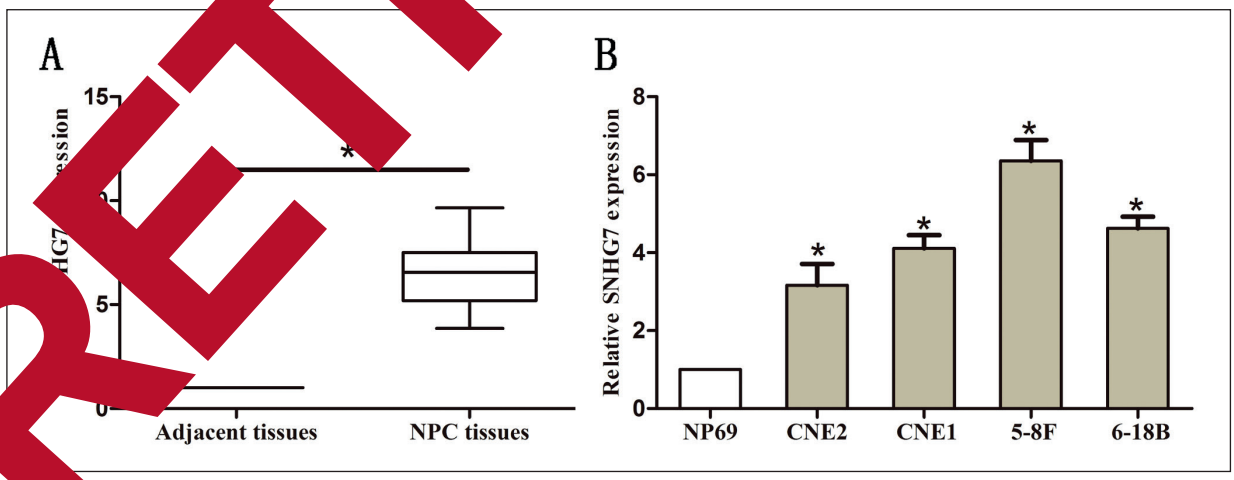

Figure 1. Expression levels of SNHG7 were upregulated in NPC tissues and cell lines. ***A,*** SNHG7 expression significantly increased in NPC tissues compared with adjacent tissues. ***B,*** Expression levels of SNHG7 relative to GAPDH were determined in the human NPC cell lines and immortalized normal nasopharyngeal epithelial cell line (NP69) by RT-qPCR. Data are presented as the mean ± standard error of the mean. *$p<0.05$.

NA (sh-SNHG7) and the empty vector (EV) were synthetized and transfected into 5-8F cells. Transfection of sh-SNHG7 markedly down-regulated SNHG7 level in 5-8F cells (Figure 2A). Furthermore, CCK-8 assay showed that the proliferation of NPC cells was suppressed after SNHG7 knockdown (Figure 2B).

Knockdown of SNHG7 Repressed Cell Migration and Invasion in Vitro

Wound healing assay found that knockdown of SNHG7 inhibited migration of NPC cells (Figure 2C). Furthermore, transwell assay showed that the invasion of NPC cells was inhibited after SNHG7 knockdown (Figure 2D).

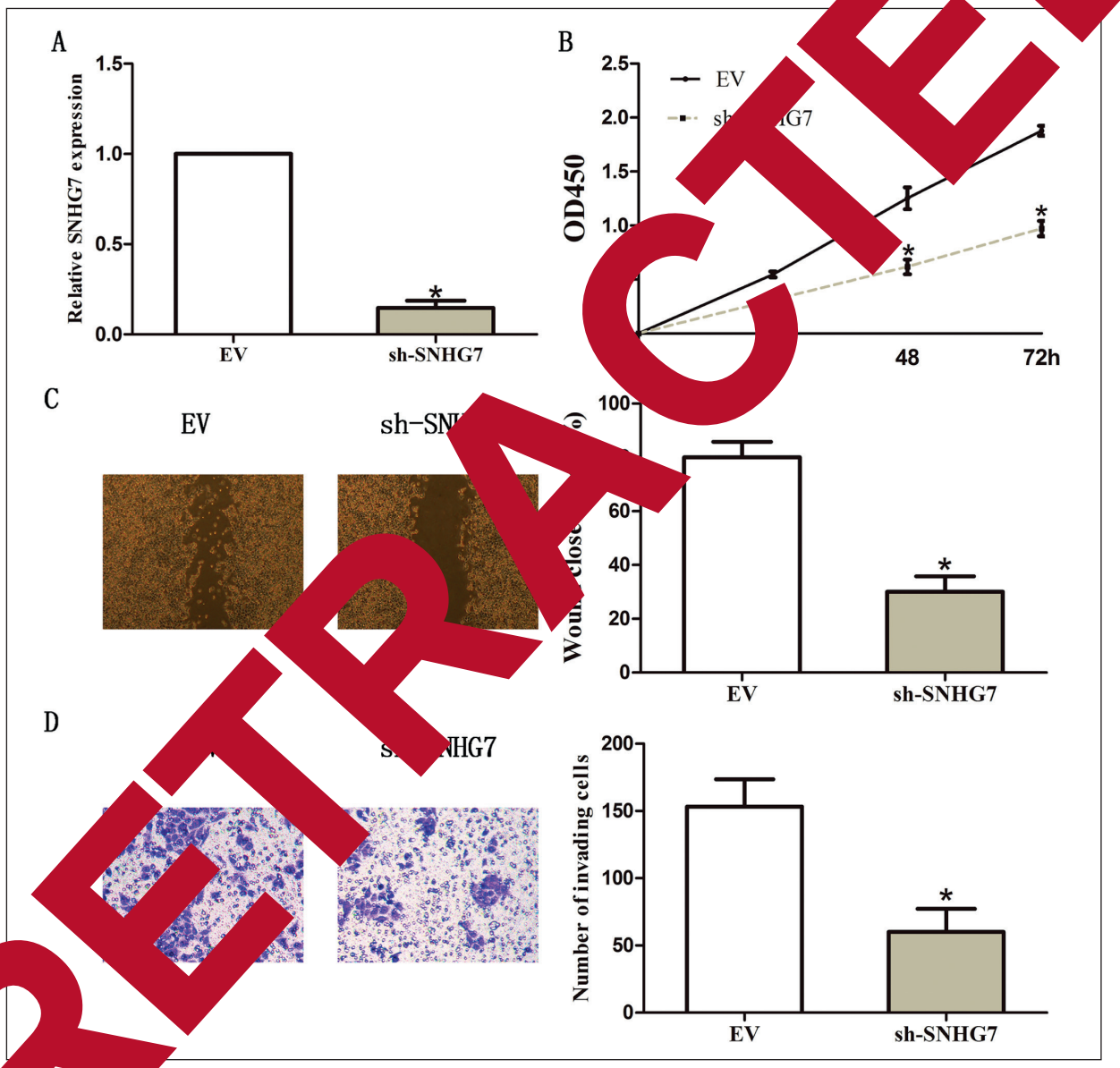

Figure 2. Knockdown of SNHG7 inhibited NPC cell proliferation, migration and invasion. ***A,*** SNHG7 expression in NPC cells transfected with empty vector (EV) or SNHG7 shRNA (sh-SNHG7) was detected by RT-qPCR. GAPDH was used as an internal control. ***B,*** CCK-8 assay showed that knockdown of SNHG7 significantly repressed proliferation in 5-8F NPC cells. ***C,*** Wound-healing assay showed that the invasive length of cells in SNHG7 lentivirus group significantly decreased compared with empty control group in 5-8F NPC cells (magnification: 40×). ***D,*** Transwell assay showed that knockdown of SNHG7 significantly repressed invasion in 5-8F NPC cells (magnification: 40×). The results represent the average of three independent experiments (mean ± standard error of the mean). *$p<0.05$, as compared with the control cells.

SNHG7 Promoted NPC Tumorigenesis via ROCK1

RT-qPCR results demonstrated that the mRNA expression of ROCK1 was downregulated in NPC cells transfected with sh-SNHG7 (Figure 3A). Western blot analysis results further verified that the protein expression of ROCK1 was downregulated in NPC cells transfected with sh-SNHG7 as well (Figure 3B). Subsequently, we further explored the interaction between SNHG7 and ROCK1. As a result, ROCK1 was upregulated in NPC tissues compared with that in adjacent tissues (Figure 3C). Linear correlation analysis showed a positive correlation between ROCK1 expression and SNHG7 expression in NPC tissues (Figure 3D).

SNHG7 Knockdown Inhibited Tumor Formation and Metastasis in Vivo

In vivo ability of SNHG7 in tumor formation and metastasis of NPC was detected. The tumor size in sh-SNHG7 group was smaller compared with that in EV group (Figure 4A). The weight of dissected tumors in sh-SNHG7 group was smaller compared with that in EV group (Figure 4B). The number of metastatic nodules in the lung from the sh-SNHG7 group was significantly decreased compared to EV group (Figure 4C). More SNHG7 expression in dissected tumor tissues was detected by RT-qPCR. The results showed that SNHG7 was highly expressed in sh-SNHG7 group compared with that in EV group (Figure

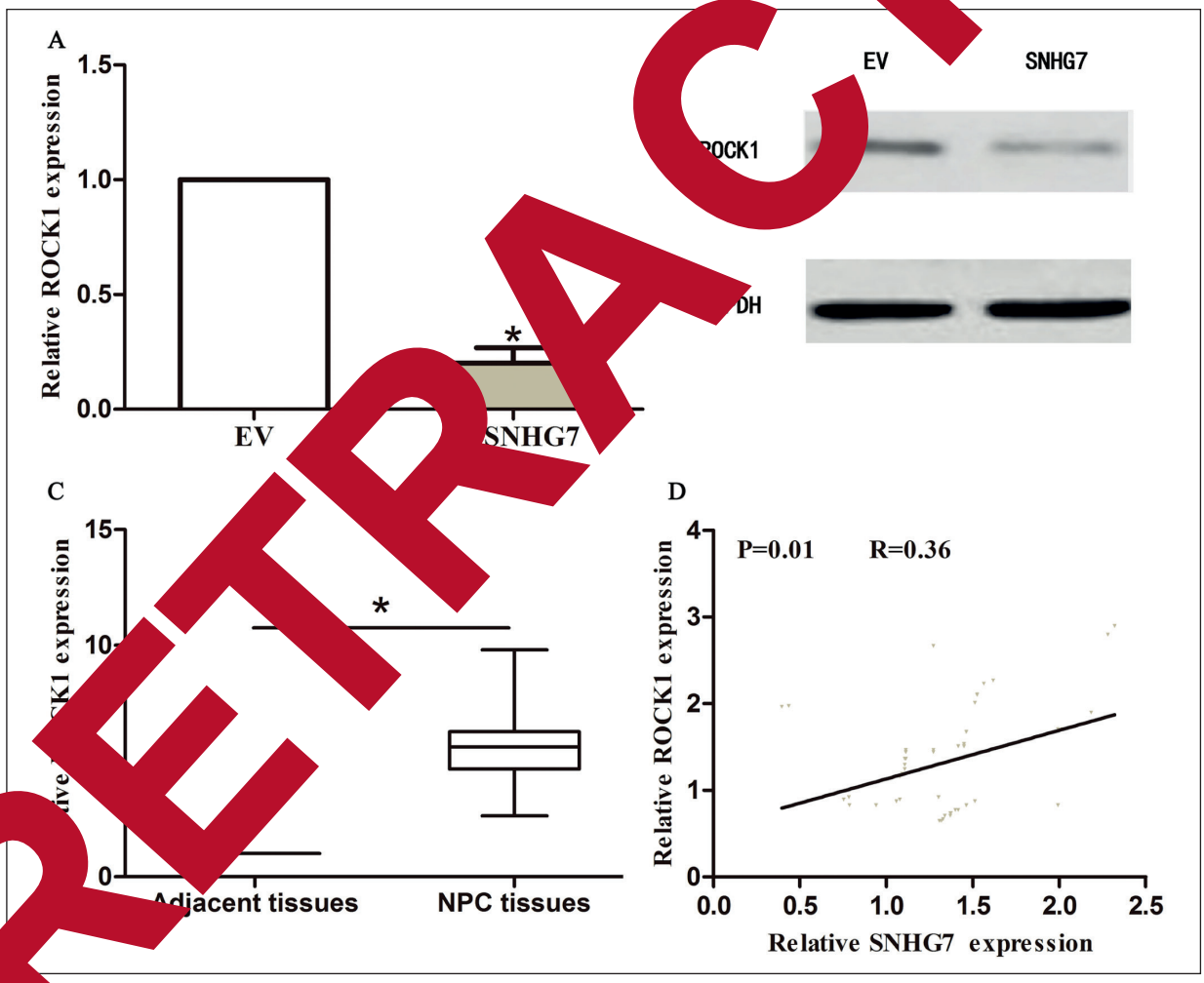

Figure 3. Interaction between ROCK1 and SNHG7 in NPC. ***A,*** The RNA level of ROCK1 in sh-SNHG7 group significantly decreased compared with EV group in 5-8F cells. ***B,*** Protein expression of ROCK1 was downregulated after knockdown of SNHG7 in 5-8F cells. ***C,*** ROCK1 was significantly upregulated in NPC tissues compared with adjacent tissues. ***D,*** The linear correlation between the expression levels of ROCK1 and SNHG7 in NPC tissues. The results represent the average of three independent experiments Data are presented as the mean ± standard error of the mean. *$p<0.05$.

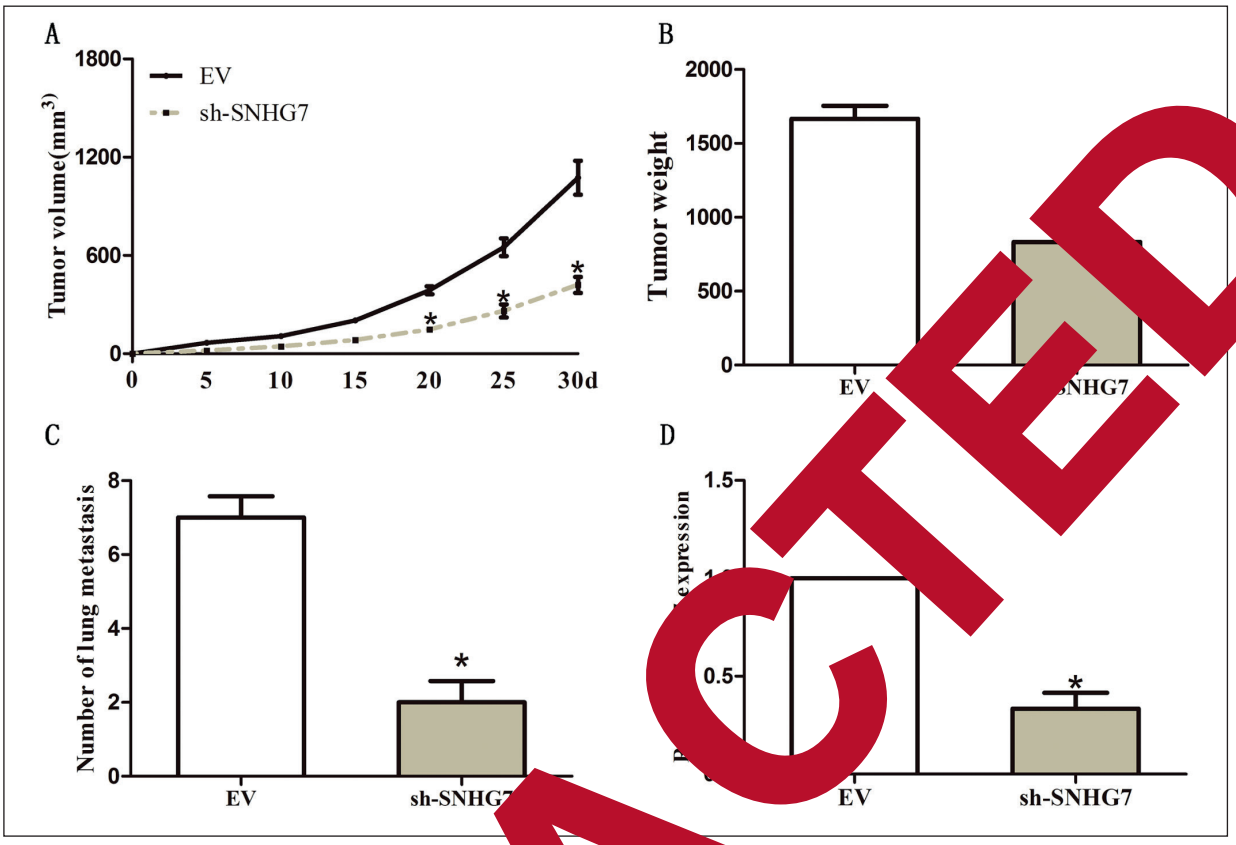

Figure 4. Knockdown of SNHG7 inhibited tumor fo on a of NPC *in vivo*. ***A,*** The tumor size in sh-SNHG7 group was smaller compared with EV group. ***B,*** The w ssected tumors in sh-SNHG7 group was smaller compared with EV group. ***C,*** The number of metastati odules in th rom the sh-SNHG7 group was significantly reduced compared to EV group. ***D,*** SNHG7 in those dis rs was l xpressed in sh-SNHG7 group compared with EV group. The results represent the average of th depe t experim mean ± standard error of the mean). *p<0.05, as compared with the control cells.

4D). Above results gested t NHG7 could induce tumor fo n and met of NPC *in vivo*.

Discussi

nce gested that lncRNAs are crucial regula arcino is of NPC. For instan- upreg d ex sion of lncRNA AFAP1- romo rogression of NPC and is neg ely rela to the poor prognosis of NPC pa . LncRNA ROR enhances cell prolife- on, ion, and chemoresistance in NPC a suppressing p53 signaling pathway[9]. Throu- rgeting miR-214, lncRNA LINC0086 serves as mor suppressor in NPC and may provide a potential treatment target for NPC[10]. LncRNA FOXCUT facilitates cell proliferation and migration in NPC *via* targeting FOXC1, which may be a potential NPC biomarker[11]. Small nucleolar RNA host gene 7 (SNHG7) is an oncogene located on chromosome 9q34.3, which is 2176 bp in length. Numerous researches have revealed that SNHG7 promotes cell proliferation, invasion and migration in many cancers[12]. For example, SNHG7 facilitates the epithelial-to-mesenchymal transition and tumor proliferation in osteosarcoma by regulating miR-34a[13]. Knockdown of SNHG7 significantly inhibits cell proliferation and migration in glioblastoma through inhibiting miR-5095[14]. SNHG7 promotes the progression of non-small cell lung cancer by enhancing miR-193b level and reducing FAIM2 expression[15]. In addition, SNHG7 is upregulated in colorectal cancer and negatively related to its prognosis by regulating PI3K/Akt/mTOR pathway[16]. In the present study, SNHG7 was found to be upregulated in both NPC tissues and cells. Furthermore, SNHG7 knockdown attenuated growth, migration and invasion

of NPC cells. In addition, knockdown of SNHG7 inhibited tumor formation and metastasis of NPC *in vivo*. These data indicated that SNHG7 functioned as an oncogene and promoted the tumorigenesis of NPC. Rho-associated kinase 1 (ROCK1), a protein serine/threonine kinase, has been reported to participate in a variety of biological and pathological processes, including cell motility, tumor metastasis and epithelial-to-mesenchymal transition (EMT)[17]. For instance, Mst1 regulates mitochondrial injury-induced cell apoptosis in NSCLC by ROCK1/Factin pathway[18]. Silencing of URG11 represses the proliferation and EMT in benign prostatic hyperplasia cells through RhoA/ROCK1 pathway[19]. LncRNA LOC441178 inhibits cell invasion and migration in oral squamous carcinoma *via* targeting ROCK1[20]. In our study, ROCK1 was downregulated after SNHG7 knockdown *in vitro*. Moreover, ROCK1 was remarkably upregulated in NPC samples compared with that in adjacent tissues. A positive correlation was discovered between ROCK1 and SNHG7 expressions in NPC tissues. It is revealed that SNHG7 may realize its function *via* regulating ROCK1.

Conclusions

LncRNA SNHG7 promotes NPC carcinogenesis *via* regulating ROCK1, which served as a promising marker for NPC.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

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