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LncRNA SNHG7 promotes the proliferation and inhibits apoptosis of renal cell cancer cells by downregulating CDKN1A

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Abstract. – OBJECTIVE: Recent studies have revealed that long non-coding RNAs (lncRNAs) have a crucial role in tumor progression. Renal cell cancer (RCC) is a common type of fatal gynecological cancer worldwide. This study aims to identify the role of lncRNA Small nucleolar RNA host gene 7 (SNHG7) in the progression of RCC.

PATIENTS AND METHODS: Expression of lncRNA SNHG7 in both RCC cells and 50 pairs of tissue samples was detected by Real-time quantitative polymerase chain reaction (RT-q...R). Moreover, the function of SNHG7 was id... by performing cell apoptosis assay, col... formation assay and proliferation assay *in vit*... ...he underlying mechanism assays including R...CR and Western blot assay were conducted.

RESULTS: SNHG7 expression ... remarka... upregulated in tumor tissue... compare... with adjacent tissues. Mo...er, R... cell proliferation was inhibited a... cell apo...sis was promoted after knockdo... SN... Moreover, after knoc...own ...A was upregulated at ...NA and ...in level *in vitro*. Furthermore ... expressio... ...DKN1A in tumor tissues ...atively cor... to the expression o... ...NHG...

CONCLUSIONS: The... ...ults above suggest that SNH... could promot... ...proliferation and inhibit ... apoptosis in RCC ...ugh downregulatin... ...KN1A, which may offer a new therapeutic ...ventio... ...r RCC patients.

Key Wo...
...ng no... ...g ..., SNHG7, RCC, CDKN1A.

Introduction

...enal Cell Cancer (RCC), accounting for near... ...of all adult malignancies, is the 3rd most freq...nt urologic carcinoma in the world. The morbidity of RCC has raised in the past two decades[1]. ...p...ately 337,0... cases were newly dia...nosed ... RCC worldwide in 2012. Moreover, it was rep... that 52,000 patients an... ...t 145,000 died ... RCC in Europe and ...dwide in 2012, respectively (http://globocan. ...c.fr). Though ...eat advances have been made ...CC diagnos... ...nd therapeutic treatment, the o...ll survival ... remains less than 10% in patien... ...dist... metastases[2]. Thus, early detection and ...ention are very crucial for patients ...ith RCC. It's urgent to realize the underlying ...m of RCC progression and find out po...ntia... ...omarkers and therapeutic targets.

The majority of transcripts, which do not code protein, are called non-coding RNAs (ncRNAs). The ncRNAs greater than 200 nt are defined as long non-coding RNAs (lncRNAs). Numerous studies have indicated that lncRNAs play a crucial role in the development of cancers. For example, through targeting miR-221/SOCS3, lncRNA GAS5 suppresses cell proliferation, cell metastasis and gemcitabine resistance in pancreatic cancer[3]. LncRNA TP73AS1 dramatically promotes cell apoptosis, depresses cell proliferation in colorectal cancer and functions as a competing endogenous RNA for miR103 to modulate the expression of PTEN[4]. LncRNA HOTAIR facilitates cell invasion and metastasis in oral squamous cell carcinoma by indirectly recruiting EZH2 and depressing E-cadherin[5]. LncRNA ATB promotes cell migration and cell invasion in glioma by activating astrocytes through suppressing the expression of microRNA 2043p[6]. However, the clinical role of lncRNA AFAP1-AS1 and underlying biological mechanisms in RCC remains unknown.

In our study, lncRNA Small nucleolar RNA host gene 7 (SNHG7) expression was significantly upregulated in RCC samples. Moreover, func-

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tion assays revealed that SNHG7 participated in the regulation of RCC cell apoptosis and proliferation. Furthermore, we discovered that lncRNA SNHG7 played its function in RCC by regulating CDKN1A.

Patients and Methods

Cell Culture and Clinical Samples

Caki-1, 769-P, 786-O, and ACHN RCC cell lines, a normal human kidney epithelial cell (HK-2) and 293T cell (Chinese Type Culture Collection, Chinese Academy of Sciences, Shanghai, China) were used in this study. Culture medium consisted of penicillin, Dulbecco's Modified Eagle's Medium (DMEM, HyClone, South Logan, UT, USA) and 10% fetal bovine serum (FBS; Invitrogen Life Technologies, Carlsbad, CA, USA). Besides, cells were cultured in a humidified incubator, which contained 5% CO_2 and was set at 37°C. RCC tissues were obtained from 50 RCC patients who underwent surgery at Affiliated Jiangyin Hospital of Southeast University Medical College. All tissues were stored at –80°C. Written informed consent was provided by RCC patients before surgery [illegible] study was approved by the Ethics Committ[illegible]anshui County People's Hospital.

Cell Transfection

For transfection, lentivir[illegible] expressi[illegible] short-hairpin RNA (shRNA) [illegible] SNHG[illegible] was compounded and th[illegible] cloned [illegible] pLenti-EF1a-EGFP-F2A-Puro v[illegible] (Bioset[illegible] Inc. San Diego, CA, USA). The[illegible]enti[illegible]sf[illegible]s was performed usi[illegible]ipofecta[illegible] 2000 (Invitrogen, Carlsbad, [illegible] USA).

RNA Extr[illegible]ion a[illegible]al-Time Quantitative Polymeras[illegible] Chain Reac[illegible] (RT-qPCR)

TRIz[illegible] reagent (Invitro[illegible] Carlsbad, CA, USA) [illegible]s utilized to isolate to[illegible]l RNA from tissue[illegible] cells. [illegible]BR green (Roche, Basel, Switzerla[illegible]onducted to measure the relative expressi[illegible]els betw[illegible]n SNHG7 and CDKN1A [illegible]A. M[illegible] expressions were normaliz[illegible] the le[illegible] glyceraldehyde 3-phosphate deh[illegible]ogenase (GAPDH) mRNA. Following are th[illegible]sing for RT-qPCR: SNHG7 primers [illegible]war[illegible]GTGACTTCGCCTGTGATGGA-3′, [illegible]erse 5′-GGCCTCTATCTGTACCTTTAT-[illegible]′; GAPDH primers forward 5′-CCAAAAT-CA[illegible]TGGGGCAATGCTGG-3′ and reverse 5′-TGATGGCATGGACTGTGGTCATTCA-3′. The thermal cycle was as follows: 30 s at 95°C, 5 s at 95°C for 40 cycles, 35 s at 60°C.

Colony Formation Assay

1.5×10^3 of 786-O cells were placed i[illegible] plate.10 day later, colonies were th[illegible]xed wi[illegible] 10% formaldehyde for 30 min [illegible] stained for 5 min with 0.5% crystal viole[illegible]n camera (Tokyo, Japan) was used to take p[illegible] of the colonies.

Cell Proliferation A[illegible]y

Cell proliferation [illegible]e t[illegible]ed cells in 96-well plates was [illegible]onito[illegible]ry 24 h[illegible] Cell Counting Kit-[illegible]CCK-8) [illegible] (D[illegible]do Molecular Tech[illegible]ies, Inc., K[illegible]o, Japan). Spectroph[illegible] (Thermo Fi[illegible]r Scientific, Waltham, [illegible]A, U[illegible]as utilized to detect the absorbance at 450 nm[illegible]

[illegible]w Cytometric Analysis

Annexin-V-FI[illegible]CC apoptosis detection kit ([illegible] Franklin L[illegible]s, NJ, USA) was used to detect R[illegible]ell apopto[illegible] Briefly, harvested cells were was[illegible]ice[illegible]g ice-cold PBS (Phosphate-buffer sal[illegible]en, 100 µL flow cytometry binding [illegible]ffer was added. After 5 µL Annexin V/FIRCC [illegible] PI were mixed, these cells were stained [illegible]r 1[illegible]n in the dark at room temperature. Each tube was added with four hundred microliters binding buffer. FACSCalibur flow cytometer (BD Biosciences, Franklin Lakes, NJ, USA) was used for analyzing the apoptosis cells.

Western Blot Analysis

After separated with 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), the protein samples were transferred onto polyvinylidene difluoride (PVDF) membrane (Millipore, Billerica, MA, USA). Anti-CDKN1A (Abcam, Cambridge, MA, USA) and anti- GAPDH (Abcam, Cambridge, MA, USA) were used as the primary antibodies, which were utilized for incubating the membranes at 4°C overnight. Next, membranes were incubated with goat anti-rabbit secondary antibody (Abcam, Cambridge, MA, USA) for 2 h. Chemiluminescent film was applied for assessment of protein expression using ImageJ software (NIH, Bethesda, MD, USA).

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 17.0 (SPSS Inc., Chicago, IL, USA) was utilized to perform statistical analysis. Two-tailed Student's

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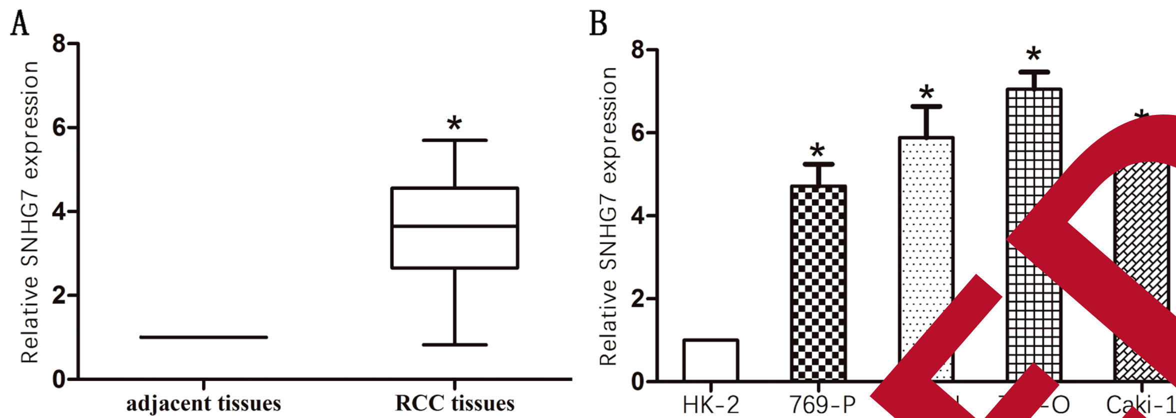

Figure 1. Expression levels of SNHG7 were increased in RCC tissues and cell lines. [illegible] SNHG7 [illegible] was [illegible]ficantly increased in the RCC tissues compared with adjacent tissues. **B,** Expression levels [illegible] NHG7 relati[illegible] [illegible] were determined in the human RCC cell lines and HK-2 (normal human kidney epithelial [illegible] RT-qPCR. Da[illegible] sented as the mean ± standard error of the mean. *p<0.05.

t-test was performed to analyze the significance. When p<0.05, the data were considered statistically significant.

Results

Expression Level of SNHG7 in Tiss[illegible] and Cells of RCC

First, RT-qPCR was conducted for det[illegible] SNHG7 expression in 50 patients' tissues a[illegible] RCC cells. As a result, SNHG7 [illegible]ignifican[illegible] upregulated in tumor tissue [illegible] that i[illegible] adjacent tissues (Figure 1A). SNHG7 [illegible]pression level of RCC cells was [illegible] than t[illegible] of HK-2 (normal human kidney epith[illegible]

Knockdown of [illegible]HG7 Inhib[illegible] Cell Prolifera[illegible] RCC Cells

According [illegible] SNH[illegible]pression in RCC cells, we chose 7[illegible]-O RCC cel[illegible] for the knockdown of SNH[illegible] RT-qPCR was ut[illegible] for detecting the transf[illegible]on efficiency (Figure [illegible]A). Moreover, the out[illegible] of CC[illegible]8 assay also revealed that after SNH[illegible]s [illegible]cked do[illegible]n, RCC cell proliferation was rem[illegible]y supp[illegible]ed (Figure 2B). The re[illegible] of col[illegible]on assay revealed that after S[illegible]7 was k[illegible]d down, the colonies of RCC cel[illegible]ere significantly decreased (Figure 2C).

[illegible]n of SNHG7 Promoted Cell [illegible]optosis in RCC Cells

[illegible]xplore whether SNHG7 functioned in RCC cel[illegible]poptosis, flow cytometric analysis was performed to detect the apoptosis rate of these treated[illegible]he results rev[illegible] that after SNHG7 w[illegible] knocked down in RCC cells, cell apoptosis [illegible] of 786-O RC[illegible] cell was remarkably increased ([illegible]ure 3).

SN[illegible]ed RCC Tumorigenesis via CD[illegible]

CDKN1A was a newly discovered gene in var[illegible]rs including RCC. We then conducted [illegible]sm assays to identify the correlation between SNHG7 and CDKN1A. RT-qPCR results demonstrated that the CDKN1A mRNA expression was upregulated in RCC cells transfected with SNHG7 shRNA (Figure 4A). Western blot analysis results further verified that the expression level of CDKN1A protein was upregulated in RCC cells transfected with SNHG7 shRNA (Figure 4B). To explore the interaction between SNHG7 and CDKN1A, the expression level of CDKN1A was detected in RCC tissues. As a result, CDKN1A expression was significantly lower in RCC tissues compared with adjacent tissues (Figure 4C). The linear correlation analysis revealed that the CDKN1A expression negatively correlated to SNHG7 expression in RCC tissues (Figure 4D).

Discussion

Emerging evidence suggested that lncRNAs play an important role in a variety of important biological processes, including the development of RCC. For instance, through negatively regulating the expression of miR-126, lncRNA DUXAP8

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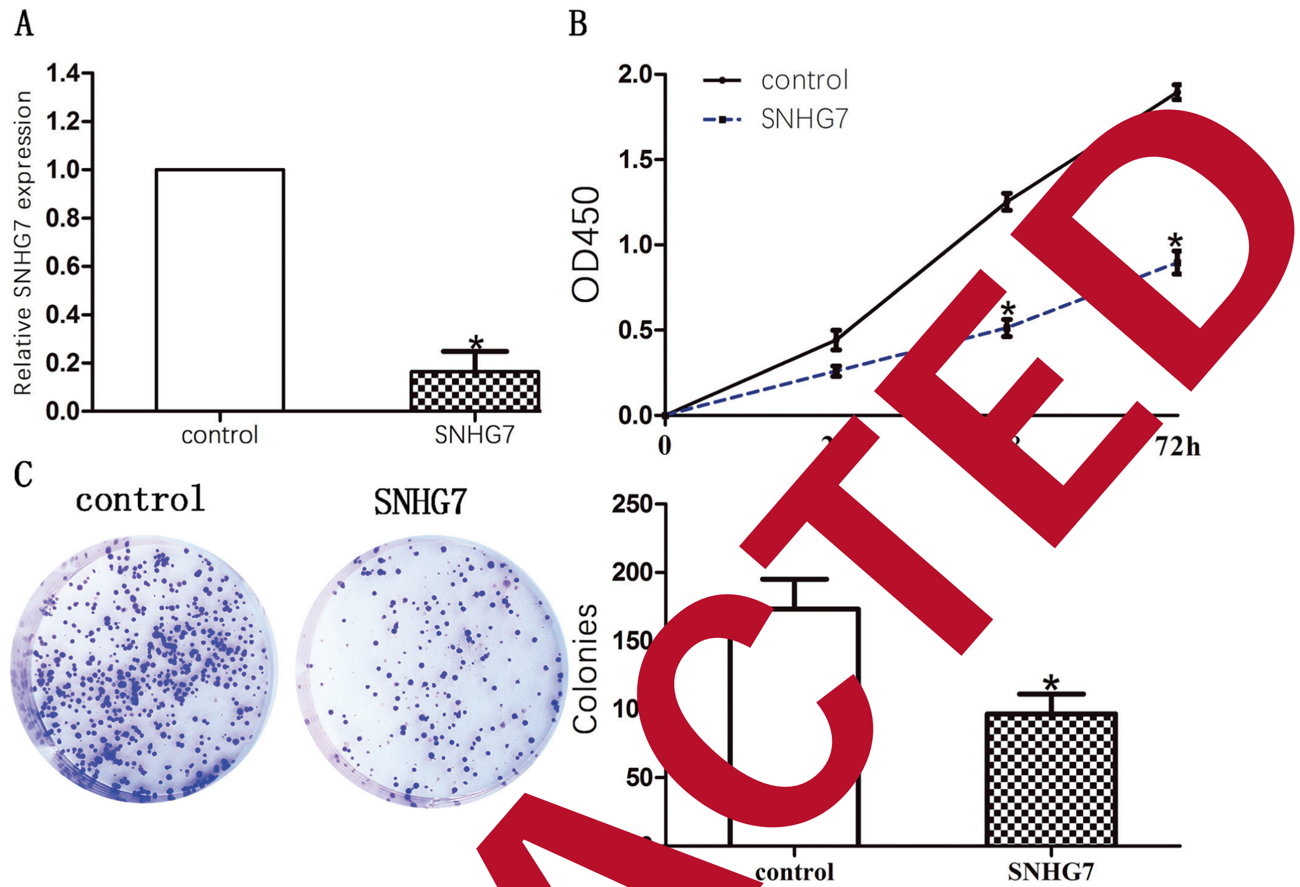

Figure 2. Silence of SNHG7 inhibited RCC cell pro[illegible], SNHG7 expression in RCC cells transduced with control vector (control) or SNHG7 shRNA (SNHG7) was detec[illegible]-qPCR. GAPDH was used as an internal control. **B,** CCK-8 assay showed that silence of SNHG7 si[illegible]ly inhibit[illegible] proliferation in RCC cells. **C,** Colony formation assay showed that silence of SNHG7 significantly [illegible] colonies [illegible]C cells (magnification: 10×). The results represent the average of three independent experiments [illegible]an ± sta[illegible]d error of [illegible]ean). $^*p<0.05$.

promotes the progr[illegible]on of [illegible] Knockdown of lncRNA MAL[illegible] remarkably [illegible]esses cell viability and m[illegible] RCC by ta[illegible]g miR-223p and acti[illegible]ing th[illegible]K/Akt signaling pathway[8]. By [illegible]nding to mi[illegible]ilence of lncRNA TUG1 i[illegible]bits the prolife[illegible] and migration of RC[illegible]ell through regulating the YAP expressio[illegible]verexp[illegible]sion of lncRNA HOTTIP enhanc[illegible] [illegible]iferation [illegible]migration, and invasion in RCC [illegible]egulati[illegible]he PI3K/Akt/Atg13 sig[illegible]g path[illegible]. In a[illegible]tion, lncRNA TUG1 functi[illegible]s an onc[illegible] in RCC[11] by suppressing the exp[illegible]sion level of miR196a.

[illegible]olar RNA host gene 7 (SNHG7) [illegible]an o[illegible]ne located on chromosome 9q34.3. [illegible]merous researches have revealed that SNHG7 p[illegible]tes cell proliferation, cell invasion and migra[illegible] in many cancers[12]. For example, SNHG7 facilitates the epithelial-to-mesenchymal transition and tumor proliferation in osteosarcoma by regulation of miR-34a[13]. Knockdown of SNHG7 significantly inhibits cell proliferation and cell migration in glioblastoma through inhibition of 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 is found to be negatively related to the prognosis of colorectal cancer[16]. SNHG7 was found to be upregulated in both RCC tissues and cells in our study. Furthermore, after SNHG7 was knocked down, the ability of cell growth was inhibited, and cell apoptosis rate was enhanced. These data indicated that SNHG7 functioned as an oncogene and promotes the tumorigenesis of RCC.

CDKN1A ($p21^{Cip1}$) belongs to cyclin-dependent kinase inhibitors, which acts as a tumor suppressor in many cancers[17]. For example, by regulating CD-

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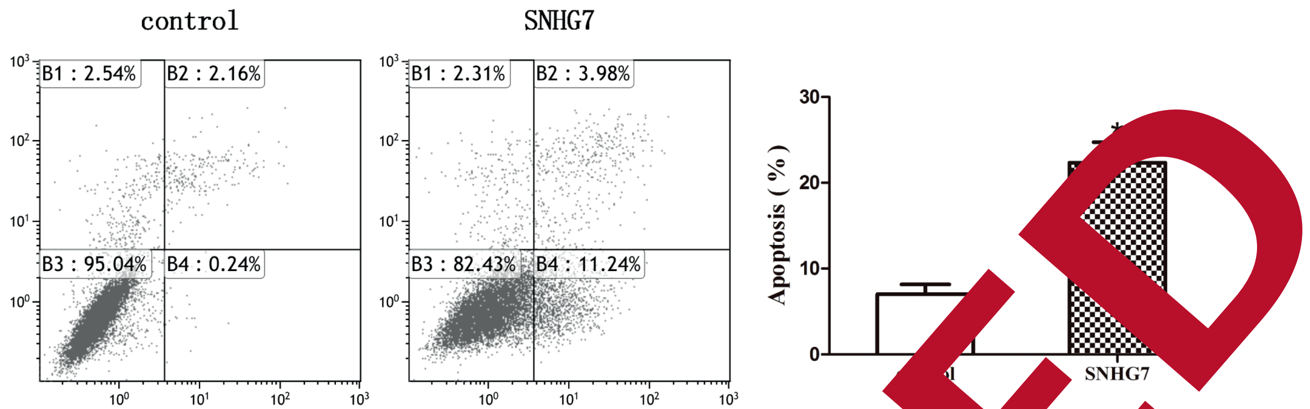
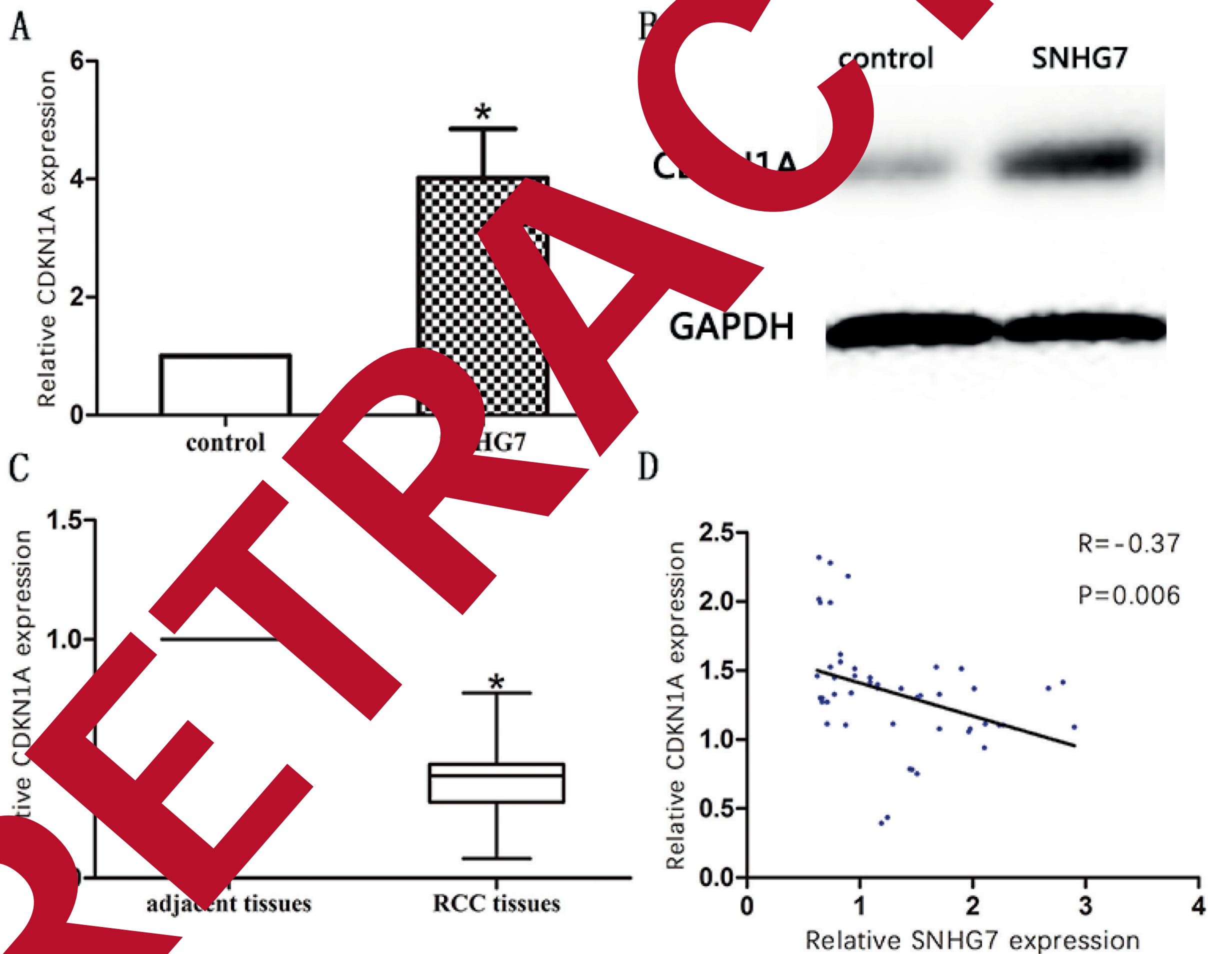


Figure 3. Silence of SNHG7 promoted RCC cell apoptosis. Flow cytometric analysis [illegible]y show[illegible] cell apop[illegible]s rate of RCC cells was significantly increased *via* silence of SNHG7 in RCC cells. The resu[illegible] epresent the a[illegible] of [illegible]e independent experiments (mean ± standard error of the mean). *$p<0.05$.



[illegible]ure 4. Interaction between CDKN1A and SNHG7 in RCC. **A,** The RNA expression level of CDKN1A in SNHG7 shRNA ([illegible]G7) cells was significantly increased compared with empty control cells in RCC cells. **B,** Protein expression of CDKN1A w[illegible]ased after silence of SNHG7 in RCC cells. **C,** CDKN1A was significantly downregulated in RCC tissues compared with adjac[illegible]t tissues. **D,** The linear correlation between the expression level of CDKN1A and SNHG7 in RCC tissues. The results represent the average of three independent experiments. Data are presented as the mean ± standard error of the mean. *$p<0.05$.

KN1A transcription expression, LRH-1 inhibits cell proliferation in breast tumor[18]. CDKN1A enhances the response of cutaneous tumors to radiotherapy by manipulating Langerhans cell survival and promoting Treg cell generation[19]. In addition, CDKN1A is closely correlated with prognosis of patients who receive gastric adenocarcinoma resection[20]. Further, by suppressing CDKN1A, EZH2 controls the proliferation of germinal centers B cell and enables cell cycle progression[21]. The result of Western blot analysis indicated that CDKN1A was upregulated after SNHG7 was knocked down *in vitro*. Moreover, negative correlation between CDKN1A and SNHG7 expression was discovered in tumor tissues. The results above revealed that CDKN1A was a target regulated by SNHG7in RCC development.

Conclusions

We found that lncRNA SNHG7 might be a new biomarker in the carcinogenesis of RCC and could be served as a promising mark for RCC.

Conflict of Interests

The Authors declare that they have no conflict of [illegible]sts.

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