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Original Article

SOX7 expression correlates with better prognosis in pancreatic cancer patients and is negatively related to pancreatic cancer associated diabetes

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Abstract: Pancreatic cancer carries a dismal prognosis with a 5-year survival rate of about 5%, and researches have shown that the malignant level and tumor associated glucose metabolism abnormality may both influence the pancreatic cancer progression and prognosis. Recently, growing evidence suggest an association of SOX7 with tumor development. However, there are no studies focusing on the prognostic effect of SOX7 in pancreatic cancer, or its relationship with pancreatic cancer associated diabetes. To investigate the association of SOX7 and prognosis in pancreatic cancer, and further to verify whether SOX7 involves in the regulation of pancreatic cancer associated diabetes. 100 pancreatic cancer-related cases with follow-up information were made into tissue microarrays. Subsequently, the relationship between SOX7 and clinicopathological characteristics was analyzed. SOX7 expression level has a positive correlation with the prognosis of pancreatic cancer patients, especially in the subgroup of tumor size < 5 cm with pathological grades I-II (P=0.014). Moreover, the results showed that SOX7 is significantly negative with diabetes history in the same subgroup (r^2=-0.405, P=0.014). SOX7 may exert a tumor suppressor effect in pancreatic cancer, and this effect may correlate with the pathogenesis of paraneoplastic islet injury.

Keywords: SOX7, pancreatic cancer, prognosis, pancreatic cancer associated diabetes

Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death in the world by 2015 [1]. The 5-year overall survival rate of these patients is less than 5%. The treatment of this malignant cancer remains as one of the most challenging clinical dilemmas. Conventional treatments such as surgery, cytotoxic chemotherapy, and chemo-radiation therapy could not significantly alter the mortality rate. Surgical resection is the most effective way to prolong the survival, which improving five-year survival rate to 25-35% after surgery [2, 3]. Unfortunately, because pancreatic cancer is often advanced at the time of diagnosis, only 15%-20% diagnosed cases can be considered candidates for resection [4]. Although in recent years, the molecular pathogenesis of pancreatic cancer research has made great progress, the clinical diagnosis and treatment of pancreatic cancer is still intractable.

Identification of potential prognostic factors may provide available information for clinical therapies. SOX7 was first identified in rats and zebrafish [5, 6], together with SOX17 and SOX18, as a member of SOXF subfamily. SOX7 exerts as a transcriptional regulator through the methylation of a CpG island at the promoter region of the target genes, has been identified as a developmental regulator in hematopoiesis and cardiogenesis [7]. SOX7 is frequently downregulated in many human cancers, such as hepatocarcinogenesis, colon, lung, and breast cancers, and its reduced expression often correlates with poor prognosis [8-10]. Furthermore, the overexpression of SOX7 could suppress cell proliferation in prostate cancer and induce apoptosis in colon cancer [8]. Consistently, the

silence of SOX7 is attributed to its promoter hypermethylation in tumors, and this effect is correlated with poor prognosis in myelodysplastic syndrome [8, 11].

In addition to involve the cancer progression and carcinogenesis, SOX7 may have more biological functions. SOX7 has been reported to interact with β-catenin and inhibit cell proliferation mediated by Wnt signaling pathways [12-14]. Interestingly, the Wnt/β-catenin pathway is widely known as a major regulator in numerous human diseases, such as diabetes and the occurrence and development of cancer [14-16]. The association between diabetes and pancreatic cancer has long been recognized [17-19]. Most pancreatic cancer patients have glucose intolerance and about 80% of pancreatic cancer patients are with either dysglycemia or diabetes in the pre-symptomatic phase [19]. The above observations were the compelling evidence for the closely connection between pancreatic cancer and diabetes. Furthermore, recent research shows that the SOXF member also has the ability to regulate the insulin trafficking and secretion [20].

However, to date there are no studies focusing on SOX7 expression in pancreatic cancer, and whether SOX7 plays a protective role in pancreatic cancer associated diabetes is still unclear. In the present study, we aimed to assess the correlation between the expression level SOX7 and the progression, prognosis of pancreatic cancer via immunohistochemical method and Tissue Microarrays.

Materials and methods

Source of samples

The study sample was consisted of 100 patients with pancreatic cancer, which was obtained from tissue specimen bank within Shanghai Biological Technology Co., LTD. The patient operation time was during September 2004 to December 2008, and then the patients were followed-up until December 2011. All the patients were pathologically diagnosed with pancreatic cancer and without any pre-surgery treatment. There were 63 males and 37 females with median age 62 years old. Each study specimen was provided with cancer tissue and adjacent-carcinoma tissue which was 1.5 cm distanced from cancer.

Tissue chip production

The tissue chip was produced by Shanghai super biological technology co., LTD. After all provided tissue wax block were conducted routine pathological hematoxylin-eosin (HE) staining, secondary diagnosis was performed by pathology experts, and tagged the typical pathological parts on HE sliced. Using tissue chip production apparatus (Beecher Instruments, Inc) receptors in wax block (blank wax block) to punch holes (1.5 mm) in diameter, then according to the tag position on the HE slice, the corresponding tissue was obtained from donor tissue wax block. Then the target tissue chip was put into the array aperture of receptor wax block. Repeating above steps, finally, a colorectal cancer tissue and matched adjacent tissue containing 180 array block points (HColAde180Sur-04) was completed. Slicer (Leica, Germany) was used in 4-5 um thickness serial section, section was attached to the glass slide which through overhand slice processing, then made into tissue microarray.

Immunohistochemical staining and scoring

The two-step EnVision method has been conducted to perform immune histochemical experiments. Three magnification visions randomly observed under optical microscope, the number of positive cells in no less than 3 × 100 cells was record, and then calculate the positive rate of positive cells to all cells. The SOX7 expression was scored according to staining intensity and positive percentage. The staining intensity was scored as no staining (0), week (1), moderate (2) and strong (3). The percentage of SOX7 positive cells was scored as 0% (0), 1-20% (1), 21-40% (2), 41-60% (3), 61-80% (4) and 81-100% (5). The synthesis scoring is: < 6 low expression grade, or ≥ 6 was treated as high expression grade.

Statistical analysis

The expression of SOX7 protein in colorectal cancer and adjacent cancer tissues were compared with paired Wilcoxon test. The association between clinical characteristics of colorectal cancer patients and SOX7 protein expression were using Pearson and Spearman's correlation test. The prognostic of colorectal cancer and SOX7 protein expression were using Kaplan-Meier survival analysis and log-rank

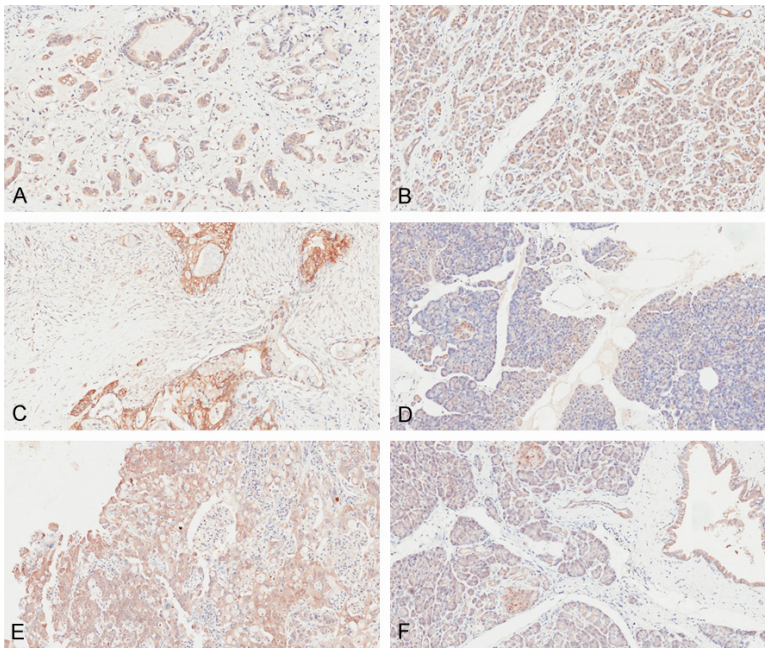


Figure 1. Representative immunostaining image of SOX7 from pancreatic cancer tissues with different pathological grades and the adjacent tissues. Cytoplasmic SOX7 immunostaining in well (A), moderate (C) and poorly differentiate (E) tumors and the corresponding adjacent normal tissues (B, D and F). [Original magnification, × 200].

Table 1. Correlation of SOX7 expression in pancreatic cancer and adjacent tissues

Category	Mean ± Std. Deviation	*P*-value
SOX7 expression in cancer tissues (n=97)	7.711 ± 2.946	0.076
SOX7 expression in adjacent tissues (n=79)	7.478 ± 2.879	

test for univariate analysis; the significant variables resulted from univariate test were included in the Cox multivariate regression analysis. The *P*-value less than 0.05 was considered statistically significant.

Results

Expression of SOX7 in pancreatic cancer and adjacent pancreas tissues

The immunohistochemical analysis showed that SOX7 expression is mainly in the cytoplasm of pancreatic cancer tissues and the adjacent tissues, and the representative image of SOX7 from pancreatic cancer tissues with different pathological grades and the adjacent tissues was shown in (**Figure 1**). Meantime, SOX7 expression score in pancreatic cancer tissues (7.711 ± 2.946) appeared to be higher than that in the adjacent tissues (7.478 ± 2.879), but without significant difference (P=0.076) (**Table 1**).

Additionally, Spearman's rank correlation analysis displayed the relationship between expression of SOX7 and clinical parameters (**Table 2**). Unfortunately, our current analysis does not yield any significant results (P > 0.05), despite subsequent Spearman's rank-order correlation analysis indicated a negative correlation between SOX7 level in pancreatic cancer and the adjacent tissues (P < 0.001). The most probable explanation of this unexpected result is that all of the enrolled pancreatic cancer patients had been assessed as the predicted radical-resectable group (it represents only 15-20% of all pancreatic cancer patients). Therefore, the correlation between SOX7 and clinicopathologic characteristics needs further investigation with a more diversified and larger volume samples.

Association between SOX7 expression level and survival

The current survival analysis including the Kaplan-Meier survival analysis and Log-rank statistical test revealed that pancreatic cancer patients with higher SOX7 expression in cancer tissues seems have a better 5-year survival rate than those with lower SOX7 expression (P=0.143, **Figure 2A**). However, the expression level of SOX7 in the adjacent tissue dose not renders the same effect (**Figure 2B**). Based on the current results and the existing reports, we speculate SOX7 might be a tumor suppressor in some special pathological pancreatic cancer.

To verify this speculation, we analyze the prognostic correlation between SOX7 expression and different pancreatic cancer subtypes. Kaplan-Meier survival analysis and Log-rank statistical test revealed that the expression of SOX7 has a positive correlation with the prognosis in patients with tumor size < 5 cm (P=0.04, **Figure 2C**) or the pathological grades

Table 2. Correlation research about SOX7 expression and clinicopathologic characteristics

		Gender	Age	Tumor size	Grade	T	N	M	Clinical stage
SOX7 expression in cancer tissue	Correlation coefficient	.131	.012	.025	-.033	-.010	.012	.163	.026
	Sig. (2-tailed)	.202	.911	.807	.748	.925	.910	.112	.808
	N	97	97	95	97	95	90	97	92

I-II (P=0.038, **Figure 2E**), rather than in the patients with tumor size > 5 cm (**Figure 2D**) or with the pathological grades III-IV (**Figure 2F**).

Subsequently, we used the combination of tumor size and pathological grade as classification criteria, and divided pancreatic cancer patients into two groups (subgroup-1: tumor size < 5 cm with pathological grades I-II, **Figure 2G**; subgroup-2: tumor size > 5 cm with pathological grades III-IV, **Figure 2H**). The current analysis showed that the prognosis of patients in subgroup-1 exhibited dramatically positive correlation with the expression of SOX7 (P=0.014, **Figure 2G**).

Multivariate Cox regression analysis revealed SOX7 as an independent prognostic factor in a certain subgroup

Not surprisingly, further multivariate analysis revealed that pathological stage (P < 0.001) and lymph node metastasis (P=0.002) were the most effective independent prognostic factors in the overall patients with pancreatic cancer. Same with the former analysis, we further performed the analysis in different subgroup patients. It is rather remarkable that, SOX7 expression level is the only one independent prognostic factor for the subgroup-1 (tumor size < 5 cm with pathological grades I-II, P= 0.039, **Table 3**). Quite the opposite, SOX7 expression was not significantly correlated with OS in the subgroup-2 patients (tumor size > 5 cm with pathological grades III-IV).

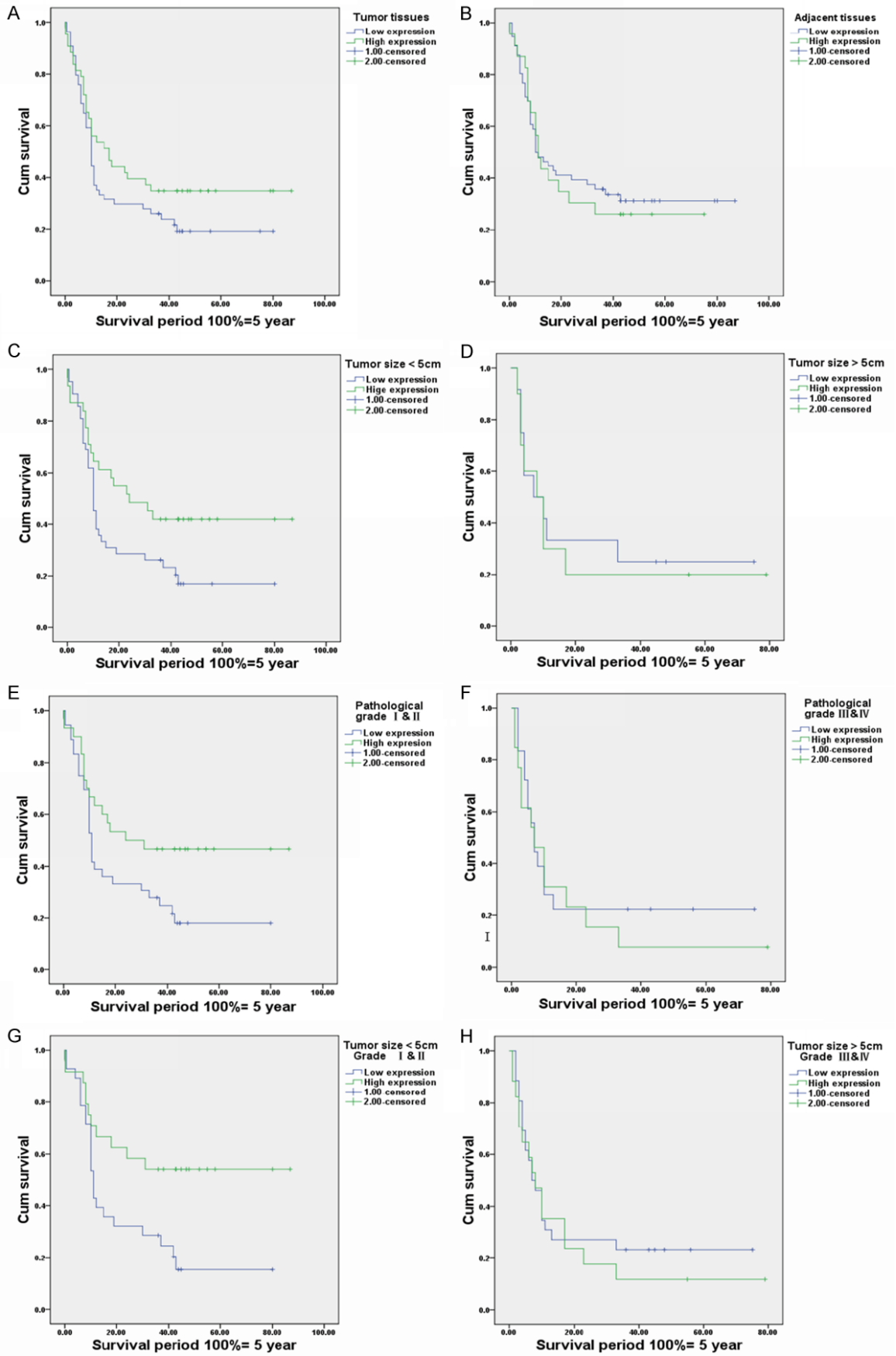
Neoplastic expressed SOX7 is negatively correlated with diabetes history in a subgroup of pancreatic cancer patients

We further analyzed the correlation of SOX7 and diabetes history in all pancreatic cancer patients, and the results showed that SOX7 is negatively correlated with diabetes history (r^2=-0.231), but without significant difference (P=0.073). As the previous analysis showed that tumor size and pathological grades were the independent prognostic factors correlated with SOX7, we further analyzed the correlation of SOX7 between diabetes history of the above two subgroups. Interestingly, the results showed that SOX7 is significantly negative with diabetes history in the subgroup of tumor size < 5 cm and pathological grades I-II r^2=-0.405, (P= 0.014, **Table 4**). Conversely, SOX7 exhibited no correlation with diabetes history in the other subtype (P=0.922). Taken together, these results indicated SOX7 might exert as a tumor suppressor factor in specially subtype pancreatic cancer, and this effect may correlated with the pathogenesis of pancreatic cancer resulted para-neoplastic islet dysfunction.

Discussion

In this study, we examined the expression of SOX7 in the pancreatic cancer and adjacent tissues by immunohistochemical techniques. Our results showed that the level of SOX7 in the cancer tissues was higher than that in the adjacent tissues. Subsequently, the Spearman's rank-order correlation analysis indicated a positive prognosis correlation between SOX7 and the cancer subtype of tumor size < 5 cm and pathological grades I-II (P=0.014). The 5-year survival between the two subtypes showed significant difference, as the subtype survival of tumor size < 5 cm and pathological grades I-II is 54.2%, the other subtype is just 17.9%. Moreover, we found that SOX7 is significantly negative with diabetes history in the subtype of tumor size < 5 cm and pathological grades I-II (r^2=-0.405, P=0.014).

Human SOX7 mRNA and/or SOX7 protein is up-regulated in gastric, pancreatic and esophageal cancer cell lines, and down-regulated in kidney, lung, breast, prostate and colorectal tumors [21]. Multiple studies have shown that SOX7 is a tumor suppressor, and down-regulated SOX7 expression always related to the more aggressive tumor behavior and much worse prognosis. In some tumors, such as acute myeloid leukemia, colorectal and prostate can-


A
Tumor tissues
Low expression
High expression
1.00-censored
2.00-censored
Cum survival
Survival period 100%=5 year
B
Adjacent tissues
Low expression
High expression
1.00-censored
2.00-censored
Cum survival
Survival period 100%=5 year
C
Tumor size < 5cm
Low expression
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2.00-censored
Cum survival
Survival period 100%=5 year
D
Tumor size > 5cm
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Low expression
High expression
1.00-censored
2.00-censored
Cum survival
Survival period 100%= 5 year

Figure 2. Kaplan-Meier survival analysis of SOX7 expression level in pancreatic cancer patients segmented by expression site (A. tumor tissues, B. adjacent tissues); tumor size (C. tumor size < 5 cm, D. tumor size > 5 cm); pathological grades (E. grades I-II, F. grades III-IV); or the combination of tumor size and pathological grade (G. tumor size < 5 cm with pathological grades I-II, H. tumor size > 5 cm with pathological grades III-IV).

Table 3. SOX7 expression level is the most effective independent prognostic factor for pancreatic cancer patients with tumor size < 5 cm and pathological grades I-II

							95.0% CI for Exp (B)	
	B	SE	Wald	df	*P*-value	Exp (B)	Lower	Upper
SOX7	-.816	.396	4.244	1	.039	.442	.203	.961

Table 4. SOX7 is significantly negative with diabetes history in the subgroup of tumor size < 5 cm and pathological grades I-II

			Diabetes history
Spearman's rho	SOX7 expression score	Correlation Coefficient	-.405*
		Sig. (2-tailed)	.014
		N	36

cer, SOX7 down-regulation is due to tumor-specific promoter hypermethylation [8, 11]. Increasing results from scientific studies confirmed that SOX7 achieves its anti-tumor effects mainly through the involvement of the regulation of Wnt/β-catenin signaling. SOX7 expression and activity changes may modulate by Wnt/β-catenin and β-catenin inhibition by SOX7 has been reported in endometrial, colorectal, and prostate cancers [13]. SOX7 could specifically reduce the active form of β-catenin by direct binding, and deletion of β-catenin binding site in SOX7 significantly ameliorated its leukemia suppressive effect [11]. Furthermore, SOX7 has been shown to repress β-catenin-mediated activation [6]. New research results even confirmed the overexpression of miR-935 [22], miR-595 [23], miR-452 [24] and miR-492 [25] all can directly promote tumor cell proliferation and invasiveness by inhibiting SOX7 expression. Consistent with our present results, these above researches all demonstrated the SOX7 plays the role of tumor suppressor through multiple mechanisms.

A growing number of studies suggest that the pancreatic cancer associated diabetes is a paraneoplastic glucose metabolism abnormality, and this complication can even influence the prognosis of pancreatic cancer patients. Meanwhile, despite the much of the pancreas was excised during radical pancreactomy, the ameliorated diabetes was observed in 56.7% [26] -89% [27] pancreatic cancer associated diabetes patients. These epidemiological studies suggest that the prognostic factor of pancreatic cancer may play a role in the pathogenesis of pancreatic cancer associated diabetes.

Our present study not only revealed that the SOX7 may serve as a prognostic factor for pancreatic cancer patients, the results also givesa hint that SOX7 may have more biological functions. Recent reports demonstrated that a member of SOXF (SOX17) can regulate the insulin trafficking and secretion [20], and SOX17 can cooperatively regulate illness development with SOX7 [28]. Meantime, SOX7 and SOX17 can also contribute to the gene expression during the differentiation of F9 cells [29]. And more notably, SOX17 is also a prognostic factor [30] and suppressor [31, 32] in several cancer diseases. Moreover, it has been reported that insulin receptor substrates (IRS1/2) activates Wnt/β-catenin signaling and further promotes the induction of epithelial-mesenchymal transition (EMT) and cell proliferation in response to Wnt stimulation [33]. IRS proteins are already well known to play a crucial event in the development of diabetes [34], and they also play an important role in the carcinogenesis of pancreatic cancer [35]. Our results showed SOX7 is significantly negative associated with diabetes history in the subtype of tumor size < 5 cm and pathological grades I-II, thus, we speculate that SOX7 may exert as a tumor suppressor in the diabetes-derived pancreatic cancer, and this protective effect may emerge when the pancreatic cancer occurring. The high expression of SOX7 inhibits the IRS and Wnt/β-catenin may be the potential anti-tumor mechanisms of SOX7 in pancreatic cancer.

In conclusion, our results firstly revealed the positive prognostic correlation between SOX7

and pancreatic cancer patients. Meantime, we firstly presented the negative association between SOX7 expression and pancreatic cancer associated diabetes. However, further studies are required to elucidate whether the SOX7 has the anti-tumor effect in pancreatic cancer, and whether SOX7 has a protective effect to paraneoplastic islet dysfunction.

Disclosure of conflict of interest

None.

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