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LncRNA SNHG17 predicts poor prognosis and promotes cell proliferation and migration in hepatocellular carcinoma

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Abstract. – OBJECTIVE: The objective of this study was to investigate the role of long noncoding RNAs small nucleolar RNA host gene 17 (SNHG17) in hepatocellular carcinoma (HCC).

PATIENTS AND METHODS: Here, the expression level of SHNG17 was determined using reverse-transcription quantitative PCR in tissue specimens and cell lines. The chi-squared test was used to analyze the associations between SNHG17 expression and clinical pathological factors in HCC patients. Kaplan-Meier and log-rank analyses were used to evaluate the prognosis of HCC patients, and proportional hazards model (Cox) regression was utilized for univariate and multivariate analyses. Knockdown of SNHG17 was achieved by transfection with si-SNHG17 in HepG2 and SNU-182 cells. Cell function was analyzed using CCK-8 assay, colony formation assay, Flow cytometry analysis and transwell assays.

RESULTS: Our data showed that SNHG17 expression was significantly upregulated in cancer regions of HCC compared with adjacent regions. Increased SNHG17 expression level was correlated with tumor size, TNM stage and poor survival prognosis in HCC patients. Further functional experiments indicated that inhibition of SNHG17 significantly inhibited HCC cell proliferation, migration and invasion, caused cell cycle G0/G1 phase arrest and apoptosis.

CONCLUSIONS: In summary, our findings suggest that SNHG17 might function as novel therapeutic target for the treatment of HCC.

Key Words:
Hepatocellular carcinoma, LncRNA, SNHG17, Cell proliferation, Migration.

Introduction

Hepatocellular carcinoma (HCC), accounting for approximately 90% of liver cancer, is one of the major causes of tumor-associated mortality worldwide[1,2]. Some main risk factors, including alcohol consumption, obesity, chronic hepatitis B and C infection, were identified to contribute to the complex process of liver tumorigenesis[3]. Although considerable progresses have been made in some therapeutic strategies, such as surgical resection, systemic chemotherapies and radiofrequency ablation[4], the overall five-year survival rate for HCC patients remains below 20%[5]. Therefore, it is of great importance to explore the molecular mechanism underlying the progression of HCC is of great importance for its early diagnosis and treatments.

Long non-coding RNAs (lncRNAs) are a class of non-coding transcripts with a length of greater than 200 nucleotides as key regulators in various cellular processes, such as cell proliferation, apoptosis, invasion and metastasis[6-8]. Many studies[9,10] suggested that lncRNAs are aberrantly expressed and exert oncogenic and suppressive functions in cancers, including HCC. Recently, host gene 17 (SNHG17) located on 20q11.23 has been identified as a newfound lncRNA with a length of 1, 186-nt, which is a member of noncoding genes hosting small RNAs family[11]. Clinically, SNHG17 has been reported to participate in cancer biology in various tumors. For example, Ma et al[12] found that SNHG17 expression was significantly upregulated in col-

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orectal cancer (CRC). Moreover, SNHG17 expression was closely correlated with tumor-node-metastasis (TNM) stage, tumor size and lymph node metastasis in CRC patients. In addition, the overexpressed SNHG17 was also demonstrated to be associated with shorter overall survival and progression-free survival in gastric cancer patients[13]. Functionally, SNHG17 promotes cell proliferation, migration, and invasion in gastric cancer[14] and non-small cell lung cancer[15]. However, the clinical and functional significance of SNHG17 in HCC have been rarely reported up to now.

In this study, we detected the expression levels of SNHG17 in HCC tissues and cell lines and evaluated its clinical significance in HCC patients. Moreover, we also examined the biological function of SNHG17, including proliferation, migration and invasion in HCC cells. Our data will help to understand the crucial role of SNHG17 in HCC.

Patients and Methods

Clinical Tissue Samples

Fifth-eight cases of tumor and matched adjacent tissues were acquired from HCC patients at Qingdao No.6 People's Hospital (Shandong, China). After confirmed by histopathologists, tissue samples were immediately snap-frozen in liquid nitrogen and subsequently stored at -80 °C for further analyses. None of patients received any transcatheter arterial chemoembolization (TACE), radiofrequency ablation (RFA), immunotherapy or targeted therapy before surgery. The clinicopathological features for HCC patients were described in Table I. Our study was approved by the Institute Research Ethics Committee at Qingdao No. 6 People's Hospital (approval no. QDP-235) and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent prior to enrollment in the study.

Cell Lines and Transfection

A normal transformed human liver epithelial-2 cell line (THLE-2) and two HCC cell lines (HepG2 and SNU-182) authenticated by karyotyping were provided by American Type Culture Collection (ATCC, Manassas, VA, USA). All HCC cells were grown in Dulbecco's Modified Eagle's Medium (DMEM; Gibco, Carlsbad, CA, USA), while THLE-2 cells were grown in Roswell Park Memorial Institute-1640 (RPMI-1640) medium (Gibco). All mediums were supplemented with 10% fetal bovine serum (FBS) (Gibco) and kept at 37 °C in a humidified incubator containing 5% CO_2.

Three different small interfering RNAs targeting SNHG17, including si-SNHG17-1 (AAACGAGCGTAGCTTCCTT), si-SNHG17-2 (GCAGTGTCTCGTCCTCTTT) and si-SNHG17-3 (CCCATTCAATAAACCTTAC) and scrambled negative control (si-NC) were synthesized by GenePharma (Shanghai, China). The above oligonucleotides at a final concentration of 50 nM were transiently transfected into HepG2 and SNU-182 cells for 48 h using Lipofectamine 3000 (ThermoFisher Scientific, Waltham, MA, USA).

Reverse-transcription Quantitative PCR (RT-qPCR)

Using TRIzol Reagent (Takara, Dalian, China), we isolated total RNA from tissue samples or cell lines. The reverse-transcription of lncRNA was performed by an M-MLV RT Kit (ThermoFisher Scientific, Waltham, MA, USA). Quantitative PCR analysis was carried out in triplicate using SYBR Green PCR Master Mix (ThermoFisher Scientific, Waltham, MA, USA) with the primer sequences as follows: SNHG17 forward: 5′-TGCTTGTAAGGCAGGGTCTC-3′, reverse: 5′-ACAGCCACTGAAAGCATGTG-3′; GAPDH forward: 5′-TATGATGATATCAAGAGGGTAGT-3′, reverse: 5′-TGTATCCAAACTCATTGTCATAC-3′. GAPDH was served as the endogenous control. Relative expression of SNHG17 was calculated by the $2^{-\Delta\Delta Ct}$ method.

CCK-8 Assay

Transfected cells at a density of 3,000 cells per well in triplicate were seeded into 96-well plates and cultured for 24, 48 and 72 h, respectively. At each time point, cells in each well were incubated at 37 °C with 10 μL CCK-8 reagent (Beyotime, Shanghai, China) for 1 h. The detection of absorbance was carried out by a Microplate Reader at 450 nm.

Colony Formation Assay

Transfected cells at a density of 500 cells per well were seeded in a six-well plate and cultured for two weeks. After two weeks, the naturally formed colonies were washed twice with PBS, fixed with methanol and stained with 0.1% crystal violet (Sigma-Aldrich, St Louis, MO, USA). Stained colonies (at least 50 cells per colony) were washed again with PBS, air-dried and counted under a microscope.

Flow Cytometry

For cell cycle analyses, transfected cells were harvested, washed and fixed overnight in 75% eth-

Table I. Association of SNHG17 expression with clinicopathological features of HCC patients.

Variables	Cases (n = 58)	SNHG17 expression		p-value
		High (n = 37)	Low (n = 21)	(chi-square test)
Sex				0.155
Male	32	23	9	
Female	26	14	12	
Age				0.328
< 50	15	8	7	
≥ 50	43	29	14	
Tumor size (cm)				0.002*
< 5	41	21	20	
≥ 5	17	16	1	
HBsAg				0.066
Negative	34	25	9	
Positive	24	12	12	
Differentiation				0.560
Well/moderate	36	24	12	
Poor	22	13	9	
TNM stage				0.008*
I-II	30	24	6	
III-IV	28	13	15	
Vascular invasion				0.258
Yes	25	18	7	
No	33	19	14	

Note: *Statistically significant; Abbreviations: HCC, hepatocellular carcinoma; TNM, tumor-node-metastasis

anol at 4 °C. Then, fixed cells were incubated with RNase A (Sigma-Aldrich) at 37 °C for 30 min to remove the RNA. Then, cells were stained with PI solution using the Cycletest PLUS DNA Reagent Kit (BD Biosciences, San Jose, CA) for 30 min at room temperature. The percentage of cells at G0/G1, S and G2/M phases was counted using flow cytometry (FACScan, BD Biosciences, San Jose, CA). For apoptosis analyses, transfected cells underwent trypsinization, re-suspension in 1 × binding buffer and double stained with 5 μL of FITC-Annexin V and 5 μL PI (BD Biosciences, San Jose, CA) for 15 min in the dark. Subsequently, the early apoptotic, late apoptotic and total apoptotic cells were analyzed and quantified by flow cytometry (FACScan, BD Biosciences, San Jose, CA).

Cell Migration and Invasion

Cell migration and invasion were assessed by transwell assay in HCC cells after 48 h transfection. For migration, transfected cells re-suspended in serum-free medium were seeded in a transwell chamber with 8 μm pore size (Corning, Corning, NY, USA) and medium containing 10% FBS was added to the bottom chamber. After incubation for 24 h at 37 °C, the cells on the bottom chamber were fixed with 4% paraformaldehyde and stained with 0.5% crystal violet for 30 min. After being washed with phosphate-buffered saline (PBS) three times, stained cells were counted in five randomly selected fields under a microscope (Olympus, Tokyo, Japan). For invasion assay, the upper chamber was pre-coated with Matrigel (Corning) and then similar migration assay was conducted above.

Statistical Analysis

Statistical analysis was conducted by SPSS statistics 20.0 (IBM, Armonk, NY, USA). The chi-squared test was used to analyze the associations between SNHG17 expression and clinical pathological factors in HCC patients. Quantitative data were expressed as mean ± SD. Differences were analyzed using Student's *t*-test (two groups) or one-way analysis of variance followed by Bonferroni post-hoc tests (multiple groups). The value of p less than 0.05 was considered to be statistically significant.

Results

SHNG17 was Upregulated in HCC and Correlated with Clinicopathological Features

To gain insight into the role of SNHG17 in the progression of HCC, the expression levels of SNHG17

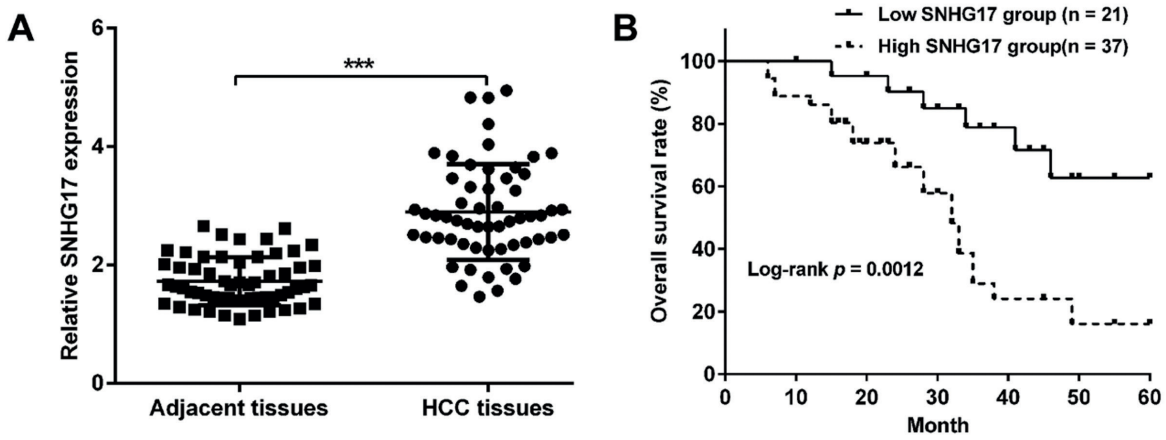

Figure 1. High SNHG17 expression predicted poor prognosis of HCC patients. **A**, Reverse-transcription quantitative PCR analysis of SNHG17 expression in 58 paired HCC tissues and adjacent non-tumor tissues. ***$p < 0.001$, compared with adjacent tissues; **B,** Kaplan-Meier method and log-rank test analysis of the association between SNHG17 expression and the overall survival of HCC patients. HCC patients (n = 58) were classified into the low SNHG17 expression group (n = 21) and the high SNHG17 expression group (n = 37) according to the median value of SNHG17 expression.

were first evaluated in tumor and adjacent tissues of 58 HCC patients using RT-qPCR analysis. The results showed the transcript levels of SNHG17 were significantly increased in cancer regions of HCC compared with adjacent regions (Figure 1A). Next, all HCC patients were stratified into high (n = 37) and low (n = 21) SNHG17 expression groups according to its median level. As data shown in Table I, high SNHG17 level in HCC tissues was significantly associated with tumor size and TNM stage, but not associated with other factors, such as sex, age, HBsAg and differentiation. Moreover, we found the overall survival rate was significantly higher in patients with low expression of SNHG17 than those with high expression of SNHG17 ($p = 0.0012$) (Figure 1B). More importantly, univariate and multivariate Cox regression analysis further indicated that tumor size, TNM stage and SNHG17 expression were independent prognostic markers for overall survival in patients with HCC (Table II).

Knockdown of SNHG17 Inhibited HCC Cell Proliferation

In addition, we observed that SNHG17 was remarkably upregulated in HCC cell lines (HepG2 and SNU-182), as compared with that in the normal transformed human THLE-2 cells (Figure 1B). Considering that SNHG17 was overexpressed, we then performed loss-of-function assays in HepG2 and SNU-182 cells with higher SNHG17 expression by transfecting with three different siRNAs specifically targeting SNHG17. As demonstrated in Figure 2A, transfection with three designed siRNAs obviously suppressed the expression of

Table II. Univariate and multivariate analysis for overall survival in HCC patients.

	Univariate analysis		Multivariate analysis	
Characteristics	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Sex	1.418 (0.765-2.786)	0.423	NA	NA
Age (years)	2.213 (0.975-3.705)	0.256	NA	NA
Tumor size (cm)	1.987 (1.015-4.213)	0.006	1.823 (0.735-3.512)	0.021
HBsAg	0.798 (0.476-1.865)	0.562	NA	NA
Differentiation	1.566 (0.794-2.475)	0.674	NA	NA
TNM stage	2.125 (1.765-4.126)	0.021	1.739 (0.882-3.322)	0.045
Vascular invasion	1.285 (0.895-3.123)	0.014	2.335 (1.046-3.855)	0.059
SNHG17 expression	1.895 (1.115-3.552)	0.008	1.426 (0.796-3.434)	0.017

Abbreviations: HCC, hepatocellular carcinoma; HR: hazard ratio; CI: confidence interval; NA, not analyzed.

SNHG17 in HepG2 and SNU-182 cells. Notably, si-SNHG17-2 had stronger suppressive effects on the expression of SNHG17, compared with si-SNHG17-1 and si-SNHG17-3. We thus selected si-SNHG17-2 for the subsequently functional experiments. The results from CCK-8 assay showed that si-SNHG17-2 transfection significantly impaired the cell viability, compared with si-NC transfection in HepG2 (Figure 2B) and SNU-182 (Figure 2C) cells. Similarly, colony formation assay consistently indicated that SNHG17 knockdown remarkably decreased the number of colonies in both HepG2 and SNU-182 cells (Figure 2D).

Knockdown of SNHG17 Induced Cell Cycle G0/G1 Arrest and Apoptosis in HCC Cells

To further investigate whether the effect of SNHG17 knockdown on cell proliferation was associated with cell cycle progression and apoptosis, flow cytometry assay was conducted in HCC cells. As shown in Figure 3A, si-SNHG17-2 transfection significantly elevated the percentage of cells at G0/G1 phase (HepG2: 74.8% ± 0.4% *vs.* 59.8% ± 1.1%; SNU-182: 80.5% ± 1.1% *vs.* 73.0% ± 0.3%), accordingly reduced that at S phase (HepG2: 16.3% ± 0.7% *vs.* 23.1% ± 0.2%; SNU-182: 9.7% ± 0.7% *vs.* 13.6% ± 0.6%) and G2/M phase (HepG2: 9.0% ± 0.8% *vs.* 17.1% ± 1.0%; SNU-182: 9.8% ± 1.7% *vs.* 13.2% ± 0.4%), compared with si-NC transfection in HepG2 and SNU-182 cells. Moreover, cell apoptosis assay further demonstrated that HepG2 and SNU-182 cells with si-SNHG17-2 transfection had a higher percentage of apoptosis, including early, late and total apoptotic rate, as compared with si-NC transfection (Figure 3B).

Knockdown of SNHG17 Suppressed the Migration and Invasion Ability of HCC Cells

Using transwell assay, we additionally investigated the effect of SNHG17 on HCC cell migration and invasion. As results depicted in Figure 4A, we found that the migrated HepG2 (78.0 ± 8.0 *vs.* 149.3 ± 4.6) and SNU-182 (86.7 ± 8.6 *vs.* 165.3 ± 8.7) cells were significantly reduced in si-SNHG17-2 group, compared with si-NC group. Similar results were obtained in the invasion assay, which showed that SNHG17 knockdown sup-

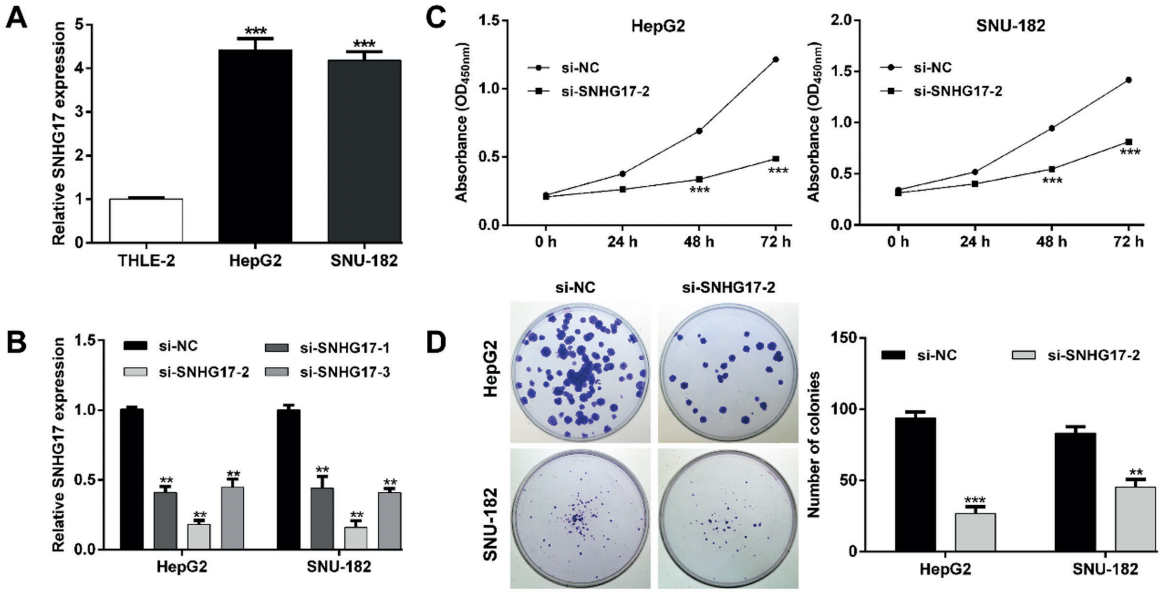

Figure 2. Effects of SNHG17 knockdown on HCC cell proliferation. **A**, Reverse-transcription quantitative PCR analysis of SNHG17 expression in the normal transformed human THLE-2 cells and two HCC cell lines. Data were shown as mean±SD and the experiment was performed in triplicate. ***$p<0.001$, compared with THLE-2; **B**, Reverse-transcription quantitative PCR analysis of SNHG17 expression in HepG2 and SNU-182 cells after transfected with si-SNHG17-1, si-SNHG17-2 or si-SNHG17-3 for 48 h. **C**, Cell viability was analyzed in HepG2 and SNU-182 cells after transfected with si-SNHG17-2 or si-NC using CCK-8 assay. **D**, Colony formation assay was performed in HepG2 and SNU-182 cells after transfected with si-SNHG17-2 or si-NC (a magnification of ×200). Data were shown as mean±SD and the experiment was performed in triplicate. **$p<0.01$, ***$p<0.001$, compared with si-NC.

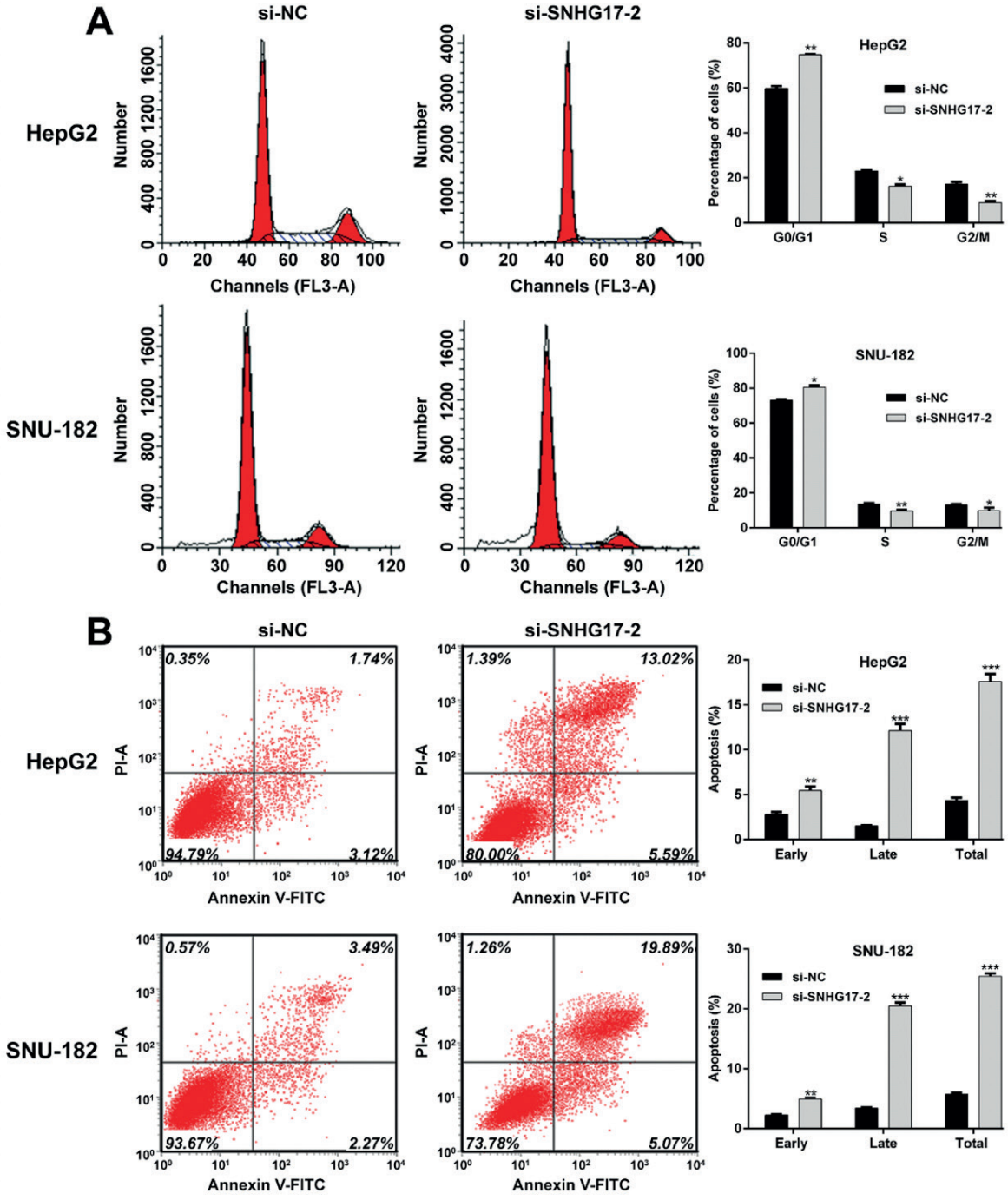

Figure 3. Effects of SNHG17 knockdown on HCC cell cycle progression and apoptosis. HepG2 and SNU-182 cells were transfected with si-SNHG17-2 or si-NC for 48 h. **A**, The cell cycle distribution was analyzed using flow cytometry with PI staining in HepG2 and SNU-182 cells. **B**, Cell apoptosis was determined in HepG2 and SNU-182 cells by double Annexin V/PI staining with flow cytometry assay. Data were shown as mean ± SD and the experiment was performed in triplicate. $^{**}p < 0.01$, $^{***}p < 0.001$, compared with si-NC.

pressed the number of invasive cells from 127.7 ± 10.8 to 50.7 ± 5.0 in HepG2 and from 144.3 ± 7.1 to 64.3 ± 9.1 in SNU-182 cells (Figure 4B). Taken together, the data indicate that knockdown of SNHG17 exerts suppressive effects on HCC cell migration and invasion.

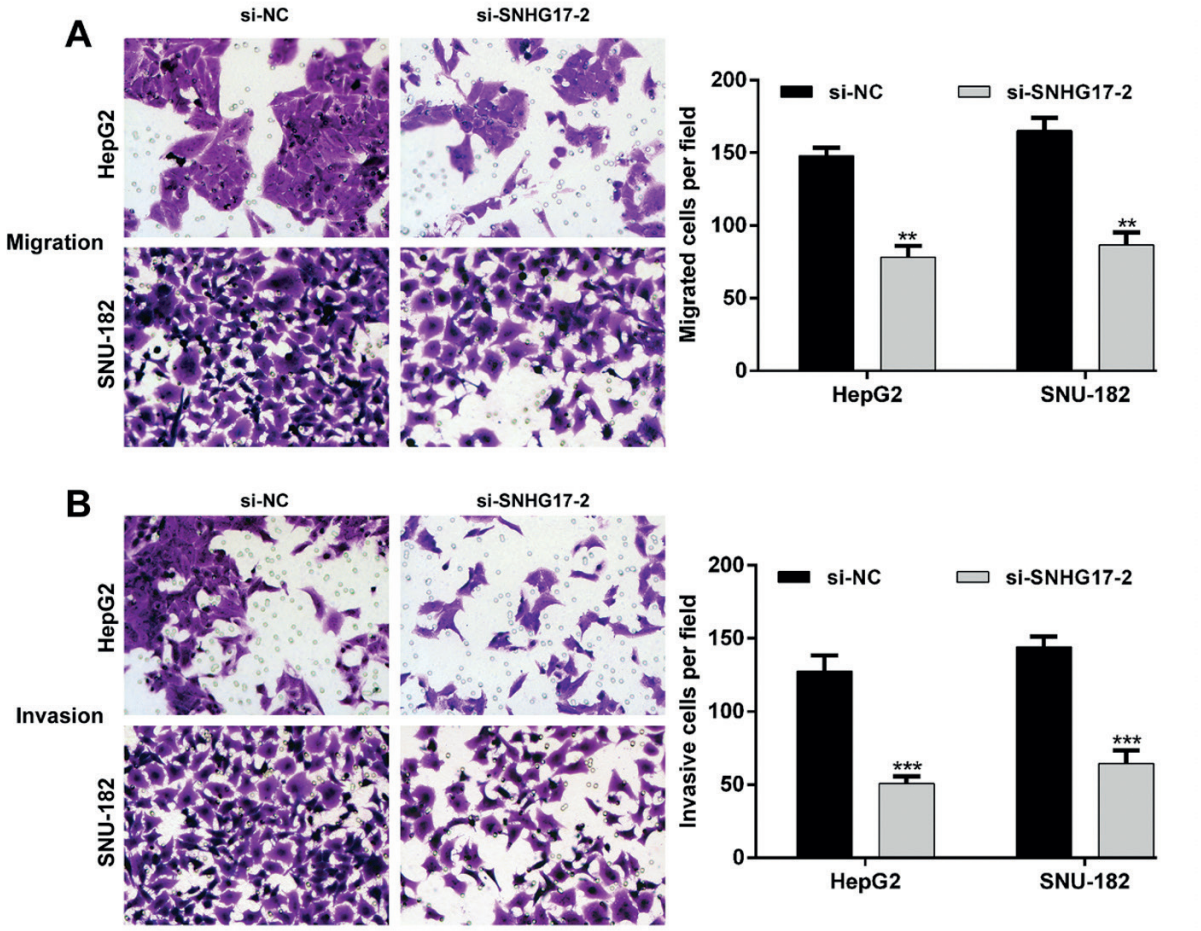

Figure 4. Effects of SNHG17 knockdown on HCC cell migration and invasion. Transwell assay was performed to assess cell migration **(A)** and invasion **(B)** ability in HepG2 and SNU-182 cells transfected with si-SNHG17-2 or si-NC for 48 h (magnification of ×200). Data were shown as mean±SD and the experiment was performed in triplicate. $^{**}p<0.01$, $^{***}p<0.001$, compared with si-NC.

Discussion

In recent years, emerging studies[16,17] have pointed out that lncRNAs have been important regulators involved in the initiation and progression of tumor cellular process by exerting as suppressors or oncogenes. Among them, large family of noncoding genes hosting small RNAs fascinated us for their potential oncogenic features in HCC. For instance, Chang et al[18] showed that SNHG6 promoted HCC cell growth and metastasis by endogenous competing miR-101-3p. Significantly increased SNHG8 expression in HCC was an independent prognostic factor of tumor recurrence[19]. Moreover, Li et al[20] demonstrated that higher expression of SHNG may serve as prognostic biomarkers for HCC prognosis. In agreement with these studies, our data showed that the transcript levels of SNHG17 were significantly upregulated in HCC tissues and significantly correlated with tumor size, TNM stage and poor survival prognosis. Consistently, SNHG17 has been reported to be highly expressed in CRC and was correlated with advanced clinical stage and poor prognosis of patients of this disease[12]. Liu et al[21] showed that SNHG17 was associated with early-stage colon adenocarcinoma.

Functional experiment revealed that the knockdown of SNHG17 suppressed cell proliferation, induced cell cycle G0/G1 phase arrest and apoptosis in HepG2 and SNU-182 cells. It is convinced that cell cycle deregulation or apoptosis was closely linked with uncontrolled cell proliferation as unique characteristics of tumor cells[22-24]. The high metastatic potential is considered as the pivotal reason that is associated with high mortality

in malignancies including HCC[25]. In the metastatic cascade of carcinomas, tumor cell migration and invasion are thought to be an essential step[26]. As expected, SNHG17 knockdown remarkably suppressed the migratory and invasive ability of HepG2 and SNU-182 cells, suggesting its promoting metastatic potential in HCC. As demonstrated by Ma et al[12] down-regulation of SNHG17 significantly inhibited cell proliferation, induced G0/G1 phase arrest and apoptosis in CRC cells. Zhang et al[14] showed that SNHG17 promoted cell proliferation, migration, invasion in gastric cancer. Similar suppressive effects of SNHG17 knockdown on cell proliferation and migration were also reported by Xu et al[15]. To sum up, these findings collectively proved that SNHG17 might be a key regulator in increasing the proliferative and invasive potential of HCC.

Conclusions

Our study indicated the SNHG17 was overexpressed in HCC tissues and associated with poor survival, and we also identified an SNHG17-mediated regulator of HCC cell proliferation, migration and invasion. These findings provide a new perspective for SNHG17 as a promising target for HCC treatments.

Ethics Approval and Consent to Participate

Our study was approved by the Institute Research Ethics Committee at QingDao No.6 People's Hospital (approval no. QDP-235) and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent prior to enrollment in the study.

Authors' Contributions

Lei Du conceived and designed the study. Xiaomeng Zhu and Lin Li mainly performed the experiments and gathered the data. Lili Ren and Yanming Wang analyzed the data and wrote the paper. All authors read and approved the final manuscript..

Consent for Publication

Not applicable.

Conflict of Interest

Not applicable.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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