Somatostatin receptor-1 induces cell cycle arrest and inhibits tumor growth in pancreatic cancer

Min Li,[1,4] Xiaochi Wang,[2] Wei Li,[3] Fei Li,[1] Hui Yang,[1] Hao Wang,[1] F. Charles Brunicardi,[1] Changyi Chen,[1] Qizhi Yao[1] and William E. Fisher[1,4]

[1]Molecular Surgeon Research Center, Elkins Pancreas Center, Michael E. DeBakey Department of Surgery, [2]Department of Immunology, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030, USA; [3]School of Chinese Medicine, Shandong University of Traditional Chinese Medicine, 53 Jingshi Road, Jinan 250014, China

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Functional somatostatin receptors (SSTR) are lost in human pancreatic cancer. Transfection of SSTR-1 inhibited pancreatic cancer cell proliferation *in vitro*. We hypothesize that stable transfection of *SSTR-1* may inhibit pancreatic cancer growth *in vivo* possibly through cell cycle arrest. In this study, we examined the expression of *SSTR-1* mRNA in human pancreatic cancer tissue specimens, and investigated the effect of SSTR-1 overexpression on cell proliferation, cell cycle, and tumor growth in a subcutaneous nude mouse model. We found that *SSTR-1* mRNA was downregulated in the majority of pancreatic cancer tissue specimens. Transfection of *SSTR-1* caused cell cycle arrest at the G_0/G_1 growth phase, with a corresponding decline of cells in the S (mitotic) phase. The overexpression of SSTR-1 significantly inhibited subcutaneous tumor size by 71% and 43% ($n = 5$, $P < 0.05$, Student's *t*-test), and inhibited tumor weight by 69% and 47% ($n = 5$, $P < 0.05$, Student's *t*-test), in Panc-SSTR-1 and MIA-SSTR-1 groups, respectively, indicating the potent inhibitory effect of SSTR-1 on pancreatic cancer growth. Our data demonstrate that overexpression of SSTR-1 significantly inhibits pancreatic cancer growth possibly through cell cycle arrest. This study suggests that gene therapy with SSTR-1 may be a potential adjuvant treatment for pancreatic cancer. (*Cancer Sci* 2008; 99: 2218–2223)

Pancreatic cancer has the number one fatality rate of all cancers, and is the fourth leading cause of cancer related deaths in North America. Overall 5-year survival rate is less than 5%. The risk of developing ductal adenocarcinoma, which constitutes 95% of the pancreas neoplasms, increases with age, cigarette smoking, chronic pancreatitis and a family history of the disease.[1] Unfortunately, there are no effective screening tests, and pancreatic cancer is typically diagnosed at an advanced stage. The vast majority of patients present with non-specific symptoms, and diagnosis does not occur until the onset of jaundice and weight loss, signs of advanced disease. The only effective treatment of pancreatic cancer is surgical resection; however, 80% of pancreatic adenocarcinomas are unresectable at presentation. In addition, even the minority of patients who undergo resection, often develop local recurrence and die within 15 months of diagnosis.[2,3] Clearly, there is a need to understand more about the mechanism of pancreatic cancer and to develop more effective treatments for this deadly disease.

A small cyclic neuropeptide called somatostatin, and its analogs such as octreotide, lantreotide and vapreotide, have been used for treating pancreatic carcinoma in preclinical trials as adjuvants because of their inhibitory effects in a variety of biological processes including cell proliferation and growth hormone release.[4,5] Somatostatin interacts with five different types of somatostatin receptors (SSTR) at different affinities to transduce the signals inside the cells. SSTR are G-protein-coupled receptors, and the five SSTR play different physiological roles and function via different signaling pathways. Although there are five SSTR subtypes, studies with CHO cells expressing each SSTR subtype reveal a predominant role for SSTR-1 and SSTR-2 in mediating the antiproliferative effect.[4] SSTR-1 activation inhibits hormone secretion and cell viability, and inhibits adenylyl cyclase activity when expressed in CHO-K1 cells.[6,7] SSTR-2 is the most abundant SSTR subtype detected in many tissues, and most clinically used somatostatin analogs preferentially bind to SSTR-2, which plays a major role in regulating hormone secretion, apoptosis and cell proliferation in pancreatic cancer. Studies using *SSTR-2* stably transfected cell lines showed significant inhibition of cell growth and induction of apoptosis by SSTR-2.[8–10] Inhibition of tumor growth *in vivo* by overexpressed SSTR-2 was also observed in a nude mouse model.[11] Our study also indicated that after co-transfection of *SSTR-1* and *-2* genes in Panc-1 cells, somatostatin analog treatment augmented the growth inhibitory effect in a dose-dependent manner beyond that seen with individual *SSTR* gene transfer alone.[12]

Despite promising cell culture and animal studies, clinical trials of somatostatin analogs in the adjuvant treatment of advanced pancreatic cancer have failed to demonstrate a response.[13–16] Presence of SSTR was not examined in these clinical trials. However, the published work suggests that the reason animal and cell culture studies have shown a response to somatostatin but clinical trials have failed, is a loss of functional SSTR in most human pancreatic cancers. This indicates that increasing the concentration of SSTR on human pancreatic adenocarcinoma cells may render pancreatic cancers vulnerable to growth inhibition, and represent a novel gene therapy strategy to treat pancreatic cancer. Most of the previous studies are focused on SSTR-2, and little is known about the role of SSTR-1 in pancreatic cancer suppression. In the present study, we transfected *SSTR-1* gene into Panc-1 cells, and assessed the cell cycle after the transfection, and also investigated the inhibitory effect of SSTR-1 in a nude mouse model with subcutaneous xenografts.

Materials and Methods

Chemicals and reagents. Rabbit anti-SSTR-1 antibody was purchased from Novus Biologicals (Littleton, CO, USA), and other chemicals were purchased from Sigma (St Louis, MO, USA). Fluorescein isothiocyanate-conjugate secondary antirabbit immunoglobulin G was purchased from Vector Lab (Burlingame, CA, USA). RNAqueous-4PCR kit and DNAse I removing reagent were purchased from Ambion (Austin, TX, USA). iQ SYBR Green supermix, and reverse transcription kit

[4]To whom correspondence should be addressed.
E-mail: wfisher@bcm.edu, or minli@bcm.edu

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were obtained from Bio-Rad (Hercules, CA, USA). MTS reagent was purchased from Promega (Madison, WI, USA).

Cells and human tissue specimens. Human pancreatic cancer cell lines, Panc-1 and MIA PaCa-2, were purchased from the American Type Culture Collection (ATCC, Rockville, MD, USA). All cells were cultured as previously described.[17,18] Human pancreatic adenocarcinoma specimens were collected from patients who underwent surgery according to an approved human protocol at Baylor College of Medicine (Houston, TX, USA).

RNA extraction. Total RNA was extracted from Panc-1 and MIA Paca-2 cells and pancreatic cancer tissue specimens, using an Ambion RNAqueous-4PCR kit following the manufacture's instructions. Briefly, cells or homogenized tissues were lyzed by Ambion lysis buffer for 20 min and the lysates were transferred to an Ambion mini-column, and centrifuged at 10 000 *g* for 1 min. The column was washed three times. After incubation with 50 μL of elution buffer, the flow-through was collected using a new tube. The RNA solution was treated with DNAse I to remove the trace amount of genomic DNA contamination by using an Ambion DNA removing kit. DNAse I (1 μL) was added to 20 μL of RNA solution with proper DNAse I buffer, and incubated at 37°C for 2 h. The DNAse I was removed by adding 0.1–0.2 volume of DNAse removing agent, and the purified RNA was collected by centrifugation at 10 000 *g* for 1 min.

Primer design and real-time reverse transcription polymerase chain reaction. Specific primers for the *SSTR-1* gene were designed using Beacon Designer ver. 5.0 software (PREMIER Biosoft International, Palo Alto, CA, USA) as described previously.[18,19] The primer sequences for the human *SSTR-1* gene are as following: 5′-GGCGAAATGCGTCCCAG-3′ sense and 5′-CGGAGTA GATGAAAGAGATCAGGA-3′ antisense. The mRNA levels for SSTR-1 were analyzed by real-time reverse transcription polymerase chain reaction (RT-PCR) using a Bio-Rad iCycler system (Bio-Rad). The mRNA were reverse-transcribed into cDNA using an iScript cDNA synthesis kit. The primer specificity was tested by running a regular PCR for 40 cycles at 95°C for 20 s and 60°C for 1 min, and followed by an agarose gel electrophoresis. The real-time PCR was performed by using a SYBR supermix kit, and running for 40 cycles at 95°C for 20 s and 60°C for 1 min. Each cDNA sample was run in triplicate and the corresponding non-reverse transcriptase (non-RT) mRNA sample was included as a negative control. The β-actin primer was included in every plate to avoid sample variations. The mRNA level of each sample for each gene was normalized to that of the β-actin mRNA. Relative mRNA level was presented as 2^(Ct[β-actin] – Ct[gene of interest]). All data shown were the mean ± standard deviation of three separate experiments.

Cell cycle analysis. Panc-1 cells transfected with *SSTR-1* gene or vector control were serum starved for 24 h in serum-free medium and then released using medium with 2% serum. Cells were then collected by trypsinization, and processed using the CycleTEST PLUS DNA Reagent Kit (Beckton Dickinson, San Jose, CA, USA) according to the manufacturer's instructions. Briefly, after trypsinization the cells were centrifuged, and cells were washed in a buffer containing sodium citrate, sucrose and dimethylsulfoxide. Cells were then incubated sequentially for 10 min each in solution A (containing trypsin in a spermine tetrahydrochloride detergent buffer for the enzymatic digestion of cell membranes and cytoskeletons), solution B (containing trypsin inhibitor and ribonuclease A in citrate-stabilizing buffer with spermine tetrahydrochloride to inhibit the trypsin activity and to digest the RNA) and solution C (containing propidium iodide [PI] and spermine tetrahydrochloride in citrate stabilizing buffer for the stoichiometric binding of PI to the DNA at a final concentration of 125 μg/mL). Flow cytometry analysis was carried out to examine the cell cycle distribution in a Beckton Dickinson FACSCalibur analyzer (Becton Dickinson). Data was further analyzed using the software FLOWJOW ver. 6.1.1 (Tree Star, San Carlos, CA, USA) with the 'Watson pragmatic model'.

Stable cell line selection. SSTR-1 overexpression cells were selected in Panc-1 and MIA PaCa-2 cells, respectively, with retrovirus vector pBabe (Clontech, Mountain View, CA, USA), following manufacturer's instructions as described previously.[20,21] Briefly, full length human *SSTR-1* cDNA was cloned into pBabe vector, and the recombinant plasmid was co-transfected into 293T cells with plasmid PegPam3 and RDF. Viral supernatants were collected and transduced to the target cells. Stable cell lines were selected by adding 0.5–1 μg/mL puromysin. The overexpression of SSTR-1 in the stable cell lines was confirmed by real-time RT-PCR.

Cell proliferation assay. Cell proliferation was analyzed with the MTS assay. Stable Panc-1 or MIA PaCa-2 cells were seeded in 96-well plates (2×10^3 cells/well), and serum-starved (0% fetal bovine serum) for 24 h. Cell growth was assessed at 2 days after starvation. MTS reagent (20 μL) mixed with 100 μL growth medium was added to each well, and incubated in 37°C for 2 h. Absorbance was recorded at 490 nm with an EL-800 universal microplate reader (Bio-Tek Instruments, Winooski, VT, USA).

Subcutaneous pancreatic cancer mouse models. Subconfluent stable pancreatic cancer cells with SSTR-1 overexpression were harvested by trypsinization, and resuspended in Dulbecco's modified Eagle's medium. A quantity of 3×10^6 cells were inoculated into the right flank of 5–6-week-old male nude mice (NCI-Charles River) as described previously.[20,21] The tumor size was measured weekly using a digital caliper (VWR International, Marietta, GA, USA) and the tumor volume was determined with the formula: tumor volume (mm^3) = (length [mm]) × (width [mm])^2 × 0.52. The tumor weight was measured at week 6. The animals were euthanized when their tumor size reached 2 cm in diameter or the animals became moribund during the observation period, and the time they were killed was recorded as the time of mortality.

Statistical analysis. Quantitative results are shown as means ± standard deviations. The statistical analysis was performed by Student's *t*-test for paired data between control and treated groups or one-way ANOVA for data from multiple groups. $P < 0.05$ was considered significant.

Results

SSTR-1 is downregulated in human pancreatic cancer tissue specimens. SSTR-1 expression was found to be decreased in pancreatic cancer. To confirm the expression of SSTR-1 in human pancreatic cancer tissues, we examined SSTR-1 expression in a large number of human pancreatic cancer tissues with the surrounding normal tissues ($n = 26$). SSTR-1 mRNA was substantially decreased in 18 of 26 (70%) clinical pancreatic-adenocarcinoma samples compared with that in their surrounding normal tissues (Fig. 1). Overall, the average mRNA expression in 26 pancreatic cancer tissues was 61% decreased compared with that in normal tissues. Therefore, decreased expression of SSTR-1 in the majority of pancreatic cancer tissue specimens suggests that suppressing SSTR-1 may contribute to pancreatic cancer growth.

Transfection of *SSTR-1* caused cell cycle arrest at G_0/G_1 phase in Panc-1 cells. Our previous results and other studies have shown that transfer of *SSTR-1* or *-2* subtype genes inhibited Panc-1 cell proliferation, indicating a possible role of *SSTR* genes as tumor suppressors.[11,12,22,23] In the current study, we further examined the effect of SSTR-1 in cell cycle control of pancreatic cancer cells. We transfected the *SSTR-1* gene into Panc1 cells, and confirmed the expression of SSTR-1 proteins by flow cytometry. As shown in Fig. 2, only 0.61% of cells showed positive staining for SSTR-1 in mock-transfected Panc-1 cells. After transfection of the *SSTR-1* gene, the

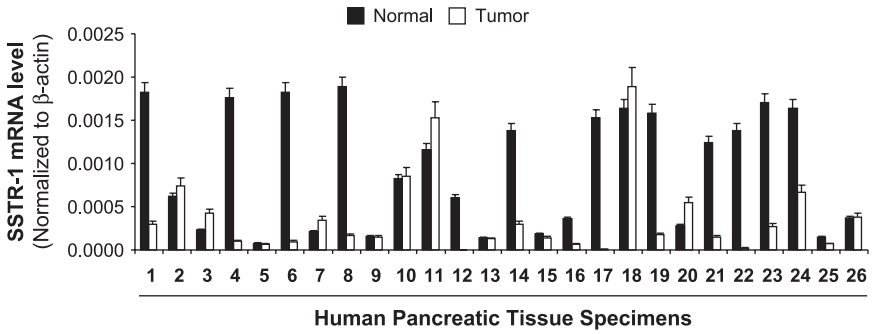

Fig. 1. Somatostatin receptor (SSTR)-1 expression in human pancreatic cancer tissue specimens. Total RNA was extracted from clinical human pancreatic cancer tissue specimens and the mRNA levels for SSTR-1 were analyzed by real-time polymerase chain reaction, and normalized to that of the house keeping gene, β-actin. All data shown are the mean ± standard deviation of three separate experiments.

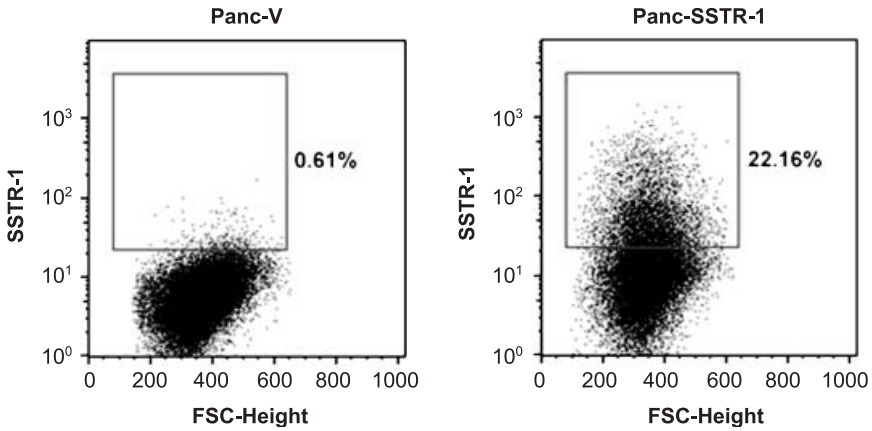

Fig. 2. Flow cytometry analysis of somatostatin receptor (SSTR)-1 in Panc-1 cells upon transfection. Panc-1 cells transfected with the SSTR-1 gene were incubated with anti-SSTR-1 antibody. Cells were then stained with fluorescein isothiocyanate-conjugated secondary antibody. Data were collected by a BD Caliber flow cytometer, and analyzed by FLOWJO software.

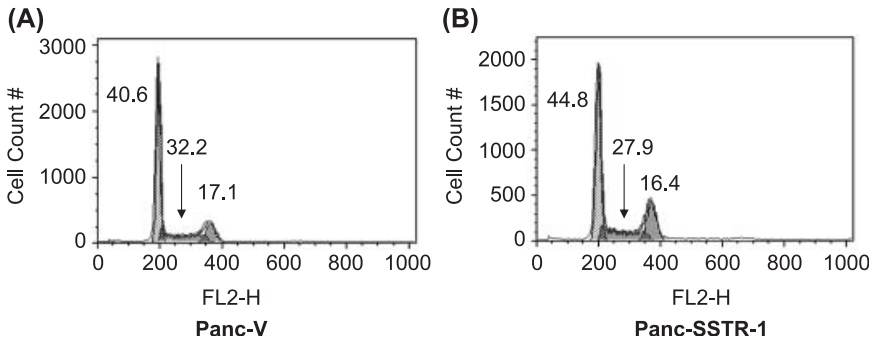

Fig. 3. Transfection of somatostatin receptor (SSTR)-1 caused cell cycle arrest at G_0/G_1 phase in Panc-1 cells. Mock transfected (A), or SSTR-1 transfected (B) Panc-1 cells were starved and released by growth medium. Cells were stained with propidium iodide, and cell cycle arrest was indicated by accumulation of cells at G_0/G_1 phase, with a corresponding decline in cells in the S (mitotic) phase.

Table 1. Cell cycle analysis of somatostatin receptor (SSTR)-1 transfected Panc-1 cells

Sample	RMS†	%G_0/G_1	%S	%G_2/M
Panc-V	3.65	40.6	32.2	17.1
Panc-SSTR-1	4.53	44.8	27.9	16.4

†RMS, root mean squared, error of the fit, indicates how well the model used fits the data. Lower RMS values indicate a better model fit.

expression of SSTR-1 protein was significantly upregulated in Panc-1 cells, 22.16% of the cells were stained positive for SSTR-1 (Fig. 2).

To assess the cell cycle in Panc-1 cells, mock-transfected and *SSTR-1*-transfected Panc-1 cells were harvested, stained with PI and subjected to fluorescent-activated cell sorting analysis. We found that upregulation of SSTR-1 induced a G_0/G_1 growth phase arrest in Panc-SSTR-1 cells, indicated by accumulation of cells at this stage, with a corresponding decline of cells in the S (mitotic) phase. In Panc-V cells, 40.6% of cells were in G_0/G_1 phase and 32.2% were in S phase. On the contrary, 44.8% of Panc-SSTR-1 cells were in G_0/G_1 phase, and only 27.9% of cells entered S phase. That is 10% increased cells population arrested at G_0/G_1 phase, and 13% decreased cells entering S phase, respectively (Fig. 3 and Table 1). Thus, upregulation of SSTR-1 in Panc-1 cells is associated with cell cycle arrest at G_0/G_1 phase.

Stable overexpression of SSTR-1 decreased the proliferation of pancreatic cancer cells. To study the potential functions of SSTR-1 in pancreatic cancer, stably overexpressing SSTR-1 cell lines were established in Panc-1 (Panc-SSTR-1) and MIA PaCa-2 cells (MIA-SSTR-1) using a retrovirus vector (pBabe, Clontech). Stable cells containing empty vectors (Panc-V and MIA-V) cells were also established in Panc-1 and MIA PaCa-2 cells as controls. Overexpression of SSTR-1 in the stable Panc-SSTR-1 and MIA-SSTR-1 cells were confirmed and compared with Panc-V and MIA-V controls by real-time RT-PCR. SSTR-1 mRNA was overexpressed for 125.8-fold in Panc-SSTR-1 cells and 445.7-fold in MIA-SSTR-1 cells compared with their corresponding vector control cells ($P < 0.01$, Fig. 4A,B). MTS assay showed that overexpression of SSTR-1 in

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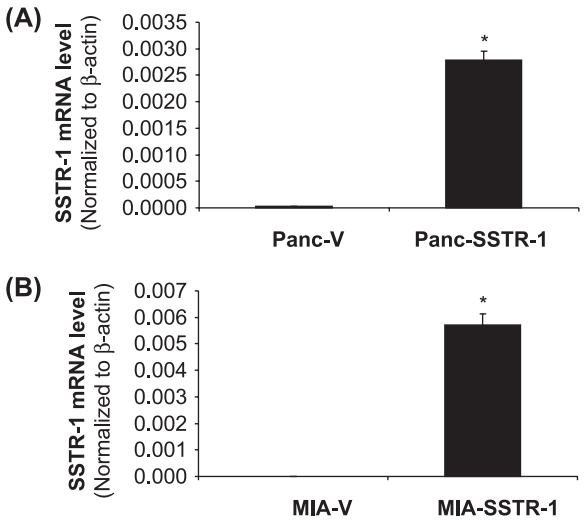

Fig. 4. Expression of somatostatin receptor (SSTR)-1 in stable Panc-1 and MIA PaCa-2 cells. Stably overexpressing SSTR-1 cells were established in Panc-1 and MIA PaCa-2 cells. The mRNA levels of SSTR-1 in Panc-1 (A), and MIA PaCa-2 (B) cells were examined with real-time reverse transcription polymerase chain reaction. Human SSTR-1 mRNA levels were normalized to that of human β-actin. SSTR-1 mRNA levels in Panc-SSTR-1 and MIA-SSTR-1 cells were significantly higher than that in Panc-V and MIA-V cells. $*P < 0.01$. All data shown are the mean ± standard deviation of three separate experiments.

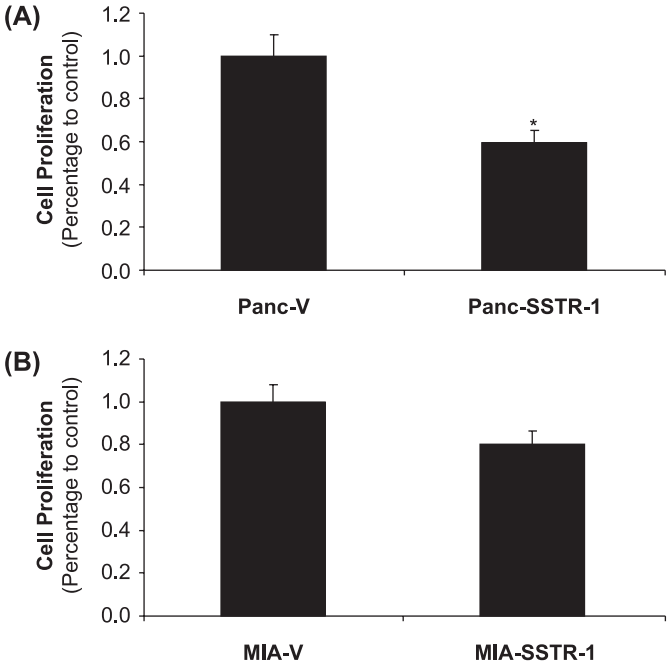

Fig. 5. Stable overexpression of somatostatin receptor (SSTR)-1 decreased the proliferation of pancreatic cancer cells. (A) Panc-SSTR-1, (B) MIA-SSTR-1, and their corresponding vector control cells were seeded in 96-well plates (2×10^3 cells/well), and serum-starved for 24 h before examining the cell proliferation. Absorbance at 490 nm was recorded on day 2 after starvation. Data were expressed as the mean ± standard deviation of triplicate values. $*P < 0.05$.

Panc-SSTR-1 and MIA-SSTR-1 cells were associated with decreased cell proliferation by 41% and 20%, respectively, compared with that in Panc-V and MIA-V cells ($P < 0.05$, Fig. 5A,B). These results indicate that SSTR-1 plays an important role in regulating cell proliferation in these pancreatic cells.

SSTR-1 inhibited pancreatic cancer growth in the nude mouse model of subcutaneous xenograft. We further analyzed the role of SSTR-1 on tumor growth *in vivo* using an immunodeficient nude mouse model. Panc-SSTR-1 cells showed a dramatic decrease (71%) in tumor volume after 6 weeks compared with Panc-V control cells in the subcutaneous tumor model ($P < 0.01$, Fig. 6A). MIA-SSTR-1 cells also showed significantly decreased tumor volume by 43% after 6 weeks compared with MIA-V control cells in the subcutaneous tumor model ($P < 0.05$, Fig. 6B). The tumor weight was also significantly reduced in Panc-SSTR-1 and MIA-SSTR-1 groups by 69% and 47%, respectively, compared with the vector control groups ($P < 0.05$, Fig. 6C,D). These results indicate that overexpression of SSTR-1 inhibits pancreatic cancer progression.

Discussion

This study revealed that SSTR-1 may inhibit pancreatic cancer growth by causing cell cycle arrest. We found that SSTR-1 mRNA was downregulated in the majority of human pancreatic cancer tissues specimens, and transfection of SSTR-1 gene caused Panc-1 cell cycle arrest at G_0/G_1 phase. Overexpression

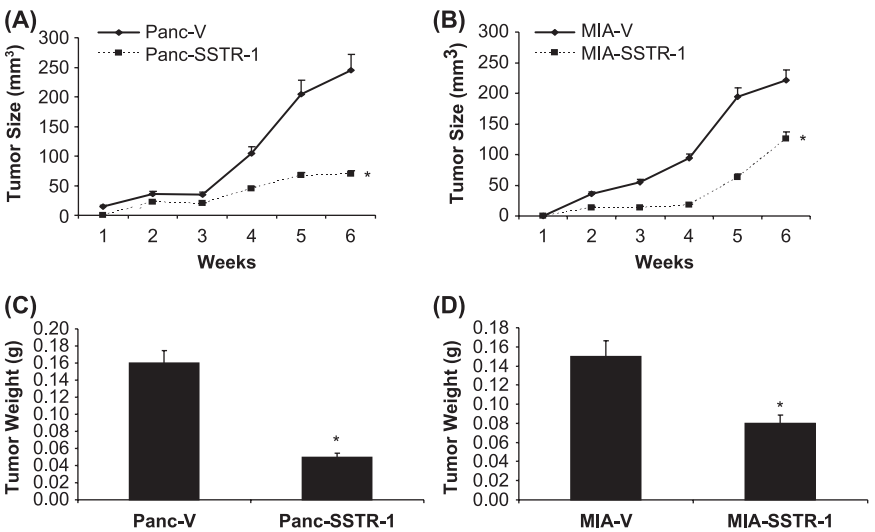

Fig. 6. Somatostatin receptor (SSTR)-1 inhibited pancreatic cancer growth in the nude mouse model of subcutaneous xenograft. (A) Panc-SSTR-1, (B) MIA-SSTR-1, and their corresponding vector control cells (3×10^6) were subcutaneously inoculated into the right flank of nude mice ($n = 5$/treatment group). Tumor size was measured weekly for 6 weeks. Tumor volume was calculated by the formula: tumor volume (mm^3) = (length [mm]) × (width [mm])^2 × 0.52. $*P < 0.05$. Tumor weight from (C) Panc-SSTR-1, (D) MIA-SSTR-1 group, and their corresponding vector control groups were also measured at week 6. $*P < 0.05$.

of SSTR-1 in stable Panc-SSTR-1 or MIA-SSTR-1 cells led to decreased cell proliferation *in vitro* and tumor growth *in vivo* in a subcutaneous nude mice model, indicating the potent inhibitory effect of SSTR-1 on pancreatic cancer growth.

A fundamental obstacle in our understanding of pancreatic carcinogenesis is the confusion on the histogenesis of this disease. Many investigators think pancreatic cancer arises from pancreatic ductal cells because the vast majority of tumors are ductal adenocarcinomas. Others believe these tumors arise from transdifferentiated acinar cells[24] or from precursor (reserve stem) cells that are distributed along the ductal trees, but are particularly plentiful within islets.[25,26] This controversy complicates investigation of the role of SSTR in pancreatic carcinogenesis because the cell of origin cannot be isolated and studied. Important insights are gained by studying the progressive development of precursor lesions and invasive cancers in animal models of pancreatic cancer. Human islet cells express all five SSTR.[27–29] There is no absolute specificity of any SSTR for an islet cell type. Outside the islet, cells expressing SSTR-2 have been identified in the walls of many small and medium arterioles and scattered non-islet cells express SSTR-1 and -2.[29] The SSTR status of precursor reserve stem cells in the human pancreas is unknown. In hamsters treated with a pancreatic carcinogen, there is a progressive decrease in SSTR expression, as measured by autoradiography, in normal pancreas, pre-neoplastic lesions and invasive cancers.[30] In our current study, we found that the *SSTR-1* gene was downregulated in the majority of the pancreatic cancer tissue specimens. Presumably, evolving cancer cells within or near islets would be exposed to a high concentration of islet peptide products, including somatostatin. Loss of SSTR may result in loss of a check on cell proliferation and cell cycle, analogous to loss of other tumor suppressor genes. Multiple tumor suppressor pathways such as Rb/p16, transforming growth factor-β/DPC4 and p53, are known to be abrogated in most human pancreatic carcinomas.[31,32] We hypothesize that SSTR gene expression is another tumor suppressor pathway important in human pancreatic carcinogenesis.

Somatostatin causes antiproliferative effects through SSTR by at least two receptor-dependent mechanisms. One is by inhibition of mitogenic signaling of growth factor receptor kinases causing growth retardation due to arrest of cell cycle progression. Second, morphological and flow cytometric studies have confirmed the induction of apoptotic cell death. Activation of SSTR-1 and -2 results in induction of the retinoblastoma tumor suppressor protein Rb, p21 and G1 cell cycle arrest.[33] Another group has shown that binding of somatostatin to SSTR-2 upregulates p27, thus leading to cell cycle arrest in the G_0-G_1 phase, and subsequently to apoptosis. In our study, we found that transfection of the *SSTR-1* gene caused cell cycle arrest at the G_0-G_1 phase, along with a corresponding decline of cells in the S phase. Although many studies have been done to investigate the mechanism of the growth inhibition by SSTR-1 and SSTR-2, the most promising pathway seems to involve SHP1/2, ERK1/2 and p27/p21 signaling. It has been shown that mouse SSTR-2 interacts with SHP-1/2, and stimulates ERK1/2 activation through a Ras, Rap-1 and B-Raf-dependent signal pathway. Activated ERK1/2 leads to induction of $p27^{kip1}$ inhibition of cyclin E-cdk2 kinase activity and cell cycle arrest.[23,34–37] A similar pathway has been indicated in SSTR-1 expressing CHO-K1 cells.[37–39] Upon ligand stimulation, Gβγ-dependent Src activation leads to SHP-2 activation and subsequent SHP-1 recruitment. PI3K is expected to play a role in this pathway as well.

Forced overexpression of SSTR have been shown to inhibit pancreatic cancer progression. Growth of two human pancreatic cancer cell lines, BxPC-3 and Capan-1 cells, was inhibited after transfection with SSTR-2 even without the addition of somatostatin to the growth medium.[40] In addition to *in vitro* studies, the growth of pancreatic cancer cells stably transfected with *SSTR-2* is decreased in athymic mice.[10] Delivery of a SSTR-2 transgene by direct injection of adenoviral vector or linear polyethylenimine (PEI) vector into established tumors resulted in significant reduction of pancreatic tumor growth, indicating the feasibility of using SSTR as a novel gene therapy strategy.[41] We have shown that transfection of Panc-1 cells with SSTR-1 or SSTR-2 inhibits cell proliferation in culture.[11,12,22] However, no reports have indicated the role of SSTR-1 in inhibiting pancreatic cancer progression *in vivo*. In this current study, we have demonstrated a significant regression of tumor growth by SSTR-1 in a subcutaneous nude mouse model. Overexpression of SSTR-1 in two pancreatic cancer cell lines, Panc-1 and MIA PaCa-2, significantly inhibited tumor growth. Further studies are warranted to optimize the delivery efficiency and expression specificity of SSTR-1 in pancreas.

Taken as a whole, our study suggested a potent inhibitory effect of SSTR-1 in pancreatic cancer cells, which may serve as potential therapeutic targets for treatment of pancreatic cancer. Given the poor prognosis of patients with pancreatic cancer and the lack of effective therapy, a better understanding of the pathogenesis of pancreas cancer and any novel treatment approach that has translational potential would be of medical and economic importance. This unique approach of using SSTR as a therapeutic target is particularly attractive because of the low toxicity of the naturally occurring peptide, somatostatin, which may allow combination of this antiproliferative signal with standard chemotherapy without synergistic toxicity. With this novel approach, expression of the transgene, SSTR, could also be clinically tracked or used to deliver adjuvant tumor-specific radiation.

Acknowledgments

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