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High Trophinin-Associated Protein expression and its role in prognosis of pancreatic cancer

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Running Title: The prognosis of TROAP in pancreatic cancer

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Abstract:

Background: Trophinin-associated protein (TROAP) was known as the tasin, which originally recognized as a cytosolic protein involved in embryo implantation. Increasing studies have revealed that high expression of TROAP is related with poor outcomes in cancers. However, there have been few studies on the correlation of TROAP and pancreatic cancer. This study aimed to explore the prognostic significance of TROAP in pancreatic cancer by mining the data collected from The Cancer Genome Atlas (TCGA) dataset.

Methods: Clinical information and the RNA expression data were obtained from the TCGA dataset. The correlations between clinical information and TROAP mRNA expression were performed by chi-square and Fisher exact tests. Univariate Cox analyses were used to filter the potential prognostic factors. The correlations between TROAP expression and clinical characteristics of patients with pancreatic cancer were confirmed by multivariate Cox analyses.

Results: Analysis of tumor data showed that high expression of TROAP was correlated with poor outcomes in pancreatic cancer patients. Univariate and multivariate Cox analyses demonstrated that TROAP mRNA expression played an important role in shorting overall survival (OS) and relapse-free survival (RFS), which might serve as the useful biomarker and prognostic factor for pancreatic cancer.

Conclusions: TROAP was an independent risk factor for pancreatic cancer. TROAP has the potential to be a biomarker, especially in predicting prognosis.

Keywords: pancreatic cancer, TROAP, prognosis, TCGA

Background

Pancreatic cancer is one of the leading lethal malignancies globally with a 5-year survival less than 8% [1]. There have been approximately 460,000 new cases of pancreatic cancer occurred in 2018 worldwide [2]. Despite therapies for patients with pancreatic cancer are improving now, the recurrence and metastasis of this disease are still unsurmountable obstacles for us. Like most human cancers, the deaths caused by pancreatic cancer are related with its clinical stages. However, this kind of disease is usually diagnosed at an advanced stage and most pancreatic tumors are unresectable [3]. Moreover, it is a great challenge to predict the clinical outcomes for pancreatic cancer patients. Therefore, it is significant to find an effective screening strategy such as new specific markers to identify prognosis for patients.

Trophinin-associated protein (TROAP) was known as the tasin. Originally, it was recognized as a cytosolic protein involved in the connection of trophoblast cells with endometrial epithelium in the initial stages of embryo implantation by forming complexes with bystin and trophoblast [4-7]. The process of embryo implantation is similar to malignant cancer, which mostly is invasion and metastasis. Recently, some research found that the loss of TROAP expression was led to multipolar spindles and mitotic block by regulating the formation of monopolar spindle [8]. These studies suggest that TROAP might be associated with the regulation of proliferation, invasion and metastasis, which are the basic characteristic of malignant tumor.

Meanwhile, increasing studies have revealed that high expression of TROAP is related with poor outcomes in epithelial ovarian carcinoma [9], lung adenocarcinoma [10], gastric cancer [11], hepatocellular carcinoma [12], and colorectal cancer [13]. However, the significance of TROAP expression in prognosis has not been reported in pancreatic cancer yet. This study aimed to assess the prognostic capability of TROAP for overall and relapse-free survival of patients with pancreatic cancer. From The Cancer Genome Atlas Pancreatic Adenocarcinoma (TCGA-PAAD) dataset, we obtained the expression of TROAP in pancreatic cancer. Our results indicated that TROAP might serve as the useful biomarker and prognostic factor for pancreatic

cancer.

Methods

Data Mining

Clinical information and the RNA expression data were obtained from the Cancer Genome Atlas (TCGA) dataset. The RNA-sequencing expression data for normal pancreatic tissue were obtained from The Genotype-Tissue Expression (GTEx) dataset. Data processing were conducted by R software[14] and related packages.

Statistical analyses

The expression of TROAP in the TCGA-Pancreatic Adenocarcinoma (TCGA-PAAD) dataset was assessed using box plots. The diagnostic capability of TROAP expression was evaluated by drawing the receiver operating characteristic (ROC) curve using the pROC package [15]. According to the value determined by ROC curve, patients were divided into two groups (low/high). The OS and RFS between the two groups were compared by Kaplan-Meier analyses using the survival package in R[16, 17].The correlations between clinical information and TROAP mRNA expression were performed by chi-square and Fisher exact tests.

Univariate Cox analyses were used to filter the potential prognostic factors. The correlations between TROAP expression and clinical characteristics of patients with pancreatic cancer were confirmed by multivariate Cox analyses. Statistical analyses were performed with R software (version 3.6.1).

Results

Patient Characteristics

Clinical information derived from 179 patients with pancreatic cancer were downloaded and organized from The Cancer Genome Atlas Pancreatic Adenocarcinoma (TCGA-PAAD), including age, gender, alcohol history, histological type, anatomic location, TNM classification, histologic grade, lymph nodes positive, max dimension, residual tumor, radiation therapy, targeted molecular therapy, surgery performed type, therapy outcome, vital status, sample type, overall survival and relapse-free survival (Table 1).

High TROAP expression and its diagnostic capability in pancreatic cancer

We compared the expression of TROAP mRNA in normal pancreatic tissue and pancreatic cancer via box plots (Fig 1). The results demonstrated that TROAP expression was higher in pancreatic cancer tissues ($P < 0.001$).

The ROC curve was performed using the expression data from TCGA-PAAD to analyze the diagnostic capability of TROAP (Fig 2). The area under the curve (AUC) was 0.781, which suggested the moderate diagnostic capability of TROAP. The subgroup analyses manifested the diagnostic capability in different stages of pancreatic cancer with the AUC values of 0.631 (stage I), 0.810 (stage II), 0.750 (stage III), and 0.700 (stage IV) (Fig 2).

Correlations between clinical features and TROAP expression

We divided the patients into two groups based on the medium value for analyses of the correlations between clinical features and TROAP mRNA expression. The threshold TROAP level identified from the ROC curve was used to distinguish the low and high groups (Table 2). Chi-square test suggested that high expression of TROAP was significantly correlated with vital status ($P = 0.0008$) and overall survival ($P = 0.001$).

TROAP mRNA expression is correlated with overall survival

To evaluate the diagnostic capability of TROAP in patients with pancreatic cancer, Kaplan-Meier survival curve was executed, which indicated that high expression of TROAP was related with the poor overall survival ($P=0.0015$; Fig 3). The subgroup analyses suggested that high expression of TROAP was correlated with the poor overall survival of cases with histological grade G1/G2 ($P=0.005$), clinical stage I/II ($P=0.0023$), T1 ($P=0.0082$) and N1 ($P=0.018$).

Univariate analyses selected the critical variables including TROAP expression, residual tumor, histological type, N classification and T classification. Multivariate Cox analyses suggested that the expression of TROAP ($P=0.008$), residual tumor ($P=0.01$), histological type ($P=0.041$) and N classification ($P=0.033$; Table 3) were independent risk factors for poor overall survival in patients with pancreatic cancer.

TROAP mRNA expression is correlated with relapse-free survival

To evaluate the diagnostic capability of TROAP in patients with pancreatic cancer, Kaplan-Meier survival curve was executed, which indicated that high expression of TROAP was related with relapse-free survival ($P=0.017$; Fig 4). The subgroup analyses showed that high TROAP expression was correlated with the poor RFS of cases with histological grade G1/G2 ($P=0.0023$), clinical stage I/II ($P=0.01$) and T1 ($P=0.025$).

Univariate analyses selected the critical variables including TROAP expression and residual tumor. Multivariate cox analyses suggested that the expression of TROAP ($P=0.011$) and residual tumor ($P=0.001$; Table 4) were independent risk factors for RFS in patients with pancreatic cancer.

Discussion

Pancreatic cancer is a lethal malignancy which associated with a high mortality rate globally. Despite the rapid development of medicine, the high recurrence and metastasis of pancreatic cancer remain unsolvable. Therefore, it is insightful to find reliable biomarkers of pancreatic cancer for further diagnosis and better prognosis. In recent years, bioinformatics has attracted much attention because of its significance in screening markers. We also have been working on the exploration of tumor biomarkers by bioinformatics[18-31] .

Consistent with all previous studies in different type of cancers, we found higher TROAP expression levels in PAAD tissues and high expression of the TROAP mRNA was related with poor survival status. High TROAP expression was correlated with poor outcomes in pancreatic cancer patients by Chi-square test. Univariate Cox analyses demonstrated that TROAP mRNA expression played an important role in overall and relapse-free survival, which might be a useful biomarker and prognostic factor for pancreatic cancer. The diagnostic capability of TROAP expression was also confirmed by Kaplan-Meier curves for OS and RFS.

L-selectin and trophinin are important adhesion molecules in human embryo implantation process [32]. The initial connection between trophoblast cells and endometrial epithelium is mediated by a complex of TROAP, trophonin, and bystin [4-6, 8]. In consideration of the process of trophoblasts during embryo implantation is similar to that of malignant tumor cells, some mechanisms of trophoblast the invasion of maternal uterine tissue are shared to cancer cells [33]. Previous research identified trophinin as a promoter for cell invasion, which could be a prognostic factor for the early stage of lung cancer [34]. Besides, the Kaplan-Meier analyses in this study demonstrated that high TROAP expression might be correlated with poor OS and RFS of PAAD patients in stage G1/G2, stage I/II and T1 stage, which suggested that TROAP might be a prognostic factor in the early stage of pancreatic cancer.

To reduce genomic instability and ensure the fidelity of chromosome segregation to generate genetically the same cells during cell cycle progression, the spindle assembly

checkpoint is the major cell cycle regulation mechanism in mitosis [35]. This kind of spindle assembly is related with microtubule dynamics in a temporal and spatial manner. Some studies also showed that TROAP protein peaks at the G2/M stage to regulate centrosome integrity and bipolar spindle assembly, which might be essential for the microtubular cytoskeleton [8, 36]. Research has investigated that the loss of TROAP caused by miR-519d-3p could significantly suppress cell proliferation, migration and invasion by causing cell cycle G0/G1 phase arrest in colorectal cancer cells [13]. In view of the TROAP mRNA expression was related to T classification and its high expression in PAAD, we supposed that TROAP promoted proliferation and the growth of tumor in pancreatic cancer by influencing cell cycle.

This is the first study suggested the relationship between clinical characteristics and TROAP in pancreatic cancer patients by mining TCGA database so far, which indicated that TROAP might serve as an independent risk factor for poor survival in pancreatic cancer. TROAP has the potential to be a biomarker, especially in predicting prognosis. However, due to sample size limitation, it is difficult to establish a predicting model for TROAP expression and clinicopathological variables in pancreatic cancer. In further study, we will expand the sample size to check the prognostic capability of TROAP expression and build an appropriate predicting model for the prognosis of patients.

Conclusions

In conclusions, we assessed the prognostic capability of TROAP expression by mining TCGA dataset. Our results demonstrated that TROAP was highly expressed in pancreatic cancer. Increased expression of TROAP was related with poor prognosis, which indicated that the expression of this molecular could act as an independent risk factor for OS and RFS. This finding identified that high TROAP expression was an independent factor involving in the prognosis of pancreatic cancer and associated with poor survival.

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Author contributions

YL and FH designed the experiment. RW and YJ undertook the data mining. RW, YJ, and YL analyzed and visualized the data. RW and YJ drafted the manuscript. YL, YW, and YL performed the statistical analyses. YW and YL revised the manuscript. The final manuscript was read and approved by all authors

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figure legends

Fig. 1 Different TROAP expression levels in the boxplot.

TROAP expression of pancreatic cancer tissues was compared with that in normal according to stage, histologic grade, gender, age, residual tumor, and TNM classification.

Fig. 2 ROC curve of TROAP in pancreatic cancer cohort.

The ROC curve for TROAP expression of pancreatic cancer tissues was compared with that in normal. The subgroup analyses for stage I, II, III, and IV.

Fig. 3 Overall survival analysis of TROAP expression.

Survival analyses and subgroup analyses according to clinical stage were performed based on Kaplan-Meier curves. The threshold TROAP level identified from the ROC curve was used to form the low and high groups.

Fig. 4 Relapse-free survival analysis of TROAP expression.

Survival analyses and subgroup analyses according to clinical stage were performed based on Kaplan-Meier curves. The threshold TROAP level identified from the ROC curve was used to form the low and high groups.

Fig. 1

Fig. 2

Fig. 3

Fig. 4

Table 1. Demographic and clinical characteristics of TCGA cohort.**Abbreviation: NA, not available.**

Characteristics	Numbers of cases (%)
Age	
<55	34(18.99)
>=55	145(81.01)
Gender	
FEMALE	80(44.69)
MALE	99(55.31)
Alcohol history	
NO	65(36.31)
YES	102(56.98)
NA	12(6.7)
Anatomic subdivision	
Body of Pancreas	14(7.82)
Head of Pancreas	139(77.65)
Tail of Pancreas	15(8.38)
Other	11(6.15)
Histological type	
Pancreas Adenocarcinoma Other Subtype	26(14.53)
Pancreas Adenocarcinoma Ductal Type	147(82.12)
Pancreas Colloid Carcinoma	4(2.23)
Pancreas Undifferentiated Carcinoma	1(0.56)
NA	1(0.56)
Histologic grade	
G1	31(17.32)
G2	96(53.63)
G3	48(26.82)
G4	2(1.12)
GX	2(1.12)
Stage	
I	21(11.73)
II	147(82.12)
III	4(2.23)
IV	5(2.79)
NA	2(1.12)
T classification	
T1	7(3.91)
T2	24(13.41)
T3	143(79.89)
T4	3(1.68)
TX	1(0.56)
NA	1(0.56)
N classification	

N0	50(27.93)
N1	124(69.27)
NX	4(2.23)
NA	1(0.56)
M classification	
M0	80(44.69)
M1	5(2.79)
MX	94(52.51)
Lymph nodes positive	
0	49(28)
1	126(72)
Max dimension	
<=5	143(86.14)
>5	23(13.86)
Residual tumor	
R0	107(59.78)
R1	53(29.61)
R2	5(2.79)
RX	4(2.23)
NA	10(5.59)
Radiation therapy	
NO	120(67.04)
YES	43(24.02)
NA	16(8.94)
Targeted molecular therapy	
NO	48(26.82)
YES	117(65.36)
NA	14(7.82)
Surgery performed type	
Distal Pancreatectomy	23(12.85)
Other Method (please specify)	13(7.26)
Total Pancreatectomy	4(2.23)
Whipple	137(76.54)
NA	2(1.12)
Therapy outcome	
Complete Remission/Response	69(38.55)
Partial Remission/Response	10(5.59)
Progressive Disease	51(28.49)
Stable Disease	8(4.47)
NA	41(22.91)
Vital status	
DECEASED	93(51.96)
LIVING	86(48.04)
Sample type	

Metastatic	1(0.56)
Primary Tumor	178(99.44)
Overall survival	
NO	85(47.75)
YES	93(52.25)
Relapse-free survival	
NO	98(62.82)
YES	58(37.18)
TROAP	
High	89(49.72)
Low	90(50.28)

Table 2. Relationship between the clinical features of pancreatic cancer and TROAP expression.

Parameter	Variables	N	High	%	Low	%	χ^2	P
Age	<55	34	16	(17.98)	18	(20)	0.0238	0.8773
	>=55	145	73	(82.02)	72	(80)		
Gender	FEMALE	80	37	(41.57)	43	(47.78)	0.4685	0.4937
	MALE	99	52	(58.43)	47	(52.22)		
Alcohol history	NO	65	29	(34.94)	36	(42.86)	0.793	0.3732
	YES	102	54	(65.06)	48	(57.14)		
Anatomic subdivision	Body of Pancreas	14	5	(5.62)	9	(10)	3.6294	0.3044
	Head of Pancreas	139	70	(78.65)	69	(76.67)		
	Tail of Pancreas	15	10	(11.24)	5	(5.56)		
	Other	11	4	(4.49)	7	(7.78)		
Histological type	Pancreas Adenocarcinoma	26	10	(11.36)	16	(17.78)	2.4237	0.4892
	Other Subtype							
	Pancreas Adenocarcinoma	147	75	(85.23)	72	(80)		
	Ductal Type							
	Pancreas Colloid	4	2	(2.27)	2	(2.22)		
	Carcinoma							
	Pancreas Undifferentiated	1	1	(1.14)	0	(0)		
Carcinoma								
Histologic grade	G1	31	10	(11.24)	21	(23.33)	6.5645	0.1608
	G2	96	52	(58.43)	44	(48.89)		
	G3	48	24	(26.97)	24	(26.67)		
	G4	2	2	(2.25)	0	(0)		
	GX	2	1	(1.12)	1	(1.11)		
Stage	I	21	9	(10.23)	12	(13.48)	0.6842	0.8769
	II	147	75	(85.23)	72	(80.9)		
	III	4	2	(2.27)	2	(2.25)		
	IV	5	2	(2.27)	3	(3.37)		
T classification	T1	7	2	(2.27)	5	(5.56)	4.6636	0.3236
	T2	24	9	(10.23)	15	(16.67)		
	T3	143	76	(86.36)	67	(74.44)		
	T4	3	1	(1.14)	2	(2.22)		
	TX	1	0	(0)	1	(1.11)		
N classification	N0	50	27	(30.34)	23	(25.84)	1.3523	0.5086
	N1	124	61	(68.54)	63	(70.79)		
	NX	4	1	(1.12)	3	(3.37)		
M classification	M0	80	37	(41.57)	43	(47.78)	1.0274	0.5983
	M1	5	2	(2.25)	3	(3.33)		
	MX	94	50	(56.18)	44	(48.89)		
Lymph nodes positive	NO	49	25	(28.41)	24	(27.59)	0	1
	YES	126	63	(71.59)	63	(72.41)		
Max dimension	<=5	143	71	(88.75)	72	(83.72)	0.5074	0.4763
	>5	23	9	(11.25)	14	(16.28)		

Residual tumor	R0	107	46	(56.1)	61	(70.11)	4.4418	0.2175
	R1	53	32	(39.02)	21	(24.14)		
	R2	5	2	(2.44)	3	(3.45)		
	RX	4	2	(2.44)	2	(2.3)		
Radiation therapy	NO	120	63	(75.9)	57	(71.25)	0.2462	0.6197
	YES	43	20	(24.1)	23	(28.75)		
Targeted molecular therapy	NO	48	29	(33.72)	19	(24.05)	1.4273	0.2322
	YES	117	57	(66.28)	60	(75.95)		
Surgery performed type	Distal Pancreatectomy	23	11	(12.64)	12	(13.33)	1.0772	0.7826
	Other Method	13	6	(6.9)	7	(7.78)		
	Total Pancreatectomy	4	1	(1.15)	3	(3.33)		
	Whipple	137	69	(79.31)	68	(75.56)		
Therapy outcome	Complete Remission/Response	69	34	(45.95)	35	(54.69)	1.1567	0.7634
	Partial Remission/Response	10	6	(8.11)	4	(6.25)		
	Progressive Disease	51	29	(39.19)	22	(34.38)		
	Stable Disease	8	5	(6.76)	3	(4.69)		
Vital status	DECEASED	93	58	(65.17)	35	(38.89)	11.3502	0.0008
	LIVING	86	31	(34.83)	55	(61.11)		
Sample type	Metastatic	1	1	(1.12)	0	(0)	0	0.9955
	Primary Tumor	178	88	(98.88)	90	(100)		
Overall survival	NO	85	31	(34.83)	54	(60.67)	10.8984	0.001
	YES	93	58	(65.17)	35	(39.33)		
Relapse-free survival	NO	98	43	(56.58)	55	(68.75)	1.9783	0.1596
	YES	58	33	(43.42)	25	(31.25)		

Table 3. Summary of univariate and multivariate Cox analyses of overall survival duration.

Parameters	Univariate analysis			Multivariate analysis		
	Hazard.Ratio.x	CI95.x	Pvalue.x	Hazard.Ratio.y	CI95.y	Pvalue.y
Age	1.22	0.73-2.05	0.446			
Gender	0.81	0.54-1.22	0.32			
Histological type	2.07	1.36-3.16	0.001	1.65	1.02-2.68	0.041
Stage	1.33	0.96-1.84	0.089			
T classification	1.64	1.08-2.49	0.021	0.99	0.59-1.65	0.955
N classification	2.16	1.29-3.63	0.004	1.80	1.05-3.1	0.033
M classification	0.77	0.18-3.22	0.723			
Residual tumor	1.36	1.06-1.76	0.018	1.41	1.08-1.84	0.01
TROAP	1.96	1.28-2.98	0.002	1.79	1.16-2.76	0.008

Table 4. Summary of univariate and multivariate Cox analyses of relapse-free survival duration.

Parameters	Univariate analysis			Multivariate analysis		
	Hazard.Ratio.x	CI95.x	Pvalue.x	Hazard.Ratio.y	CI95.y	Pvalue.y
Age	0.93	0.51-1.71	0.827			
Gender	1.12	0.67-1.89	0.667			
Histological type	1.09	0.65-1.84	0.733			
Stage	1.41	0.98-2.04	0.064			
T classification	1.51	0.94-2.41	0.088			
N classification	1.76	0.97-3.17	0.062			
M classification	0.82	0.19-3.48	0.787			
Residual tumor	1.73	1.23-2.42	0.002	1.80	1.27-2.56	0.001
TROAP	1.87	1.11-3.16	0.019	1.97	1.17-3.34	0.011