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LINC00473 functions as an oncogene and predicts poor prognosis in pancreatic cancer *via* the cAMP/β-catenin axis

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Abstract. – OBJECTIVE: To investigate the expression and function of LINC00463 in pancreatic cancer (PC), and to demonstrate the relationship between LINC00473 expression and clinical pathological characteristics and prognosis of PC.

PATIENTS AND METHODS: Expressions of LINC00473 in PC tissues and cell lines were detected using quantitative Real Time-Polymerase Chain Reaction (qRT-PCR). LINC00473 siRNA was synthesized to knock down the LINC00473 expression in PANC-1 cells. Proliferation, invasion, and migration abilities of experimental cells were analyzed using cell counting kit-8 (CCK-8) assay and transwell assay, respectively. cAMP activity was detected and protein expression of β-catenin was measured to explain the underlying mechanism of LINC00473 in PC. The prognosis and clinical pathological features of PC patients were illustrated.

RESULTS: LINC00473 was highly expressed in PC tissues and cells. Higher level of LINC00473 was relative with larger tumor size, worse tumor node metastasis (TNM) stage, worse tumor differentiation, higher rates of perineural invasion, and lymphatic invasion. Knockdown of LINC00473 significantly inhibited cell growth, invasion, and migration of PANC-1 cells. LINC00473 activated cAMP and then promoted the phosphorylation of β-catenin to promote the progression of PC. Furthermore, high expression of LINC00473 and β-catenin remarkedly indicated poor prognosis of PC patients.

CONCLUSIONS: LINC00473 was upregulated in PC tissues and cells, indicating a poor prognosis and clinical pathological features of PC. It promoted PC progression *via* activating the cAMP/β-catenin axis, which provided a novel target for the prediction for PC diagnosis, biological therapy, and prognosis.

Key Words:
LINC00473, Pancreatic cancer, cAMP, Prognosis, β-catenin.

Introduction

Pancreatic cancer (PC) is a highly aggressive malignant tumor, which is the fourth most common cancer-related fatal disease in the United States. More than half of PC patients are diagnosed at an advanced stage, with a 5-year survival rate of less than 5%[1,2]. Due to the insufficient detection of early-stage PC, most people lose the optimal surgical opportunity. It is important to look for indicators for early diagnosis and prognosis of PC.

Long non-coding RNAs (LncRNAs), as one of the non-coding RNAs responsible for regulating tumorigenesis and tumor development in recent years, have been confirmed to be involved in various biological processes such as proliferation, invasion, metastasis, and drug resistance of several types of tumors[3-5]. It could act as oncogene or tumor-suppressor gene to influence the progression of tumors[6]. In PC, many lncRNAs play important regulatory roles. As cancer-promoting lncRNAs, lncRNA-BX111 promotes tumor progression and metastasis *via* increasing ZEB1 transcription of PC. LncRNA SNHG1 could promote cell growth of PC through the PI3K/AKT signaling pathway[7,8]. Conversely, lncRNA XLOC_000647 suppresses epithelial-mesenchymal transition of tumor cells, thus alleviating the invasion and progression of PC by repressing NLRP3. LncRNA lnc-PCTST inhibits PC progression and predicts prognosis *via* downregulating TACC-3[9,10]. Although several lncRNAs have been found to be involved in the regulation of PC, the expression of LINC00473 in PC and its relationship with PC clinical features and prognosis have not been elucidated, and its function and mechanism in PC have not been discovered.

We detected the expression of LINC00473 in 54 paired PC tissue and adjacent paracan-

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cerous tissue samples, as well as in 5 PC cell lines and human pancreatic ductal epithelial cells (HDPE6-C7). Also, clinical pathological characteristics of PC patients were collected and analyzed together with the LINC00473 expression level. Using Cell Counting Kit-8 (CCK-8) and transwell assays, the influence of LINC00473 on PC proliferation and metastasis of PC cells was elucidated. Furthermore, the cAMP/β-catenin was found as underlying mechanism for LINC00473 in influencing the progression of PC.

Our study indicated LINC00473 as an oncogene in PC and suggested poor prognosis of PC patients. It promoted cell proliferation and metastasis *via* activating cAMP to promote the phosphorylation of β-catenin, which furnished available target for the diagnosis and prognosis prediction for PC.

Patients and Methods

Clinical Tissues and Features

This study collected 54 pairs of pancreatic cancer tissues and corresponding paracancerous tissue specimens (≤3 cm from the border of cancer tissue). The samples were taken from PC patients undergoing pancreaticoduodenectomy from December 2014 to March 2016 in the Department of Hepatobiliary and Pancreatic Surgery in Linyi Cancer Hospital. Tissue specimens were quickly placed in liquid nitrogen for rapid freezing, and then stored at –80°C for later use. The investigation was approved by the Hospital Ethics Committee and all patients signed informed consent. Clinical pathological data, such as patient history, tumor location, and tumor node metastasis (TNM) stage classification were collected. Follow-up was conducted by telephone, home visit, and online. The follow-up was started from the postoperative period and terminated on December 2018.

Cell Lines and Culture

Human pancreatic cancer cell lines PANC-1, Capan-1, Bx PC-3, As PC-1, HPAC, and human pancreatic ductal epithelial cells HDPE6-C7 were purchased from the American Type Culture Collection (ATCC; Manassas, VA, USA). PANC-1, HPAC, and Capan-1 cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM; Sigma-Aldrich, St. Louis, MO, USA), while Bx PC-3 and As PC-1 cells were cultured in Roswell Park Memorial Institute-1640 (RPMI-1640) medium (HyClone, South Logan, UT, USA). Both medium was added with 10% fetal bovine serum (FBS; Gibco, New York, NY, USA) and 1000 U/mL penicillin and 100 μg/mL streptomycin (Gibco, New York, NY, USA). Cells were placed in an incubator at 37°C containing 5% CO_2 in humid air.

Cell Transfection

LINC00473 siRNA (siRNA-LINC00473) and its control (siRNA-NC) were compounded by GenePharma (Shanghai, China). When the PANC-1 cells in the logarithmic growth phase grow to 40-50%, siRNA was transfected according to the instructions using Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA). The inhibition efficiency after cell transfection was detected by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR).

RNA extraction and qRT-PCR

Total RNA of PC tissues and cells was extracted using TRIzol reagent (Beyotime, Shanghai, China). Ultraviolet spectrophotometer was used to detect the purity and concentration of RNA. The RNA was reversely transcribed into DNA using TaKaRa Reverse Transcription Kit (TaKaRa, Dalian, China). Then, the PCR was completed using SYBR reagent (TaKaRa, Dalian, China) with ABI 7500 (Applied Biosystems, Foster City, CA, USA) in a 20 μL reaction system. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as an internal control, and the relative expression level of LINC00473 was calculated using the $2^{-\Delta\Delta Ct}$ method. Primers used were as follows: LINC00473 forward: 5'-GGGAGCTTGAGCTGAGATGG-3', reverse: 5'-TTCGCAGTTTCCTAGTGGGAC-3'; GAPDH forward: 5'-CTCACCGGATGCACCAATGTT-3', reverse: 5'-CGCGTTGCTCACAATGTTCAT-3'.

MTT Assay

PANC-1 cells transfected with siRNA-LINC00473 or siRNA-NC were collected and resuspended into 2×10^4 cells/ml. 200 μL of cell suspension was added to 96-well plates and 5 replicate wells were set in each group. After cell culture for 1, 2, 3, or 4 days, the culture medium was discarded and 200 μL of cell culture solution mixing 20 μL of methylthiazolyldiphenyl-tetrazolium bromide (MTT; Beyotime, Shanghai, China) solution was added to each well. After cell culture in the dark for 4 h in a CO_2 incubator, the culture solution was removed, and 150 μL of dimethyl sulfoxide (DMSO; Beyotime, Shanghai, China) solution was added to each well. After mixing, the plate reader (Bio Tek Instruments, Winooski, VT, USA) was used to detect the absorbance value at 570 nm.

Transwell Assay

The 8-μm chamber (Corning, Corning, NY, USA) was employed for the transwell assay. For invasion assay, cell suspension at 5×10^4/mL was prepared in serum-free medium. 200 μL of cell suspension was added to the chamber pre-coated with Matrigel (BD Biosciences, San José, CA, USA). In the bottom chamber, 500 μL of DMEM containing 10% FBS was added. The 24-well plate was placed in a cell culture incubator. After 24 h, the chamber was removed, fixed by paraformaldehyde, and stained with crystal violet. Invasive cells were captured under a microscope. Five fields were randomly taken from each well for cell counting, and the average value was calculated.

For migration assay, procedures were consistent with the invasion experiment except for Matrigel pre-coating.

cAMP Activity Determination

PANC-1 cells were transfected with siRNA-LINC00473 or siRNA-NC. Then, the cAMP activity of established cells was detected using cAMP Activity Assay Kit (Biovision, San Francisco, CA, USA) according to the manufacturers' instructions. The detection was repeated three times.

Western Blot

The total protein in the cells was extracted with the cell protein extraction kit (Beyotime, Shanghai, China), and the protein concentration was quantitatively detected by bicinchoninic acid (BCA) Kit (Beyotime, Shanghai, China). After mixing the protein sample with the loading buffer for 5 min, a total of 20 μg of protein was added to the well. Electrophoresis was carried out with 10% sodium dodecyl sulphate (SDS) gel. The protein was transferred to a polyvinylidene difluoride (PVDF) membrane (Millipore, Billerica, MA, USA). 5% skim milk powder was used to block the unspecific binding site at room temperature for 1 h. After washing 3 times with Phosphate-Buffered Saline and Tween-20 (PBST; with Tween in PBS), the membrane was immersed in primary antibody (1:1000) at 4°C overnight. After incubation in secondary antibody (1:2000) for 1 h at room temperature, the membrane was developed with Bio-Rad using enhanced chemiluminescence (ECL) Kit (Bio-Rad Lab, Hercules, CA, USA), and quantified using GAPDH as an internal reference. All the primary antibodies, including anti-β-catenin and anti-p-β-catenin were purchased from Abcam (Cambridge, MA, USA).

Statistical Analysis

Statistical analysis was performed using Statistical Product and Service Solutions (SPSS) 19.0 software (SPSS Inc., IBM, Armonk, NY, USA) and GraphPad 6.0 software (La Jolla, CA, USA). Normal data were expressed as mean ± SD (standard deviation). The *t*-test was used for comparison between the two groups. Kaplan-Meier method and the log-rank test were applied for survival analysis. $p<0.05$ was considered statistically significant.

Results

LINC00473 Was Over-Expressed in Pancreatic Cancer Tissues and Cell Lines

To study the expression of LINC00473 in PC, we collected 54 paired PC tissues and adjacent paracancerous tissues and detected the LINC00473 level using qRT-PCR. Clearly displayed in Figure 1A, expression of LINC00473 in PC tissues was significantly higher than the expression in adjacent paracancerous tissues. Also, expression of LINC00473 in five PC-derived cell lines, including PANC-1, Capan-1, Bx PC-3, As PC-1, and HPAC, as well as human pancreatic ductal epithelial cells HDPE6-C7 were measured. LINC00473 showed a significant increased expression level in PC cell lines (Figure 1B). These results indicated that LINC00473 might function as an oncogene in PC.

LINC00473 Was Correlated with Clinical Pathological Feathers of PC

We collected the clinical pathological characteristics of the 54 paired PC patients and analyzed the relationships between the characteristics and LINC00473 expression level. The 54 PC patients were divided into high LINC00473 expression group and low LINC00473 expression group based on the median expression level of LINC00473 as the cutoff. Table I showed that there was no significant difference in age ($p=0.7801$), sex ($p=0.7849$) or tumor location ($p=0.7028$) between high expression group and low expression group. However, high LINC00473 expression group had larger tumor size ($p=0.0103$), more advanced TNM stage ($p=0.0308$), worse tumor differentiation ($p=0.0001$), higher rates of perineural invasion (PNI) ($p=0.0242$), and lymphatic invasion ($p=0.0209$) than low LINC00473 expression group. These data suggested that elevated LINC00473 was unfavorable to PC progression.

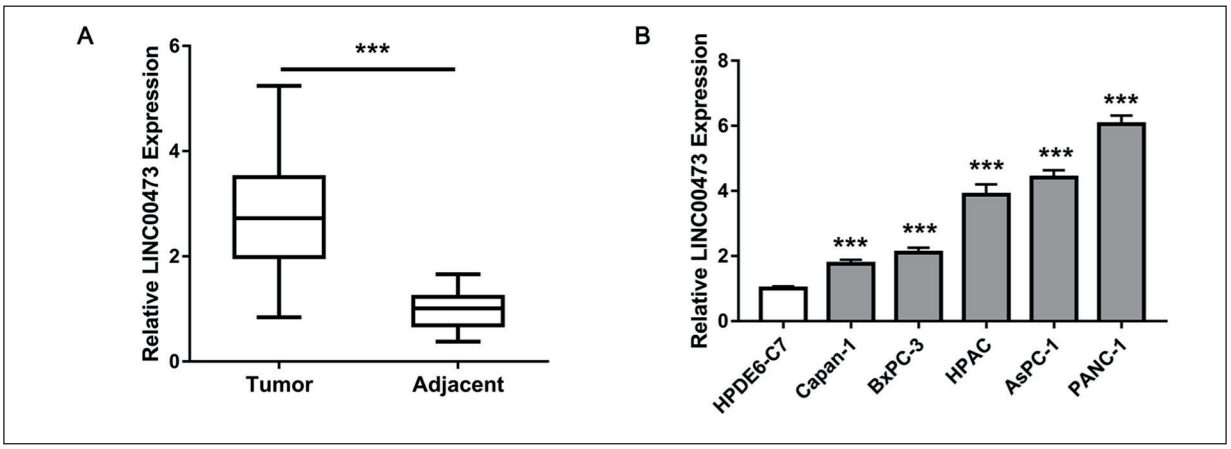

Figure 1. LINC00473 was highly expressed in PC tissues and cells. **A,** QRT-PCR showed the LINC00473 expression level in total of 54 PC tissues and adjacent paracancerous tissues. **B,** LINC00473 expression level in PC cell lines (PANC-1, Capan-1, Bx PC-3, As PC-1, HPAC) and human pancreatic ductal epithelial cells HDPE6-C7. ***p<0.001, **p<0.01 *p<0.05 compared to control group.

Ectopic Expression of LINC00473 Affected Cell Proliferation and Invasion of PANC-1 Cells

To study the function of LINC00473 on PC progression, LINC00473 siRNA was constructed. The proliferation of experimental cells was detected using the MTT assay. Knockdown of LINC00473 significantly inhibited the growth of PANC-1 cells compared with control group (Figure 2A). Transwell assay showed that transfection of si-LINC00473 suppressed the invasion and migration of PANC-1 cells compared with NC group relatively (Figure 2B-2D). These results suggested that knockdown of LINC00473 inhibited cell proliferation and metastasis of PC cells.

LINC00473 Promoted PC Progression via the cAMP/β-catenin Axis

Several studies[11] have verified that LINC00473 could act together with CREB to increase the activity of cAMP in lung cancer. Herein, we detected the cAMP activity in established PANC-1

Table I. Relationship between LINC00473 level and the clinicalpathological characteristics of 54 patients with pancreatic cancer.

			LINC00473 level		
	Group	Total	High	Low	*p*-value
Age	< 65	21	10	11	0.7801
	> 65	33	17	16	
Sex	Male	29	15	14	0.7849
	Female	25	12	13	
Tumor location	Head	36	17	19	0.7028
	Body/Tail	18	10	9	
Tumor size (cm)	< 2	19	5	14	0.0103*
	> 2	35	22	13	
TNM stage	0+I	21	7	14	0.0308*
	II	19	9	10	
	III+IV	14	11	3	
Tumor differentiation (Grade)	Well	24	4	20	0.0001*
	Moderate	19	14	5	
	Poor	11	9	2	
Perineural invasion (PNI)	Positive	34	21	13	0.0242*
	Negative	20	6	14	
Lymphatic invasion	Positive	36	22	14	0.0209*
	Negative	18	5	13	

[a]The median expression level of LINC00473 was used as the cutoff and *Indicated p-value < 0.05.

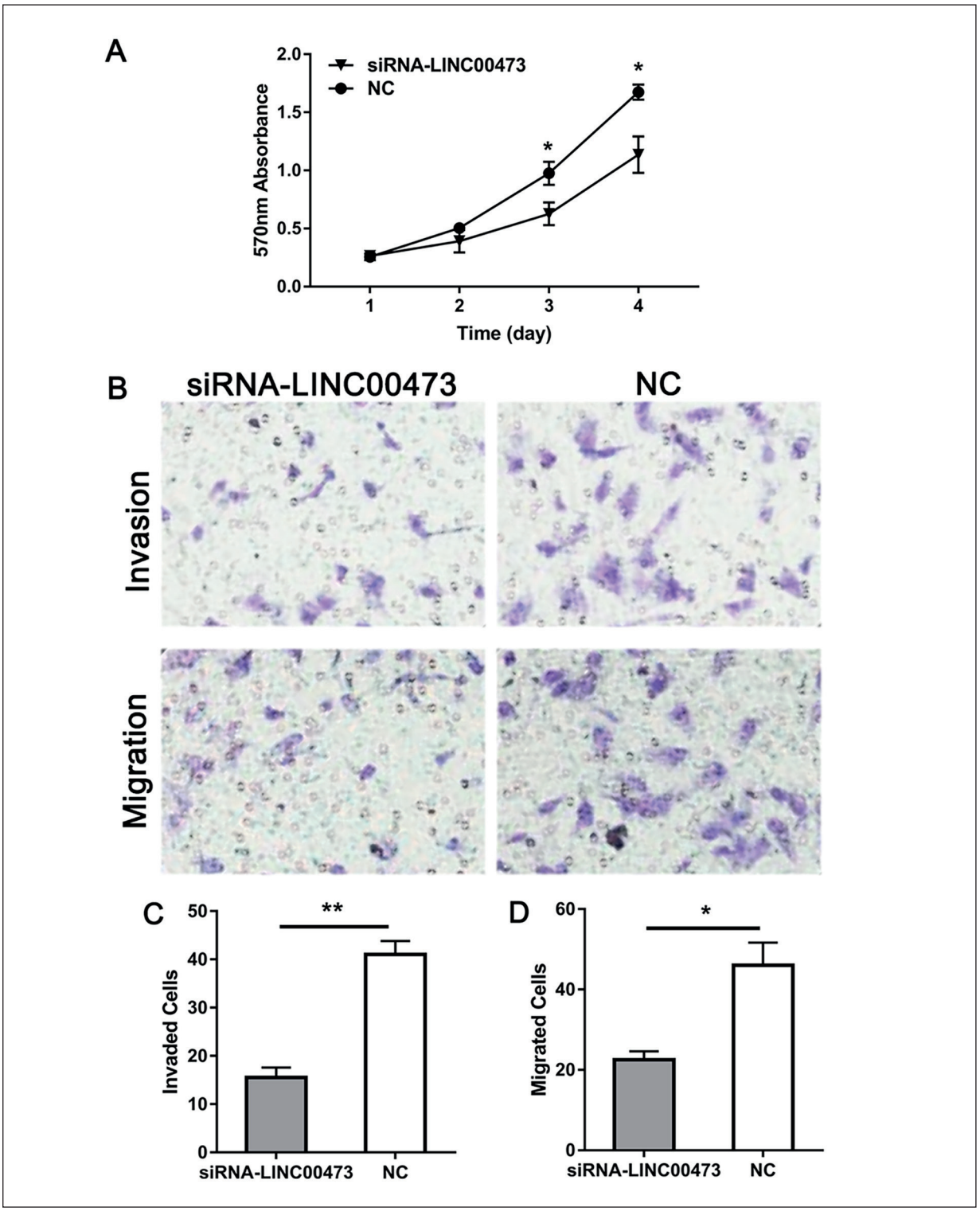

Figure 2. LINC00473 affected the proliferation and metastasis of PANC-1 cells *in vitro*. **A,** MTT assays showed the proliferation ability of PANC-1 cells transfected with si-LINC00473 or si-NC. **B, C,** Transwell invasion assay indicated the invasive cell number in established PANC-1 cells (40×). **B, D,** Transwell migration assay showed the migratory cell number in established PANC-1 cells (100×). **p<0.01, *p<0.05 compared to control group.

cells. Transfection of si-LINC00473 markedly reduced the activity of cAMP (Figure 3A). Next, as cAMP could activate the phosphorylation of β-catenin, we detected the expression levels of β-catenin and p-β-catenin by Western blot. Clearly, expression of p-β-catenin in PANC-1 cells was significantly inhibited by knockdown of LINC00473, while no difference in β-catenin was found compared to si-NC group (Figure 3B, 3C). These results indicated that LINC00473 could play its oncogene role *via* activating cAMP to promote the phosphorylation of β-catenin.

LINC00473 and p-Ð-catenin Indicated Poor Prognosis of Pancreatic Cancer

We conducted long-term follow-up of the above 54 patients, obtained their survival data, and then analyzed the relationship between LINC00473 expression and the prognosis. Kaplan-Meier curve showed that PC patients with high LINC00473 had worse survival compared to patients with low LINC00473 level (Figure 4A). Similarly, the expression of p-β-catenin was detected. High expression of p-β-catenin also indicated worse survival of PC patients (Figure 4B). These data demonstrated that elevated levels of LINC00473 and p-β-catenin indicated poor prognosis of PC patients.

Discussion

Pancreatic cancer is a common and highly malignant tumor of the digestive system. The mortality rate is the fourth leading cause of cancer-related death, and the 5-year survival rate is < 5%[2]. Surgical resection combined radiotherapy and chemotherapy is still the preferred treatment, but the overall survival of patients is not satisfactory[12,13]. Therefore, studying the molecular biological mechanism of PC can provide a new theoretical basis and molecular target for the treatment of PC.

LINC00473 has been mentioned as an oncogene in several tumors including breast cancer, gastric cancer, mucoepidermoid carcinoma, and

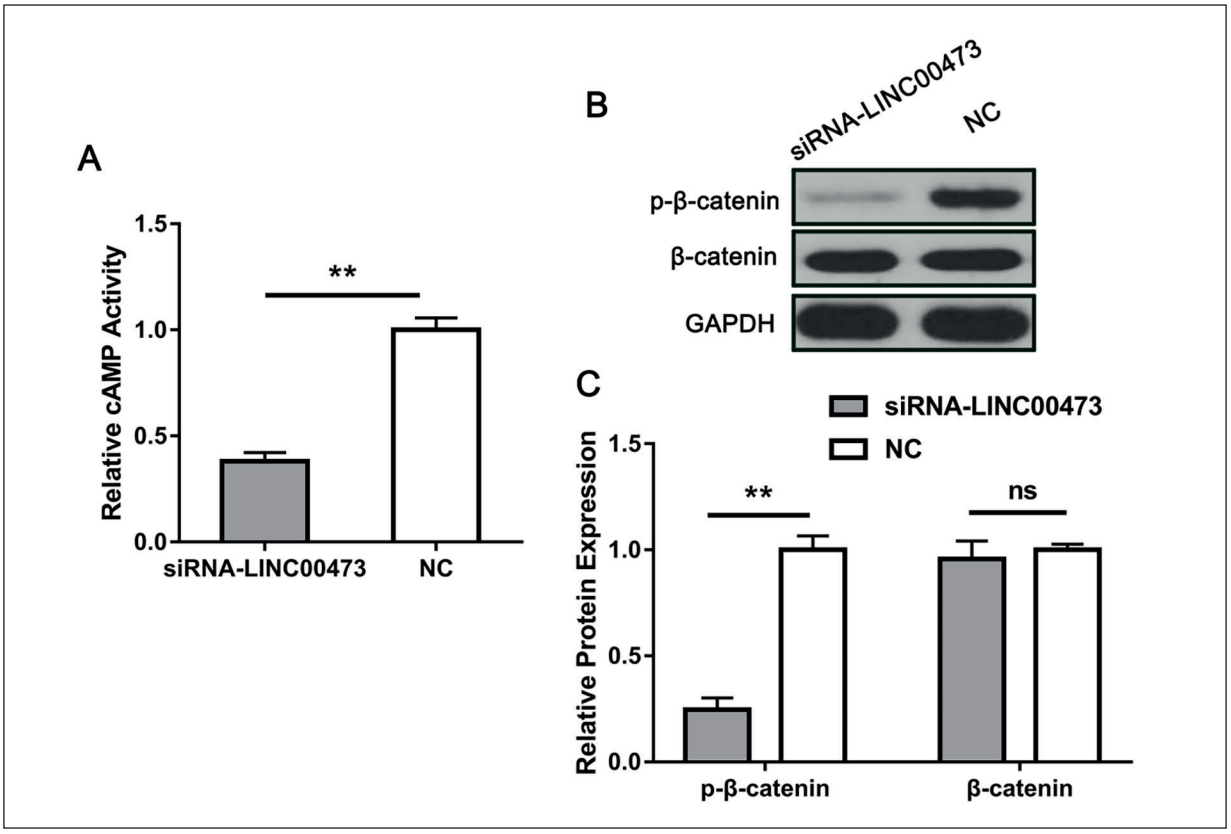

Figure 3. LINC00473 promoted PC progression through the cAMP/β-catenin axis. **A,** Activity of cAMP in PANC-1 cells transfected with si-LINC00473 and si-NC. **B, C,** Western blot showed protein expressions of β-catenin and p-β-catenin in PANC-1 cells transfected with si-LINC0339 or si-NC. GAPDH was used as control. ***p*<0.01 compared to control group.

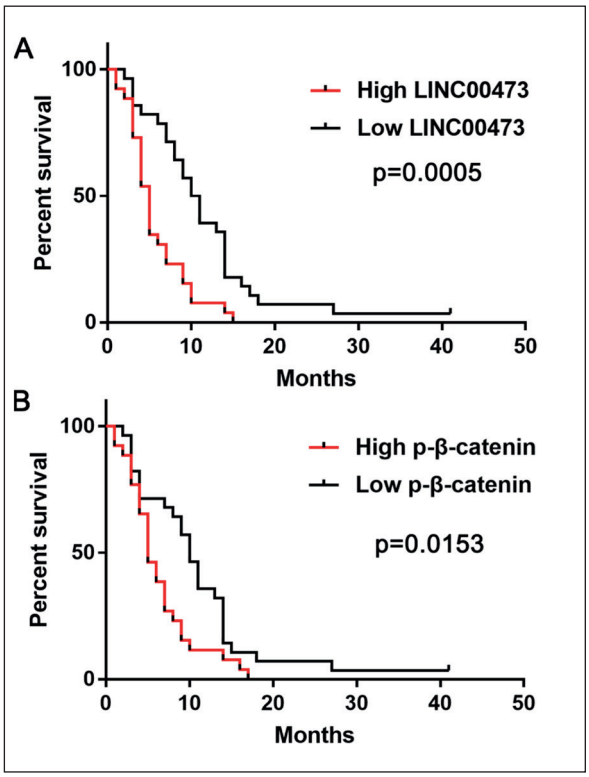

Figure 4. Kaplan-Meier survival analysis on 54 PC patients. **A,** Kaplan-Meier survival indicated PC that patients with high LINC00473 expression in tumor tissues showed significantly decreased survival compared with patients with low LINC00473 expression. **B,** Kaplan-Meier survival indicated that PC patients with high p-β-catenin expression in tumor tissues showed significantly decreased survival compared with patients with low p-β-catenin expression.

hepatocellular carcinoma[14-17]. It also increases radioresistance of HNSCC cells by activating the Wnt/β-catenin signaling and promotes Taxol resistance of colorectal cancer *via* miR-15a[18,19]. However, its expression and function in PC have not been detected before.

For the first time we measured the expression of LINC00473 in PC and found an increase of its level in PC tissues than the adjacent paracancerous tissues. Also, in PC-derived cells, LINC00473 expression was elevated. Furthermore, we analyzed the relationship between LINC00473 level and clinical pathological features. High LINC00473 indicated larger tumor size, more advanced TNM stage, worse tumor differentiation, higher rates of perineural invasion, and lymphatic invasion, indicating a progressive pancreatic cancer stage. Next, the knockdown of LINC00473 in PANC-1 cells inhibited proliferation, invasion, and migration. These might provide a novel target for the PC diagnosis and treatment.

LINC00473 has been reported to participate in the regulation of cAMP activation *via* CREB[11]. We measured the cAMP activity in PANC-1 cells transfected with si-LINC00473 or si-NC. Silence of LINC00473 inhibited cAMP activity of PANC-1 cells. Next, the activation of CREB could accelerate the Wnt/β-catenin signaling pathway[17,20-22]. We measured protein expression of p-β-catenin and it was reduced by inhibition of LNC00473 as we expected. This indicated that LINC00473 could promote the phosphorylation of β-catenin *via* the activation of cAMP. The phosphorylation of β-catenin in turn promoted cell proliferation and metastasis[23,24].

We analyzed the LINC00473-related survival of these 54 patients and found that the survival rate and median survival time of high-expression LINC00473 group were significantly worse than those of low-expression LINC00473 group. Similarly, the survival of high expression group was worse than that of low expression group. These indicated that the high expression of LINC00473 and β-catenin predicted a poor prognosis for PC patients. Although we have demonstrated that LINC00473 acted as an oncogene in PC *via in vitro* assay, further *in vivo* studies are still needed for validating our findings.

Conclusions

We first demonstrated that LINC00473 was highly expressed in PC tissues and cells, and elevated LINC00473 indicated larger tumor size, more advanced TNM stage, worse tumor differentiation, higher rates of perineural invasion, and lymphatic invasion of PC. High level of LINC00473 suggested worse prognosis of PC. LINC00473 could promote cell proliferation and metastasis of PC *via* activating cAMP to activate phosphorylation of β-catenin, which might provide a new valuable marker for PC diagnosis and prognosis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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