Elevated expression of SATB1 is involved in pancreatic tumorigenesis and is associated with poor patient survival

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Received September 13, 2016; Accepted May 26, 2017

DOI: 10.3892/mmr.2017.7683

Abstract. Special AT-rich sequence-binding protein 1 (SATB1) is a master chromatin organizer which has been reported to be implicated in tumor progression in breast and lung cancer. However, its functions in pancreatic tumorigenesis have yet to be elucidated. In the present study, the involvement of SATB1 in pancreatic cancer development was investigated in human BxPC-3 pancreatic adenocarcinoma cells. Short hairpin (sh) RNA was used to stably downregulate SATB1 expression, and functional assays, including cell proliferation, colony formation, soft agar and migration assays, were performed *in vitro*. In addition, a mouse pancreatic cancer xenograft model was created to examine the tumor-promoting properties of SATB1 *in vivo*. The present findings demonstrated that stable knockdown of SATB1 expression inhibited the proliferation, colony formation, anchorage-independent growth and suppressed the migratory capabilities of BxPC-3 cells *in vitro*. In addition, SATB1 downregulation significantly inhibited tumor growth in xenografted mice *in vivo*. Furthermore, SATB1 was revealed to be upregulated in human pancreatic cancer tissue samples compared with matched non-cancerous adjacent tissues, and high SATB1 expression was associated with poor patient survival. Overall, the present study demonstrated that SATB1 promoted the proliferation of pancreatic cancer cells *in vitro*. In addition, SATB1 expression was revealed to be upregulated in human pancreatic cancer tissues and its upregulation was associated with poor patient survival. Therefore, SATB1 may have potential as a novel prognostic biomarker and therapeutic target for the treatment of patients with pancreatic cancer.

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Key words: special AT-rich sequence-binding protein 1, pancreatic cancer, tumor progression, poor survival

Introduction

Pancreatic cancer is one of the most common causes of malignancy-associated morbidities and mortalities worldwide (1). Despite recent developments in surgical treatments and the efficacy of chemotherapeutic agents, the overall prognosis for patients with advanced pancreatic cancer remains poor, whereas the survival rate has not improved in the past few decades. This may be attributed to the asymptomatic nature of pancreatic cancer until the advanced stages of the disease, which constitutes a challenge for early diagnosis (2). The 5-year overall survival rate for patients with advanced pancreatic cancer is <10% (1). In China, the 5-year survival rate in patients with pancreatic cancer is 4.1% and the median survival time is limited to 3.9 months (3). Therefore, the need to identify novel prognostic biomarkers for the detection of pancreatic cancer at an early stage is of primary concern.

The special AT-rich sequence-binding protein 1 (SATB1) is a nuclear matrix-associated protein which is involved in higher-order chromatin organization and in the regulation of tissue-specific gene expression (4,5). SATB1 is primarily expressed in thymocytes and facilitates thymocyte development through its interaction with the Wnt-β-catenin signaling pathway (5,6). SATB1 has been associated with the development of several types of cancer, including glioma, colorectal, breast, lung and kidney cancers (7-11). Various genes that are regulated by SATB1 have been implicated in carcinogenesis, including erbB-2, Abelson murine leukemia viral oncogene homolog 1, matrix metalloproteinase 2, E-cadherin, vascular endothelial growth factor B, transforming growth factor-β1 and kisspeptin (12,13). In addition, upregulation of SATB1 expression has been associated with unfavorable clinicopathological features and poor patient survival (8,10,14), whereas SATB1 depletion has been reported to suppress the proliferation, growth and invasion of breast cancer cells, through the modulation of gene expression (15). Furthermore, silencing of SATB1 expression has been demonstrated to prevent tumor growth and metastasis, whereas transduction of SATB1 into non-metastatic cells promotes tumor invasion in mice (16). However, the effects of SATB1 on the development and progression of pancreatic cancer have yet to be elucidated.

In the present study, the effects of SATB1 downregulation on pancreatic cancer cell proliferation and tumorigenic properties were investigated *in vitro* and *in vivo*. In addition,

the expression levels of SATB1 in tumor tissue samples from patients with pancreatic cancer were detected and association with patient survival was investigated.

Materials and methods

Cell culture and treatment. The human BxPC-3 pancreatic adenocarcinoma cell line was purchased from American Type Culture Collection (Manassas, VA, USA). Cells were cultured in Dulbecco's modified Eagle's medium (DMEM; Thermo Fisher Scientific, Inc., Waltham, MA, USA) supplemented with 10% fetal bovine serum (FBS; Thermo Fisher Scientific, Inc.), and maintained at 37˚C in a 5% CO_2 atmosphere.

Patient samples. The present study was approved by the Institutional Research Ethics Committee of the People's Hospital of Xinjiang (Urumqi, China). Written informed consent was obtained from patients prior to enrollment in the present study. A total of 48 patients who were admitted in People's Hospital of Xinjiang between 2013 and 2015 were included in the present study. Patient characteristics are presented in Table I. Patients were diagnosed with pancreatic cancer based on histopathological examination. No patients received chemotherapy or radiotherapy prior to surgery. Cancer tissue and adjacent normal tissue (distance >10 cm from the primary tumor) samples were isolated from patients who underwent tumor resection, and were immediately frozen in liquid nitrogen and stored at -80˚C. Tissue samples were fixed in 10% neutral-buffered formalin at room temperature for 24 h. Following fixation, tissue samples were dehydrated by immersion in increasing concentrations of alcohol. Alcohol was cleared with xylene and tissues were embedded in paraffin by heating to 60˚C and allowed to harden at room temperature overnight.

Lentiviral transduction and stable colony selection. For the production of the lentivirus, 1 μg control short hairpin (sh)RNA (cat no. sc-108060; Santa Cruz Biotechnology, Inc., Dallas, TX, USA) or SATB1-targeting shRNAs (cat no. sc-36460; Santa Cruz Biotechnology, Inc.) were co-transfected with 1 μg packaging plasmids (0.4 μg pMD2G and 0.6 μg psPAX2; Santa Cruz Biotechnology, Inc.) into human 293FT cells (80% confluent) in DMEM supplemented with 10% FBS, using Effectene transfection reagent (Qiagen, Inc., Valencia, CA, USA) according to the manufacturer's protocol. Lentiviral supernatants were collected 48 h post-transfection and filtered through a 0.45 μm filter to remove debris. BxPC-3 cells cultured in DMEM supplemented with 10% FBS (80% confluent) were transduced at room temperature with 500 μl of viral supernatants at a multiplicity of infection of 10, containing 4 μg/ml Polybrene transfection reagent (Sigma-Aldrich; Merck KGaA, Darmstadt, Germany) for 18 h, and resistant colonies were selected with 2 μg/ml puromycin (Sigma-Aldrich; Merck KGaA) for 7 days. Successful transduction was confirmed by western blotting. Control cells were transduced with control shRNA.

Western blot analysis. Total proteins were extracted from 200,000 BxPC-3 cells following shRNA transduction, using Laemmli SDS reducing buffer (50 mM Tris-HCl pH 6.8, 2% SDS and 10% glycerol) at 4˚C, boiled and quantified using a bicinchoninic acid protein assay. Equal amounts (30 μg) of extracted protein samples were resolved by 8-10% PAGE and transferred onto polyvinylidene difluoride membranes. The membranes were blocked with 3% milk at room temperature for 1 h, incubated with primary antibodies against SATB1 (cat no. ab92307; 1:1,000; Abcam, Cambridge, UK) and GAPDH (cat no. 2118; 1:2,000; Cell Signaling Technology, Inc., Danvers, MA, USA) for 1 h at room temperature, followed by incubation with horseradish peroxidase-conjugated goat anti-rabbit secondary antibody (cat no. sc-2030, Santa Cruz Biotechnology, Inc.) at a dilution of 1:5,000 at room temperature for 1 h. Protein bands were visualized by enhanced chemiluminescence using the SuperSignal West Pico or Femto Chemiluminescent Substrate kits (Thermo Fisher Scientific, Inc.). Blots were semi-quantified using ImageJ software version 1.41 (National Institutes of Health, Bethesda, MD, USA) (17).

Cell proliferation assay. BxPC-3 cells stably expressing control shRNA or SATB1 shRNA were seeded in DMEM supplemented with 10% FBS at a density of 10,000 cells/well in 6-well plates in triplicate on day 0. Cells were trypsinized and counted using a TC20 Automated Cell Counter (Bio-Rad Laboratories, Inc., Hercules, CA, USA) on days 0, 1, 2 and 3. Each experiment was performed twice using cells from different suspensions.

Colony formation assay. BxPC-3 cells stably expressing control shRNA or SATB1 shRNA were seeded in 6-well plates at a density of 1,000 cells/well and cultured in DMEM supplemented with 10% FBS at 37˚C. Cells were cultured for 1 week and then washed three times with PBS, fixed in 4% paraformaldehyde for 15 min, and stained with 0.1% crystal violet for 30 min at room temperature. Subsequently, the colonies (diameter, >1 mm) were carefully washed with PBS until the background was clear and visualized under an optical microscope. Colony formation efficiency was calculated as the number of colonies divided by 1,000 and normalized to control shRNA infected cells using ImageJ software verson 1.41.

Soft agar assay. BxPC-3 cells (1,000 cells) stably expressing control shRNA or SATB1 shRNA were suspended in 0.375% Noble agar (Difco; BD Biosciences, Franklin Lakes, NJ, USA) in DMEM supplemented with 10% FBS and overlaid on 0.75% Noble agar in 24-well plates. Colonies were allowed to grow for 7-10 days in the growth medium. Colony formation efficiency was calculated according to the following formula: Colony formation efficiency=(mean number of colonies/well)/(number of seeded cells/well). Colonies with a diameter >0.1 mm were measured and counted, and the mean was used. Data was expressed as fold-change compared to cells expressing the control vector. GraphPad Prism software version 5 (GraphPad Software, Inc., La Jolla, CA, USA) was used for analysis.

Matrigel invasion assay. A total of 10^5 BxPC-3 cells stably expressing control shRNA or SATB1 shRNA were serum-starved overnight, suspended in DMEM and plated into the upper chambers of 8.0-μm pore Transwell inserts which were coated with 400 μg/ml Matrigel (BD Biosciences).

Table I. Characteristics of patients enrolled in the present study.

Characteristics	Patients
Age at diagnosis, median (range)	59 (34-77)
Age at time of study, median (range)	61 (36-79)
Gender	
Male, n (%)	22 (45.8)
Female, n (%)	26 (54.2)
Total, n	48
Pathology	
Ductal adenocarcinoma, n (%)	43 (89.5)
Adenocarcinoma associated with intraductal papillary mucinous neoplasm, n (%)	5 (10.5)

A total of 500 μl medium supplemented with 10% FBS was added to the lower chambers as a chemoattractant. Cells were incubated at 37˚C for 24 h. Non-migrated cells on the top of the membrane were removed using cotton swabs, and cells that had migrated to the lower membrane were stained with 6% glutaraldehyde/0.5% crystal violet solution at room temperature for 30 min. Experiments were performed in triplicate. Invaded cells were visualized under an optical microscope, and counted using ImageJ software (17), by averaging the number of stained cells/field of view in 5 random fields/chamber.

IHC. Paraffin-embedded tumor and adjacent normal 5-μm thick tissue sections were subjected to antigen retrieval by heating in a microwave at 100˚C for 10 min in 0.1 M citric acid buffer (pH 6.0), deparaffinized in xylene and rehydrated in graded ethanol. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide for 1 h at room temperature, following permeabilization with ice-cold 100% methanol for 10 min at -20˚C and rinsed in PBS for 5 min. Sections were then incubated with an anti-SATB1 antibody (1:200; cat no. ab92307; Abcam) at 4˚C overnight. Following incubation with HRP-conjugated secondary antibodies (cat no. BA-1000; 1:200; Vector Laboratories, Inc., Burlingame, CA, USA) at room temperature for 1 h, the slides were developed in 0.05% 3,3'-diaminobenzidine (Vector Laboratories, Inc.) containing 0.01% hydrogen peroxide at room temperature for 1 min. As a negative control, sections were incubated with normal goat serum (Invitrogen; Thermo Fisher Scientific, Inc.), instead of primary antibodies, at 4˚C overnight. The density of the staining was ranked as follows: 0, no staining; 1, mild staining; 2, moderate staining; and 3, intense staining. The extent of staining was scored as follows: 0, no positive cells; 1, positive cells cover <10% of total area; 2, positive cells cover 10-50% of total area; and 3, positive cells cover >50% of total area. The final staining score was obtained by multiplying the intensity score with the extent score. The samples were classified into 2 groups according to the final score: Low (0-4) and high (5-9).

Mouse xenografts. Animal experiments were approved by the Institutional Animal Care and Use Committee of the National Cancer Center (Urumqi, China). BXPC-3 cells expressing control shRNA or SATB1 shRNA ($3x10^6$ cells/injection) were subcutaneously injected into both flanks of 10 female nude mice (age, 6 weeks; weight, ~25 g). The mice were purchased from the Chinese University of Hong Kong (Hong Kong, China) and maintained in individually ventilated cages under a 12-h light/dark cycle at 20-22˚C and 40-60% relative humidity with free access to food and water. Between days 8 to 26 post-implantation, tumor volumes were measured using a caliper according to the following formula: Tumor volume (mm^3)=tumor length x (tumor width)^2/2]. Data were expressed as the mean tumor volume ± standard deviation. Mice were sacrificed 26 days post-implantation by CO_2 inhalation.

RNA isolation and reverse transcription-quantitative polymerase chain reaction (RT-qPCR). Total RNA was extracted from cancer tissue and paired normal mucosal tissue samples isolated from 48 patients with pancreatic cancer using TRIzol® (Invitrogen; Thermo Fisher Scientific, Inc.), according to the manufacturer's protocol. Total RNA (1 μg) was reverse transcribed into cDNA using RevertAid™ First Strand cDNA Synthesis kit (Thermo Fisher Scientific, Inc.). The reaction volume was 20 μl and contained 1 μg RNA and 1 μl dT primer, 4 μl reaction buffer, 2 μl dNTP, 0.5 μl inhibitor and 0.5 μl reverse transcriptase. The temperature protocol was as follows: At 65˚C for 10 min, at 25˚C for 10 min, at 55˚C for 30 min, and then at 85˚C for 5 min. PCR was performed on cDNA using a ViiA™ 7 Real-Time PCR system (Applied Biosystems; Thermo Fisher Scientific, Inc.) with SYBR® Premix DimerEraser™ (Takara Bio, Inc., Otsu, Japan) according to the manufacturer's protocol. Each experiment was performed in triplicate. Primer sequences were as follows: SABT1, forward 5'-AAAAGAAATCGGACCACCAAGC-3', reverse 5'-TGTGGTACGGAGCTGATCG-3'; and GAPDH, forward 5'-GGCCAAGGTCATCCATGACAA-3' and reverse 5'-TCTTCTGACACCTACCGGGGA-3'. Thermocycling conditions were as follows: Initial denaturation at 95˚C for 2 min, followed by 40 cycles at 95˚C for 10 sec, and at 60˚C for 30 sec, with an extension at 72˚C for 30 sec. The specificity of the amplification products was confirmed by the exhibition of a singlet in the melting curve and gene expression was quantified according to the comparative Cq method (18).

Statistical analysis. Data are expressed as the mean ± standard deviation of 3 independent experiments. Data were analyzed using one-way analysis of variance (ANOVA) or mixed-factorial ANOVA, where appropriate. Multiple comparisons were then further investigated using Tukey post hoc test. $P<0.05$ was considered to indicate a statistically significant difference. Survival curves were constructed using the Kaplan-Meier method and compared using log-rank test. Statistical analyses were performed using SPSS software version 16 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism software version 5.0 (GraphPad Software, Inc., La Jolla, CA, USA).

Results

SATB1 knockdown inhibits the proliferation and suppresses the clonogenicity of pancreatic cancer cells. To examine the functions of SATB1 on pancreatic cancer cell growth, stable

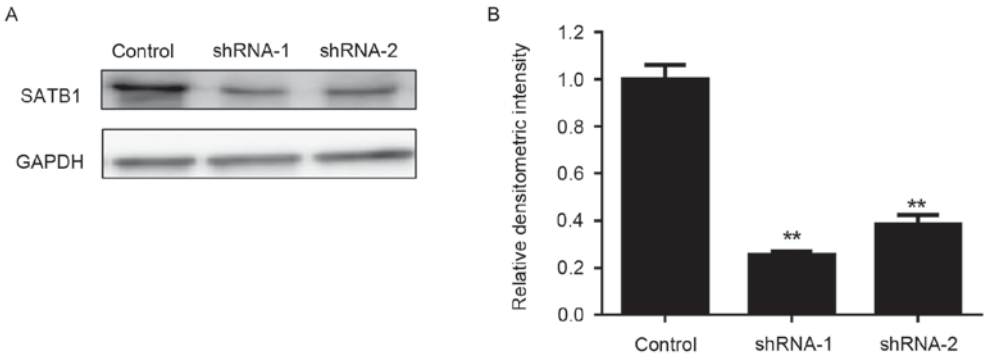

Figure 1. Downregulation of SATB1 expression using shRNAs in human BxPC-3 pancreatic adenocarcinoma cells. (A) Silencing of SATB1 expression in BxPC-3 cells using 2 independent shRNAs targeting SATB1 was confirmed using western blot analysis. (B) Blots were semi-quantified using densitometry. Control cells were transduced with control shRNA. Data are expressed as the mean ± standard deviation. **P<0.01 vs. Control. SATB, special AT-rich sequence-binding protein; sh, short hairpin.

SATB1-knockdown BxPC-3 cells were established using RNA interference. As presented in Fig. 1, following transduction with 2 independent shRNAs targeting SATB1, the protein expression levels of SATB1 in BxPC-3 cells were significantly downregulated. Knockdown of SATB1 expression significantly inhibited the proliferation of BxPC-3 cells compared with control cells, as demonstrated by a cellular proliferation assay (Fig. 2A). In addition, BxPC-3 cells transduced with SATB1-specific shRNAs exhibited significantly suppressed colony formation capabilities (Fig. 2B), thus suggesting that SATB1 may enhance the proliferation and clonogenicity of pancreatic cancer cells.

SATB1 knockdown suppresses the anchorage-independent growth and invasion of pancreatic cancer cells. Soft agar growth and Matrigel invasion assays were performed to evaluate the effects of SATB1 knockdown on the tumorigenic properties of pancreatic cancer cells. As presented in Fig. 3, following the downregulation of SATB1 expression, the anchorage-independent growth of BxPC-3 cells was significantly inhibited. In addition, the invasive capabilities of cancer cells were significantly reduced following SATB1 shRNA transduction, as demonstrated by the Matrigel invasion assay.

SATB1 knockdown inhibits tumor growth in a pancreatic cancer xenograft mouse model. To investigate the effects of SATB1 on pancreatic cancer cell growth *in vivo*, a mouse xenograft model was established following the subcutaneous injection of BxPC-3 cells expressing control shRNA or SATB1 shRNA-1 into nude mice. Tumor growth was monitored for 26 days post-xenotransplantation. As demonstrated in Fig. 4, SATB1 downregulation significantly reduced the weight and growth rate of tumor xenografts *in vivo*. These findings suggested that SATB1 may serve a role in promoting tumor growth *in vivo*.

SATB1 expression is upregulated in pancreatic cancer tissues and is associated with poor prognosis. Pancreatic cancer tissue and matched non-cancerous adjacent tissue samples were isolated from 48 patients with pancreatic cancer. Semi-quantitative RT-PCR demonstrated that the mRNA expression levels of SATB1 were significantly upregulated in pancreatic cancer tissues compared with in matched control samples (Fig. 5A). In addition, IHC results revealed that pancreatic cancer tissues exhibited stronger SATB1 staining compared with non-cancerous tissue samples (Fig. 5B). The patient cohort was divided into low and high SATB1 expression groups according to the IHC scoring, and a Kaplan-Meier survival analysis was performed. As presented in Fig. 5C, patients with high SATB1 expression had significantly shorter overall survival times compared with patients with low SATB1 expression scores.

Discussion

Pancreatic cancer is one of the most malignant types of cancer, and is characterized by a high incidence of metastasis and a low 5-year survival rate. Platinum-based antineoplastic drugs or paclitaxel combination chemotherapy are the standard regimens used for the treatment of pancreatic cancer; however, the recurrence rate of the disease remains as high as 85% (2) Therefore, the need to identify novel therapeutic targets for the treatment of pancreatic cancer is of primary concern.

SATB1 has been suggested to regulate gene expression by selectively tethering far-distal specialized DNA sequences to its cage-like network, and scaffolding them with chromatin-modifying and transcription factors in order to accurately modulate gene expression (19,20). Previous studies have reported that SATB1 is overexpressed in metastatic breast cancer cell lines and in tissue specimens isolated from patients with metastatic breast carcinoma (21,22). Depletion of SATB1 has been demonstrated to suppress cancer cell growth and inhibit tumor metastasis, whereas its overexpression promotes tumor growth and lung colonization in breast cancer (15). A previous study reported that transient silencing of SATB1 expression inhibits the proliferation and invasion of small cell lung cancer cells (23). However, the effects of SATB1 downregulation on pancreatic cancer tumorigenesis have yet to be elucidated.

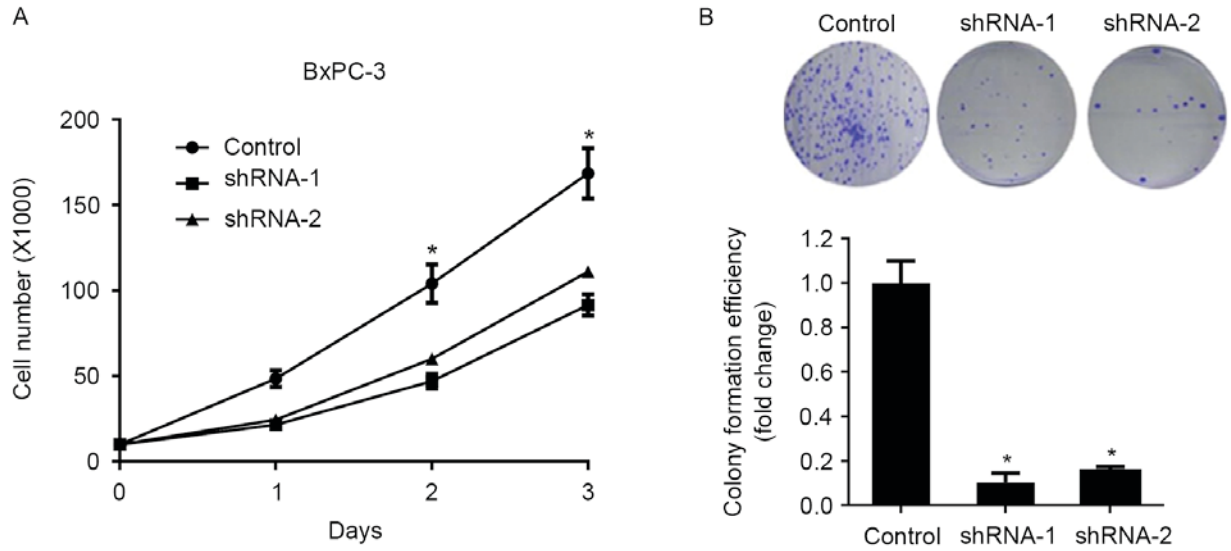

Figure 2. Downregulation of SATB1 expression suppresses the proliferation and clonogenicity of human BxPC-3 pancreatic adenocarcinoma cells. (A) Growth curves of BxPC-3 cells stably expressing control or SATB1-targeting shRNAs. (B) Colony formation capabilities of BxPC-3 cells stably expressing control or SATB1-targeting shRNAs. Data are expressed as the mean ± standard deviation. *P<0.05 vs. Control. SATB, special AT-rich sequence-binding protein; sh, short hairpin.

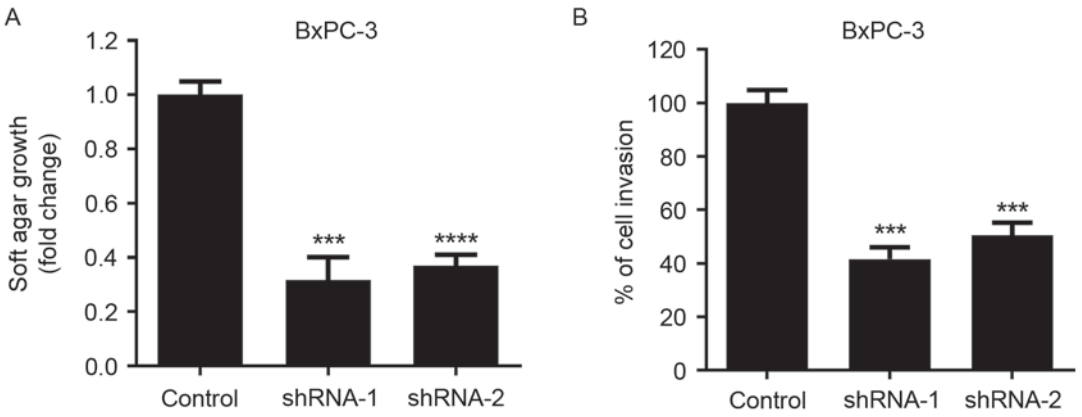

Figure 3. Downregulation of SATB1 expression suppresses the anchorage-independent growth and invasion of human BxPC-3 pancreatic adenocarcinoma cells. (A) A soft agar growth assay detected the anchorage-independent growth of BxPC-3 cells stably expressing control or SATB1-targeting shRNAs. (B) A Matrigel invasion assay assessed the invasive capabilities of BxPC-3 cells stably expressing control or SATB1-targeting shRNAs. Data are expressed as the mean ± standard deviation. ***P<0.001, ****P<0.0001 vs. Control. SATB, special AT-rich sequence-binding protein; sh, short hairpin.

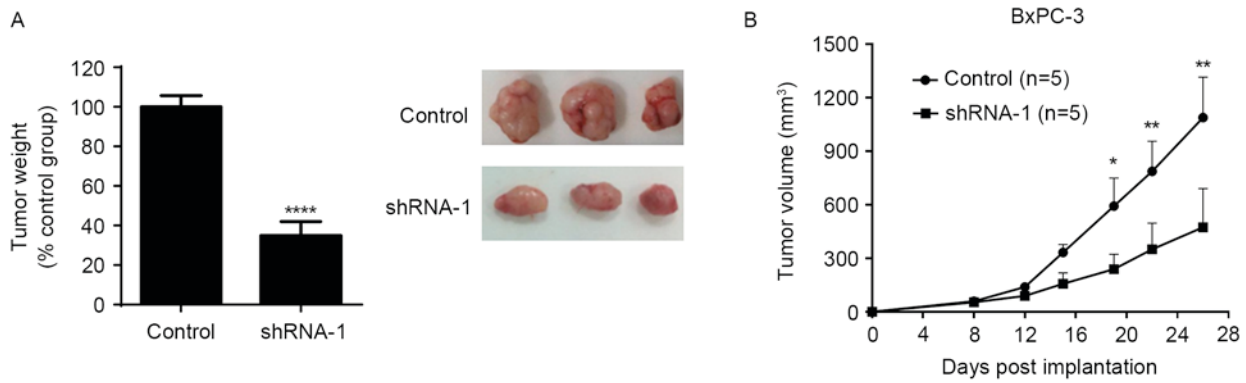

Figure 4. Downregulation of SATB1 expression inhibits tumor growth in a mouse xenograft model. (A) Weight and representative images of the xenograft tumors isolated from mice implanted with human BxPC-3 pancreatic adenocarcinoma cells stably expressing control or SATB1-targeting shRNA-1. (B) Growth curves of tumor xenografts isolated from mice implanted with human BxPC-3 pancreatic adenocarcinoma cells stably expressing control or SATB1-targeting shRNA-1 (n=5 mice/group). Data are expressed as the mean ± standard deviation. *P<0.05, **P<0.01, ****P<0.0001 vs. Control. SATB, special AT-rich sequence-binding protein; sh, short hairpin.

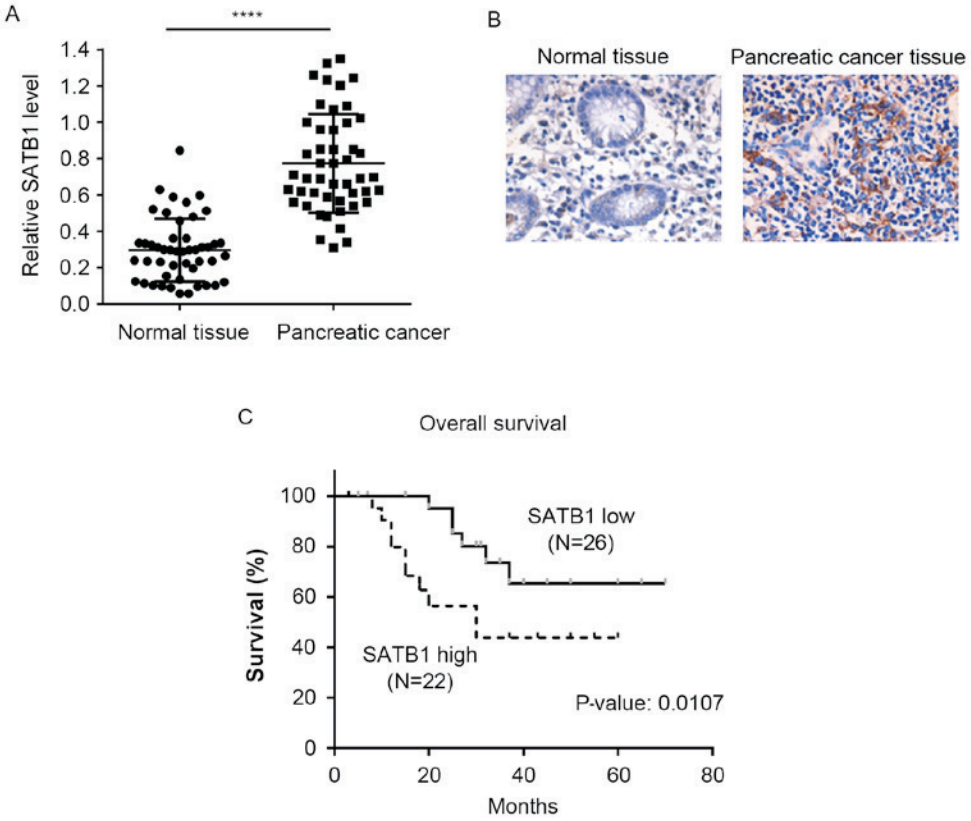

Figure 5. SATB1 expression is upregulated in tumor tissue samples isolated from patients with pancreatic cancer, and is associated with poor survival. (A) SATB1 mRNA expression was assessed in tumor and adjacent non-cancerous tissue samples isolated from 48 patients with pancreatic cancer. Dots represent the mRNA expression level of SATB1 for each patient. (B) Representative immunohistochemical staining of pancreatic cancer and adjacent non-cancerous tissue samples. Magnification, x200. (C) Overall survival in patients with pancreatic cancer with low or high levels of SATB1 expression. Survival curves were constructed using Kaplan-Mier analysis and statistical analysis was performed using the log-rank test. ****P<0.0001. SATB, special AT-rich sequence-binding protein.

In the present study, stable downregulation of SATB1 expression using RNA interference significantly inhibited the proliferative, colony formation and invasive capabilities of BxPC-3 cells, and suppressed soft agar growth. In addition, SATB1 knockdown repressed tumor growth in a xenograft mouse model. SATB1 may be implicated in pancreatic tumorigenesis through the regulation of several genes known to be involved in carcinogenesis; however, further studies are required to investigate the molecular mechanisms and downstream effectors of SATB1 that are involved in the development of pancreatic cancer. Pan *et al* (24) reported that high SATB1 expression is significantly correlated with the progression and metastasis of breast cancer, and thus with poor disease prognosis. Similarly, in the present study, SATB1 expression was revealed to be significantly upregulated in pancreatic cancer tissues compared with in matched non-cancerous adjacent tissues. Notably, Kaplan-Meier survival analysis revealed that high SATB1 expression was significantly associated with decreased patient survival, thus suggesting that SATB1 may have potential as a prognostic biomarker for patients with pancreatic cancer.

In conclusion, the results of the present study suggested that SATB1 may be implicated in pancreatic tumorigenesis. SATB1 was revealed to be significantly upregulated in pancreatic cancer tissues and was associated with poor survival of patients with pancreatic cancer. Therefore, SATB1 may have potential as a novel therapeutic target for the treatment of patients with pancreatic cancer, and as a biomarker for disease prognosis. However, further studies are required to fully elucidate the molecular mechanisms that underlie the implication of SATB1 in promoting pancreatic cancer progression.

Acknowledgements

The present study was supported by the People's Hospital of Xinjiang, Urumqi, China (grant no. 829020801).

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