ORIGINAL ARTICLES

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Long non-coding RNA SNHG1 promotes cell proliferation and tumorigenesis in colorectal cancer *via* Wnt/β-catenin signaling

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Nucleolar RNA Host Gene 1 (SNHG1) is responsible for initiation, progression, and metastasis of various cancers. However, the role and molecular mechanism of SNHG1 is poorly understood in colorectal cancer. Here we discovered that SNHG1 is high-expressed in colorectal cancer cells. We find that SNHG1 knockdown inhibits cell proliferation and induces apoptosis in colorectal cancer. Moreover, SNHG1 can promote the expression of target genes, and SNHG1 expression is positively correlated with WNT expression. Thus, SNHG1 regulates colorectal cancer by Wnt/β-catenin signaling pathway. Our study provides strong evidence that SNHG1 may significantly be associated with the development and progression of colorectal cancer.

1. Introduction

Colorectal cancer is one of the most common malignant tumors and an important public health problem of the digestive system in different populations, with high morbidity and mortality rates (Correale et al. 2016; Lai and Friedman 2016; Wang et al. 2016b). A large number of studies have shown that many genetic and environmental risk factors are involved in the development and progression of colorectal cancer, including the dietary habit, inflammation inducement and other factors, such as genetic mutations (Park et al. 2016; Sharma and Shukla 2016; Suzuki et al. 2016; Yan et al. 2016; Zhang et al. 2016a). However, knowledge about its inherent pathogenesis is far from sufficient. Identification of risk factors or biomarkers could lead to a better understanding of molecular pathways involved in colorectal cancer and provide new therapeutic targets for this disease.

Long non-coding RNA is a class of RNA which has been reported to play various roles in tumorigenesis. It is defined as a type of molecules longer than 200 nucleotides without protein coding potential (Sahu et al. 2016; Zhang et al. 2016b). Small Nucleolar RNA Host Gene 1 (SNHG1) is one kind of non-coding RNA discovered in recent years. The study of Sahu et al. (2016) has shown that higher expression of SNHG1 is significantly associated with poor patient survival. Thus, SNHG1 could be a potential prognostic biomarker for neuroblastoma (Zhang et al. 2016b). Zhang et al. (2016b) have showed that SNHG1 promotes epatocellular carcinoma cells proliferation, cell cycle progression, and inhibits epatocellular carcinoma cells apoptosis (Yin et al. 2016). In view of this, SNHG1 may be a prognostic biomarker and therapeutic target for various tumors. However, the role of SNHG1 in the progression of colorectal cancer remains unknown.

In this present study, we show that SNHG1 is upregulated in colorectal cancer cells. Furthermore, we demonstrate that the knockdown of SNHG1 inhibits cell proliferation and promotes apoptosis in colon cancer cells, while the upregulation of SNHG1 generates opposite results. In addition, we explored the mechanism and found that SNHG1 can activate the Wnt pathway and promote tumor cell proliferation and tumorigenesis. Altogether, our findings provide a new vision for the clinical diagnosis of colorectal cancer.

2. Investigations and results

2.1. *SNHG1 higher expressed in colorectal cancer*

DNA gel electrophoresis was performed to detect the expression of SNHG1. The results are summarized in Fig. 1A. The DNA gel electrophoresis results shown that SNHG1 RNA was highly expressed in the 4 couples of colon cancer cell samples, while was low-expressed in the adjacent tissues. Moreover, the northern blot assay used in the 4 couples of colon cancer cell samples confirmed the result as shown in Fig. 1B. Moreover, a large number of clinical samples were used for the qPCR detection of SNHG1 mRNA expression level. The results shown in Fig. 1C tell that SNHG1 was high-expressed in colon cancer cells. Next, we detected SNHG1 expression level of colon cancer cell lines HCT116, HCT8, HT29, RKO and SW480 by northern blot assay as shown in Fig. 1D. The conclusion was the same with what is described in Figs. 1A,B,C. Samples of 3 stages of colon cancer samples were applied to detect the SNHG1 expression level by qPCR. The results shown in Fig. 1E tell that SNHG1 present increase trend. The results in Fig. 1F shown the Kaplan-Meier survival analysis data in 232 colon cancer patients and tell that a high expression of SNHG1 is associated with low survival rates.

2.2. *Knockdown of SNHG1 inhibits cell proliferation and promotes apoptosis in colorectal cancer*

Then HT29 cells were transfected with siSNHG1 to downregulate the expression of SNHG1. As shown in Fig. 2 A, the SNHG1 expression in HT29 cells was successfully inhibited by Qpcr detection. Then, we tested the cell viability of HT29 cells after the SNHG1 knockdown by MTT. The results shown in Fig. 2 B tell that SNHG1 knockdown inhibited the cell viability in the HT29 cells. In addition, we detected the effect of SNHG1 knockdown on cell cycle. The results in Fig. 2 C tell that the SNHG1 knockdown enforced the G0 and decreased the G1 and S/G2/M phases. The cell cycle research confirms that siSNHG1 inhibits the cell cycle of HT29. Next, we investigated the cell proliferation by FACS, the Ki-67+ rate tells that SNHG1 inhibition decreased cell proliferation (Fig. 2D). The annexinV/PI results (Fig. 2E) tell that SNHG1

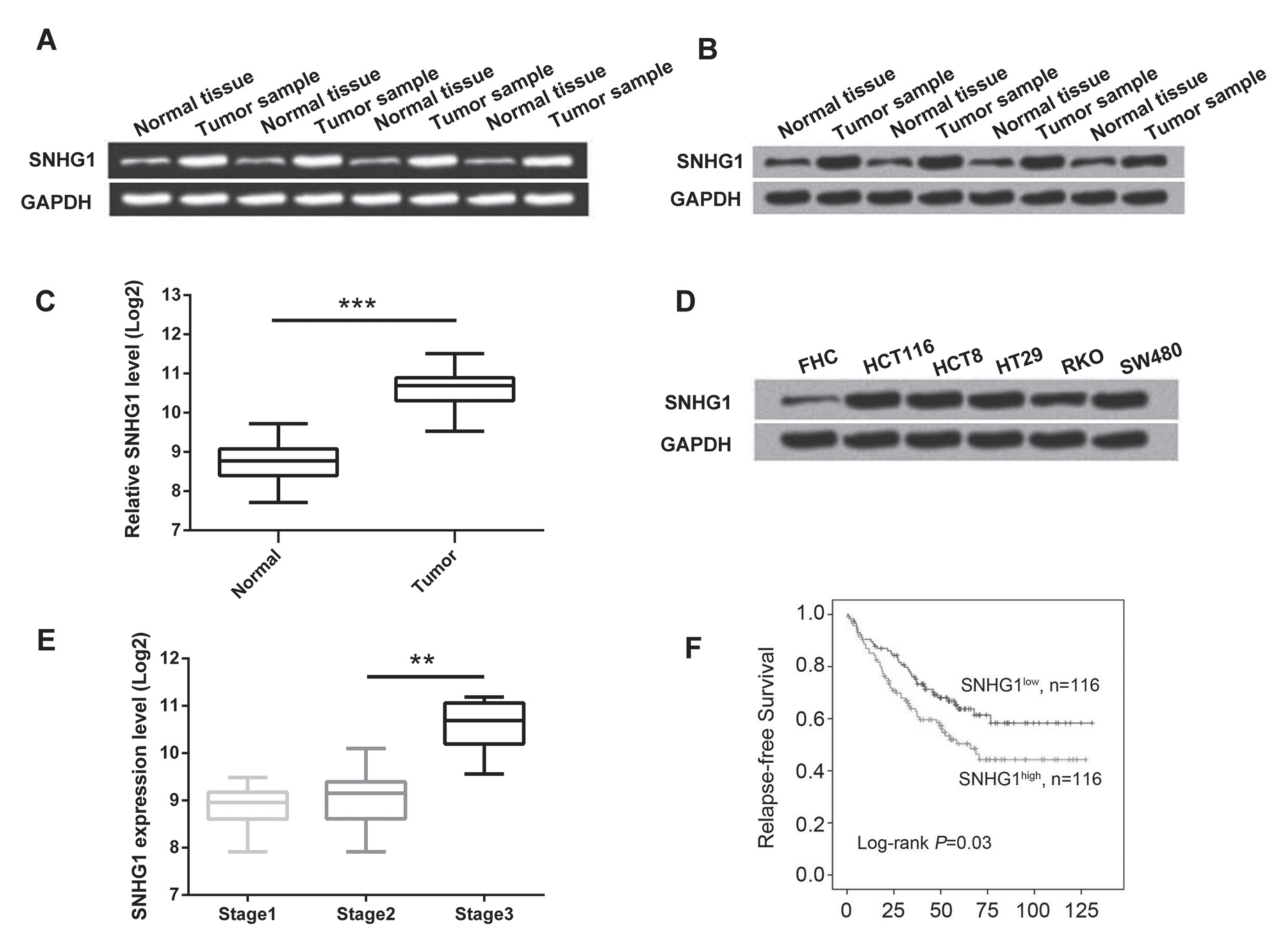

Fig. 1: Expression of SNGH1 in colorectal cancer cells. A, DNA gel electrophoresis of SNGH1 mRNA. B, Western blot results of SNGH1 in colorectal cancer and normal cells samples. C, SNGH1 mRNA level statistics of coloectal cancer samples by qPCR assay. D, Northern blot results of SNGH1 expression in colorectal cancer cells lines HCT116, HCT8, HT29, RKO and SW480. E, SNGH1 expression of different colorectal cancer stages by qPCR. F, Kaplan-Meier survival analysis in232 colorectal cancer patients.

inhibition increased HT29 cell apoptosis. Finally, the western blot assay was applied to detect the expression of BCL2, BID, BAX, Bim, and active caspase 3 in protein level. The results shown in Fig. 2F confirm that SNHG1 inhibition increased HT29 cell apoptosis.

2.3. SNHG1 upregulation promotes cell proliferation and inhibits cell apoptosis in colorectal cancer cell

HT29 cell were transfected with oeSNHG1 to up-regulate the expression of SNHG1. As shown in Fig. 3A, the SNHG1 expression in HT29 cell was successfully promoted. Then, we tested the effect of SNHG1 upregulation on cell viability of HT29 cell by MTT assay. The results shown in Fig. 3B tell that SNHG1 upregulation increased the cell viability in HT29 cells. Meanwhile, we investigated the cell proliferation by FACS as described above, the Ki-67+ rate tells that SNHG1 upregulation increased cell proliferation (Fig. 3C).

Next, the SNHG1 was separately knocked or highly expressed in HT29 cells, and then injected into nude mice. The tumor size was detected after 4 weeks. We found that knockdown of SNHG1 inhibited the tumor weight, while SNHG1 high-expression increased tumor weight (Fig. 3D).

We then tested expression of apoptosis related proteins change after the SNHG1 upregulation by western blot. The results shown in Fig. 3 E SNHG1 upregulation inhibits cell apoptosis.

2.4. SNHG1 regulates the Wnt/β-catenin signaling pathway

In this part of work, we investigated the effect of SNHG1 on the Wnt/β-catenin signaling pathway. LiCl promotes the transcription of the target gene LEF/TCF after activation of the Wnt pathway. The luciferase activity experiments proved that siSNHG1inhibits Wnt activation and gene transcriptioan, while oeSNHG1 promotes Wnt activation and gene transcription (Fig. 4A). Then, we applied western blot and qPCR to detect the β-catenin expression in both mRNA and protein levels. The results shown in Fig. 4B tell that SNHG1 could not regulate the expression of β-catenin. Then, we used western blot assay to monitor the role of SNHG1on β-catenin phosphorylation. From the results shown in Fig. 4C, we believe that siSNHG1 decreased the β-catenin phosphorylation and oeSNHG1 increased β-catenin phosphorylation. Next, western blot results show the siSNHG1 reduces β-catenin transportation to nucleus, while oeSNHG1 increases β-catenin transportation to nucleus (Fig. 4D). Finally, qPCR and western blot assays were separately

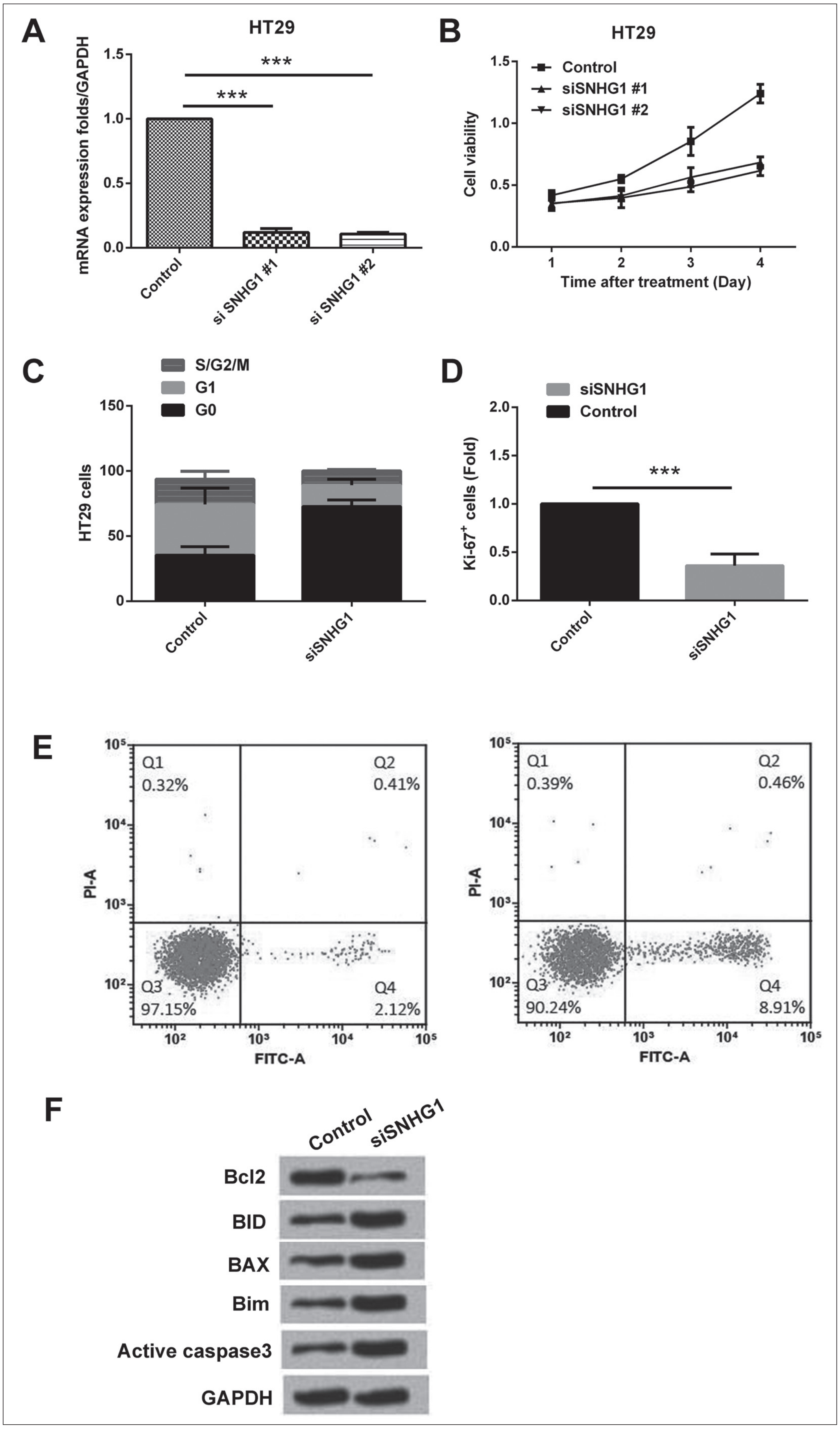

Fig. 2: Effects of SNGH1 knockdown on cell proliferation and cell apoptosis. A, SNGH1 expression was successfully inhibited in HT29 cells in mRNA level. B, SNGH1 knockdown inhibits HT29 cell viability by MTT. C, SNHG1 knockdown enforced the G0 and decreased the G1 and S/G2/M. D, Ki-67+ rate tests the cell proliferation after SNHG1 knockdown. E, AnncexinV/PI results tests HT29 cell apoptosis. F, Western blot assay test the expression of BCL2, BID, BAX, Bim, and active caspase 3 in protein level.

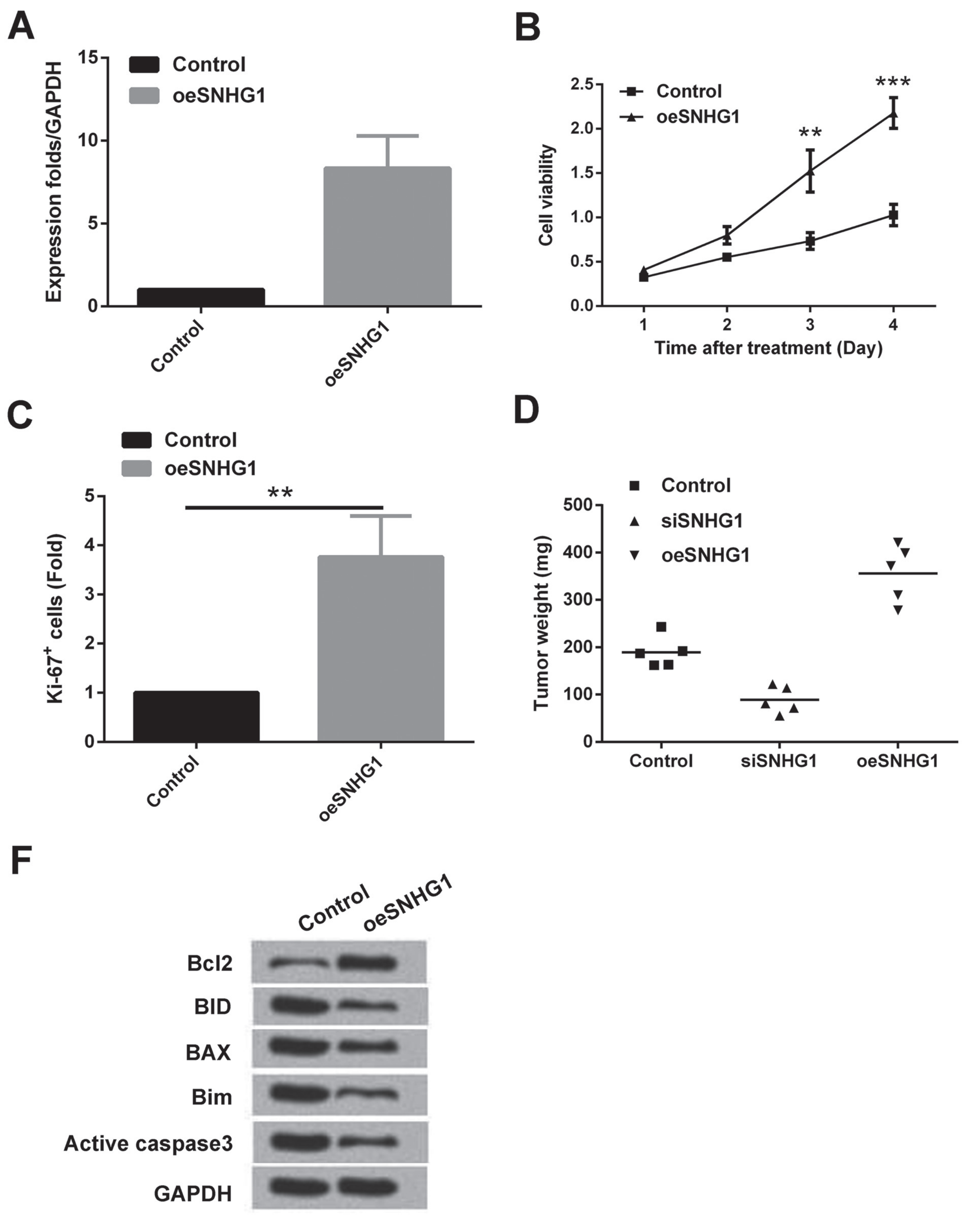

Fig. 3: Effects of SNGH1 upregulation on cell proliferation and cell apoptosis. A, SNGH1 expression was successfully promoted in HT29 cells in mRNA level. B, SNGH1 upregulation promotes HT29 cell viability by MTT. C, Ki-67+ rate results tell that SNHG1 upregulation promotes cell proliferation. D, SNGH1 upregulation increases tumor weight. E, Western blot assay test the expression of BCL2, BID, BAX, Bim, and active caspase 3 in protein level.

applied to test effect of SNHG1 on Wnt/β-catenin pathway in both mRNA and protein level. The results in Fig. 4E, F confirm that siSNHG1 downregulates the gene expression of c-Myc/MMP-7/CyclinD1/TCF7/LEF in both mRNA and protein levels, while the oeSNHG1 has shown an opposite tendency.

2.5. SNHG1 regulates colorectal cancer by the Wnt signaling pathway

First, we detected the Wnt target gene expression of c-Myc/CyclinD1/ TCF7 in tumor and normal cells by qPCR. We found

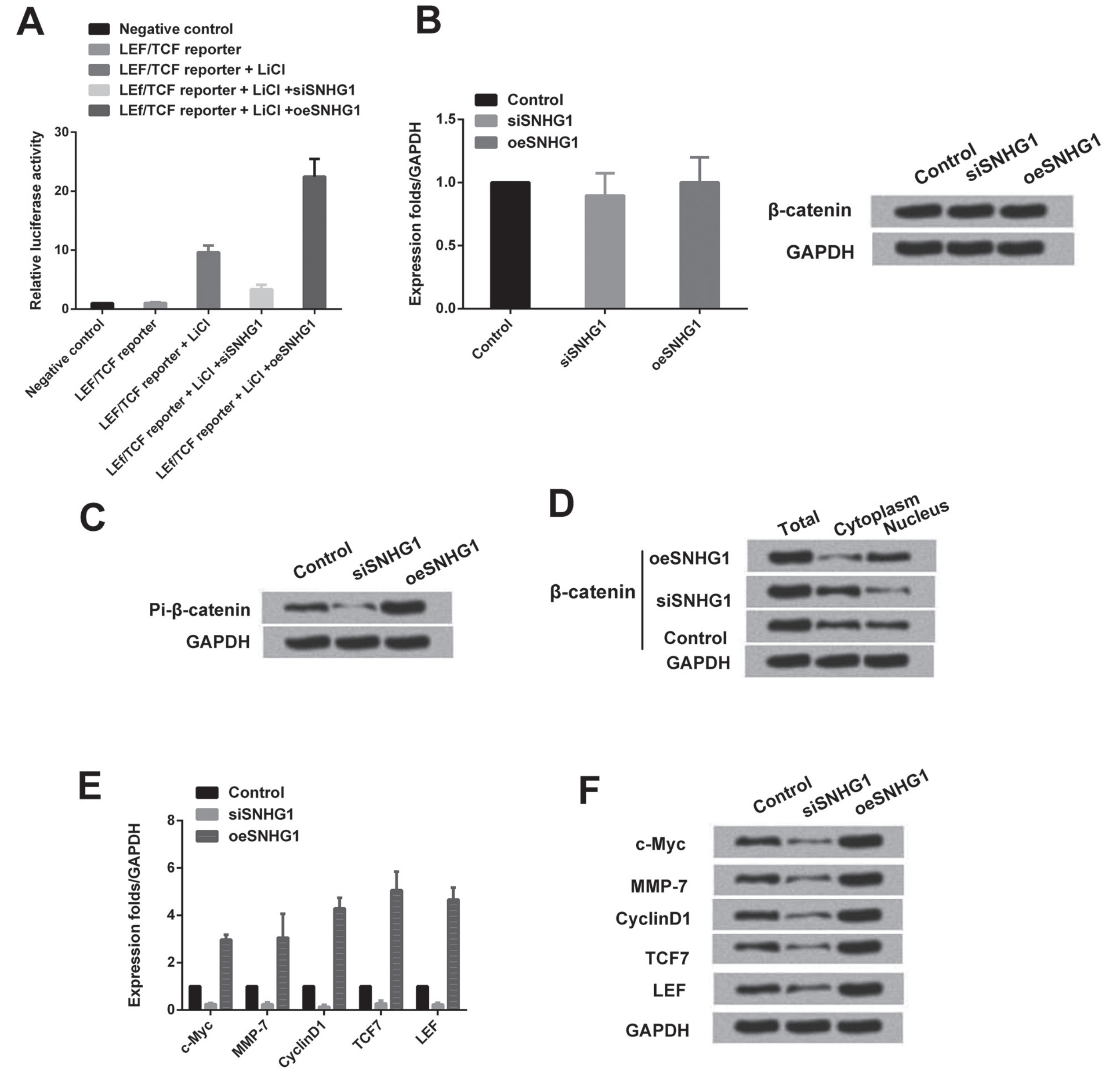

Fig. 4: Effects of SNHG1 on Wnt signaling pathway related factors. A, Testing of luciferase activity after knockdown and upregulation of SNHG1. B, Testing of β-catenin expression in both mRNA and protein level after knockdown and upregulation of SNHG1. C, Connection of SNHG1with β-catenin phosphorylation by western blot. D, Effects of SNHG1 on β-catenin transportation to nucleus. E, Knockdown of SNHG1 downregulates the gene expression of c-Myc/MMP-7/CyclinD1/TCF7/LEF in mRNA level. F, Knockdown of SNHG1 downregulates the gene expression of c-Myc/MMP-7/CyclinD1/TCF7/LEF in protein level.

that c-Myc/CyclinD1/ TCF7 highexpressed in colon cancer cells (Fig. 5A).

Next, Pearson's correlation was conducted to compare the expression of SNHG1and Myc. The results show that there was a positive correlation between SNHG1 and c-Myc expression (Fig. 5B), also with the correlation between SNHG1 and TCF7 expression as shown in Fig. 5C.

Additionally, we compared the influence of oeSNHG1 and the Wnt inhibition on colon cancer cell viability. We found that oeSNHG1 promotes cell viability, while the inhibition of Wnt after upregulation of SNHG1 decreased the cell viability (Fig. 5D).

3. Discussion

Despite of the development of therapeutic strategies, improve of screening, and lifestyle changes, colorectal cancer is the third most common cancer in the world in both men and women (Byun et al. 2014; De et al. 2015; Gao et al. 2012). Long noncoding RNAs are involved in all aspects of cellular physiology critical for cancer initiation, progression, and metastasis (Lan et al. 2017; Li et al. 2015; Wang et al. 2015; Zheng et al. 2016b). As a member of lnc RNAs, SHGH has recently emerged as vital players in tumor biology with potential value in cancer diagnosis, prognosis, and

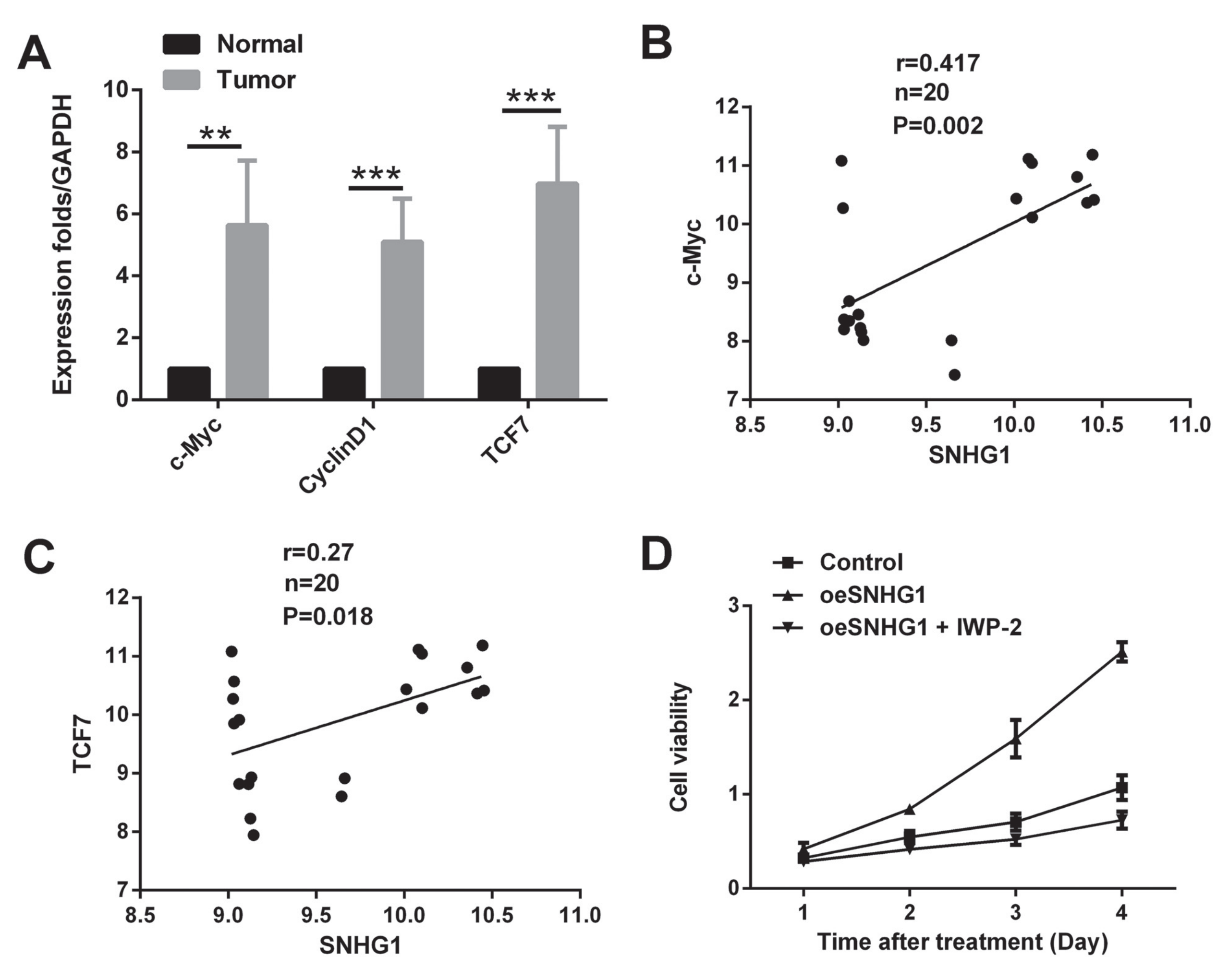

Fig. 5: SNHG1regulates colorectal cancer by Wnt/β-catenin pathway. A, Detection of of c-Myc/CyclinD1/ TCF7 expression in tumor and normal cells by qPCR. B, Pearson's correlation of SNHG1and Myc. C, Pearson's correlation between SNHG1 and TCF7. D, Influence of SNHG1 and the Wnt on colorectal cancer cell viability.

therapeutics (Amnani and Yuen 2016; Ruan et al. 2016; You et al. 2014; Zheng et al. 2016a).

Our study was designed to reveal the underlying connection between lncRNA SNHG1 and colorectal cancer pathogenesis. In our research, the HT29 cell line has been used to study the SNHG1 for colon cancer incidence and progress. We found SNHG1 in the colon cancer cell line and tumor tissues with high expression. Additionally, survival analysis confirmed that samples with SNHG1high expression were associated with a lower survival rate. Next, we found that SNHG1 can promote the proliferation of colon cancer cells through the promotion and inhibition experiment testing of SNHG1.

The Wnt/β-catenin signaling pathway is a crucial mechanism implicated in cellular maintenance and tumorigenesis, which has been reported to regulate cell cycle progression, apoptosis, proliferation, migration, and differentiation (Lee et al. 2014; Mohammed et al. 2016; Zhao et al. 2014). Dysregulation of this pathway correlates with oncogenesis in various tissues including gastric, breast, colon, as well as head and neck cancers (Chiurillo 2015; Novellasdemunt et al. 2015; Zhou et al. 2016).

We further investigated the role and connection of the Wnt/β-catenin signaling pathway with SNHG1 in colorectal cancer regulation. We found that SNHG1 can promote β-catenin phosphorylation, make it into the nucleus, so as to activate Wnt pathways and ultimately regulate the proliferation of colon cancer cells. The western blot analysis demonstrated that the SNHG1 can promote expression of the WNT pathway target genes. Further analysis of the samples found that expression of SNHG1 was positively correlated with the WNT target gene Myc.

All these findings suggest that the non-coding RNA SNHG1 plays an important role in colorectal cancer and provide new a therapeutic target for cancer treatment.

4. Experimental

4.1. Cell culture

Colorectal cancer cell lines (HCT116, HCT8, HT29, RKO, SW480) were purchased from the American Type Culture Collection (ATCC) and cultured according to the manufacturer's instruction. All cell lines used in this study were authenticated through short tandem repeat profiling less than 6 months ago when this project was started (Wang et al. 2016a).

4.2. Transfection and stable cell line construction

Lentiviral constructs expressing SNHG1 shRNA (SNHG1-shRNA-LV) were purchased from Genechem (Shanghai, China). SNHG1-shRNA-LV was transduced into cells at a multiplicity of infection (MOI) of 60 using polybrene (10 μg/ml) and Enhanced Infection Solution (Genechem, China). Meanwhile, for the control group, a non-target negative control virus GFP-LV was transduced into cells. For the negative control, SNHG1 was overexpressed via transfecting of lentiviral particles expressing SNHG1 or GFP. Infected cells were selected with media containing 5 μg/ml puromycin (Wang et al. 2016a).

4.3. MTT assay

The cell proliferative capacities were determined using a 3-(4,5-dimethylthiazol-2-yl)-2 5-diphenyl-2Htetrazolium bromide (MTT) colorimetric assay according to standard methods described before.

4.4. *Apoptosis assay*

Annexin V-FITC/PI apoptosis detection kit (Beijing Biosea Biotechnology, Beijing, China) was used to identify and quantify the apoptotic cells. The cells (100,000 cells/well) were seeded in a 6 well-plate. Treated cells were washed twice with cold PBS and resuspended in buffer. The adherent and floating cells were combined and treated according to the instruction and measured with flow cytometer (Beckman Coulter, USA) to differentiate apoptotic cells (Annexin-V positive and PI-negative) from necrotic cells (Annexin-V and PI-positive).

4.5. *qRT-PCR*

Total RNA was isolated from transfected cells by using TRIzol reagent (Invitrogen) and treated with DNaseI (Promega). Reverse transcription was performed by using the MultiscribeRTkit (Applied Biosystems) and random hexamers or oligo(dT). The reverse transcription conditions were performed as follow: 10 min at 25 °C, 30 min at 48 °C, and a final step of 5 min at 95 °C.

4.6. *Western Blot*

The protein was extracted using RIA lysis buffer (Beyotime Biotechnology, Shanghai, China) supplemented with protease inhibitors (Roche, Guangzhou, China). The proteins were quantified using the BCA™ Protein Assay Kit (Pierce, Appleton, WI, USA). The western blot system was established using a Bio-Rad Bis-Tris Gel system according to the manufacturer's instructions. Primary antibodies were prepared in 5% blocking buffer at a dilution of 1:1,000. Primary antibody was incubated with the membrane at 4 °C overnight, followed by wash and incubation with secondary antibody marked by horseradish peroxidase for 1 h at room temperature. After rinsing, the polyvinylidene difluoride (PVDF) membrane carried blots and antibodies were transferred into the Bio-Rad ChemiDoc™ XRS system, and then 200 μl Immobilon Western Chemiluminescent HRP Substrate (Millipore, MA, USA) was added to cover the membrane surface. The signals were captured and the intensity of the bands was quantified using Image Lab™ Software (Bio-Rad, Shanghai, China).

4.7. *Evaluation of tumorigenicity*

Tumorigenicity was determined by subcutaneously injecting 5×10^4 shCtrl or shSNHG1or oeSNHG1 HT29 cells into the flanks of 6-week-old female BALB/c-nu mice (Animal Center of Chongqing Medical University, China). The tumor size was measured 4 weeks later (Chen et al. 2016).

4.8. *Northern blot*

Total RNA was extracted from U-2OS and Mg63 cells according to TRIZOL methods (Invitrogen) for northern blot. LncRNA and 18S fragments were cloned into PCDNA3 plasmid and northern probes were produced using Biotin RNA Labeling Mix (catalogue 11685597910, Roche). T7 RNApolymerase (catalogue 10881767001, Roche) was used for in vitro transcription. For northern blot, the samples were separated by electrophoresis using formaldehyde gel before membrane transferring. The membranes were incubated with hydration buffer supplemented with a proper amount of probes, and then the nucleicacid signal was detected using Chemiluminescent Nucleic Acid Detection Module(catalogue 89880, Thermo Scientific) (Brown et al. 2014).

4.9. *Statistical analysis*

The results of multiple experiments are presented as the mean ± SD. Statistical analyses were performed using SPSS 19.0 statistical software. The P-values were calculated using a one-way analysis of variance (ANOVA). A P-value of <0.05 indicated a statistically significant result.

Conflicts of interest: There is no conflict of interests. The work was not supported by any funding agency.

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