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Arpin downregulation is associated with poor prognosis in pancreatic ductal adenocarcinoma

Shi-Rong Zhang [a, b, c, d, 1], Hao Li [a, b, c, d, 1], Wen-Quan Wang [a, b, c, d, 1], Wei Jin [a, b, c, d], Jin-Zhi Xu [a, b, c, d], Hua-Xiang Xu [a, b, c, d], Chun-Tao Wu [a, b, c, d], He-Li Gao [a, b, c, d], Shuo Li [a, b, c, d], Tian-Jiao Li [a, b, c, d], Wu-Hu Zhang [a, b, c, d], Shuai-Shuai Xu [a, b, c, d], Quan-Xing Ni [a, b, c, d], Xian-Jun Yu [a, b, c, d, *], Liang Liu [a, b, c, d, *]

[a] Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center, Shanghai 20032, PR China
[b] Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, PR China
[c] Shanghai Pancreatic Cancer Institute, Shanghai 200032, PR China
[d] Pancreatic Cancer Institute, Fudan University, Shanghai 200032, PR China

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ABSTRACT

Introduction: Arpin (Arp2/3 complex inhibitor), a novel protein found in 2013, plays a pivotal role in cell motility and migration. However, the prognostic value of Arpin in pancreatic ductal adenocarcinoma (PDAC) remains unknown.

Materials and methods: We analyzed the gene expression of *ARPIN* using the GEO dataset (GSE71989) and validated the results by immunohistochemistry (IHC) and Western blot in our clinical database. Tissue microarray specimens from 214 patients who underwent curative pancreatectomy for PDAC were used. The tumors that expressed high and low levels of Arpin were compared with patient outcome using Kaplan-Meier curves and the multivariate Cox proportional hazard regression model. IHC was then used in 43 paired primary tumor tissues and metastasis tissues to detect the expression of Arpin.

Results: Arpin had low expression in the tumor tissue compared with the paracancerous tissue in PDAC. Patients with low intratumoral Arpin expression had worse overall survival (OS) and recurrence-free survival (RFS) than patients with high expression in the training set ($p < 0.001$, $p < 0.001$) and validation set ($p < 0.001$, $p < 0.001$). The multivariate analysis revealed that the 8th edition TNM stage and Arpin expression were independent prognostic factors associated with OS and RFS in the training and validation sets, respectively. Arpin had lower expression in the metastasis tissues than in the primary tumors of patients with PDAC ($p = 0.048$).

Conclusion: The Arpin level is an independent prognostic factor that can be a potential predictor to aid in the management of PDAC.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a dismal malignancy with a 5-year survival rate of less than 8%, and its incidence has risen continuously in recent years [1,2]. Surgical resection offers the only potential for a cure; however, the 5-year survival rate after resection is <20% [3]. The high mortality rate is mainly due to the tendency of PDAC cells to metastasize early. Thus, we need to identify specific indicator(s) to predict the prognosis after resection and aid in the management of PDAC.

Metastasis is one of the hallmarks of a cancer cell and is the result of aberrant cell migration. Cell migration requires the generation of branched actin networks that power the protrusion of the plasma membrane in lamellipodia. In this process, the actin-related protein 2/3 (Arp2/3) complex, which is the only molecular machine that generates branched actin networks to promote cell motility and migration, plays a pivotal role and has a direct impact

* Corresponding authors. Shanghai Pancreatic Cancer Institute; Pancreatic Cancer Institute, Fudan University; Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center; 270 Dong An Road, Shanghai 200032, China.
E-mail addresses: yuxianjun@fudanpci.org (X.-J. Yu), liuliang@fudanpci.org (L. Liu).
[1] Shi-Rong Zhang, Hao Li and Wen-Quan Wang contributed equally to this work.

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on patient survival [4,5]. It is reported that in pancreatic cancer cells, silencing of the Arp2/3 complex can disturb cell migration [6]. Arpin is a newly identified Arp2/3 complex competitive inhibitor reported in *Nature*, 2013; its acidic motif can compete with the Arp2/3 complex activator, called nucleation-promoting factor (NPF), for Arp2/3 binding [7]. Arpin can negatively regulate Arp2/3 activity as cells utilize Arpin to fine-tune the actin nucleation activity at the leading edge of the lamellipodium and steer cell migration [7–9].

It is reported that Arpin is significantly decreased in tumor samples compared with paratumoral normal tissues [10–12] and is closely related to poor outcomes of patients with breast and gastric cancers [10–12]. The loss of Arpin expression can enhance cell proliferation and promote tumor cell metastasis in breast cancer and head and neck squamous cell carcinoma [12,13]. In previous experiments, our research team found that Arpin promotes liver cancer cell metastasis. However, the expression of Arpin in human PDAC tissue and the correlation with the clinicopathological characteristics and prognosis of patients are still unclear.

In this study, we examined the expression of Arpin in PDAC tissues and assessed its correlation with clinicopathological and prognostic variables in patients who underwent surgery for PDAC. We further compared the differences in Arpin expression between the primary tumor and metastatic sites.

Methods

Patients and sample collection

We enrolled two independent cohorts comprising a total of 214 patients who underwent R0 resection for PDAC identified by the pathology department at the Shanghai Cancer Center (Shanghai, China). The training set and the validation set respectively contained 73 patients from January 2012 to December 2013 and 141 patients from January 2010 to December 2011. All the patients enrolled in these two cohorts had resectable PDAC, which had no arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]); and no tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or $\leq 180^{\circ}$ contact without vein contour irregularity, and without distant metastasis. The patients' characteristics are listed in Table 1.

After reviewing our database from January 2010 to December 2016, we enrolled 43 patients from 2540 patients in the "metastasis set" in which metastasis was found during surgery while the preoperative imaging diagnosis did not detect any metastasis. We collected the primary tumor tissue and the paired metastasis samples. The information of the patients in the metastasis set is summarized in Supplementary Table 1.

Overall survival (OS) was calculated as the interval between the date of surgery and the date of death or the last follow-up visit. Recurrence-free survival (RFS) was defined as the interval between the date of surgery and the date of tumor recurrence or the last follow-up visit. All patients were followed up until December 2016. The use of human tissues was approved by the Research Ethics Committees at the associated pancreatic centers. Informed consent was obtained from all patients according to the committees' regulations.

Immunohistochemistry and evaluation of immunostaining

Immunostaining was performed on the training set and the validation set using tissue microarrays (TMAs; Shanghai Biochip Company, Shanghai, China). The TMAs were constructed as described previously using two tissue cores (1.5-mm diameter) taken from representative areas of each formalin-fixed, paraffin-embedded tumor specimen [14–16]. The metastasis set used 43 pairs of routine pathological sections of formalin-fixed, paraffin-embedded specimens, which had a paired primary tumor and a metastasis site.

Immunohistochemistry was performed as described previously and evaluated using a two-step method [14–16]. The primary antibodies composed of rabbit monoclonal antibodies Arpin (diluted 1:200, ab235421, Abcam, Cambridge, MA) was applied [10,11].

The tumor cells in which the cytoplasm was stained dark brown under light microscopy were considered positive. For the quantification of Arpin expression, both the staining intensity and the percentage of stained cells were evaluated. The cells with no staining were scored as 0 points, 1 point represented weak staining intensity, 2 points represented moderate staining intensity, and 3 points represented strong staining intensity. Additionally, the percentage of stained tumor cells was assessed: 0% corresponded to 0 points, less than 25% corresponded to 1 point, 25%–50% corresponded to 2 points, and more than 50% corresponded to 3 points. The final score for Arpin expression was equal to the sum of the two types of scores. A staining score ranging from 0 to 3 points represented a low expression level, and a score more than 3 points was considered a high expression level [10,11].

Western blot analysis

The total protein was extracted from the pancreatic cancer tissue with RIPA lysis buffer, and Western blot was performed according to standard protocols. The primary antibodies included anti-Arpin (diluted 1:1000), and anti-β-actin antibodies (diluted 1:2000, 60008-1-Ig, Proteintech Group, USA). Protein blots were repeated at least twice. The Arpin protein level was quantified on Western blot membranes selected at equal exposure time. The band intensities were measured on ImageJ (Bethesda, MD, USA) by quantifying the peak area of each band and they were corrected by background subtraction.

Statistical analyses

The continuous variables in different subgroups were compared using an unpaired *t*-test and a one-way analysis of variance. The categorical variables were compared using the chi-square test. The association between clinicopathological features and immunohistochemical variables was evaluated using the chi-square test or the Fisher exact test. OS and RFS were displayed using Kaplan-Meier survival curves with 95% confidence intervals (CIs), and the differences between the subgroups were compared using the log-rank test. The univariate and multivariate regression analyses were used to identify independent prognostic factors, and $p < 0.05$ was the criterion for variable deletion when performing the backward stepwise selection. All the tests were two-sided, and $p < 0.05$ was considered statistically significant. The statistical analyses were performed using SPSS 24.0 (SPSS Inc., Chicago, IL).

Results

Arpin had lower expression in the PDAC tissue than in the normal pancreas

Searching through the GEO datasets (GSE71989), we found that the gene expression of *ARPIN* was lower in the PDAC tissues than in the normal pancreatic tissues ($p = 6.85e^{-10}$; Fig. 1A). We then conducted immunostaining of 20 pathological sections, comprising tumor and paracancerous tissues from different patients, as a preliminary experiment. Arpin expression

Table 1
Demographics and clinicopathological characteristics of the patient sets with resectable PDAC.

Features	Training set (n = 73)	Validation set (n = 141)	*p* value
Age (years, median [range])	61 (39–83)	62 (38–79)	0.480
Sex (female/male) (%)	32/41 (43.8/56.2)	55/86 (39.0/61.0)	0.495
Tumor location (head/body, tail) (%)	39/34 (46.6/53.4)	75/66 (53.2/46.8)	0.824
Neural invasion (yes/no) (%)	59/14 (80.8/19.2)	101/40 (71.6/28.4)	0.142
Microvascular invasion (yes/no) (%)	17/56 (23. 3/76.7)	36/105 (25.5/74.5)	0.637
Tumor differentiation (well, moderate/poor) (%)	51/22 (69.9/30.1)	93/48 (66.0/34.0)	0.564
Tumor size (cm, mean ± SD)	4.18 ± 2.002	4.24 ± 2.089	0.309
Preoperative CA19-9 (U/mL, median) (range)	320 (1–2084)	141 (1–17616)	0.571
8th edition T classification (T1/T2/T3) (%)	5/29/39 (6.8/39.7/53.4)	12/70/59 (8.5/49.6/41.8)	0.273
8th edition N classification (N0/N1/N2) (%)	32/26/15 (43.8/35.6/20.5)	65/47/29 (46.1/33.3/20.6)	0.938
8th edition TNM stage (I/II/III) (%)	19/39/15 (26.1/53.4/20.5)	50/62/29 (35.5/44.0/20.5)	0.327
Arpin expression (High/Low) (%)	34/39 (46.6/53.4)	79/62 (56.0/44.0)	0.180
Disease relapse (yes/no) (%)	67/6 (91.8/8.2)	120/21 (85.1/14.9)	0.217
Site of relapse (%) Local/Liver/Other/intra-abdominal/Lung/Bone	23/35/11/7/1 (34.3/52.2/16.4/10.4/1.5)	52/62/20/5/4 (43.3/51.7/16.7/4.1/3.3)	0.437

Note: TNM: tumor node metastasis; CA19-9: carbohydrate antigen 19-9.

was significantly reduced in the tumor tissue (Fig. 1B). This result was validated by Western blot in another 20 pairs of specimens, which contained tumor tissues and paired normal pancreas tissues (Fig. 1C).

Low Arpin expression was associated with poor prognosis in resectable PDAC patients

All tumors specimens enrolled in the training set and the validation set were evaluated for Arpin expression. The percentages of low Arpin expression in the training set and the validation set were 53.4% and 44.0%, respectively. There was no heterogeneity in the expression between the two sets ($p = 0.18$, Table 1).

The relationships between the Arpin expression and the patients' clinical features are listed in Supplementary Table 1. There were no correlations identified between Arpin expression and age, sex, tumor location, neural invasion, preoperative carbohydrate antigen 19-9 (CA19-9) level or the sites of relapse after surgery. Arpin expression was correlated with microvascular invasion ($p = 0.050$, $p = 0.009$), the 8th edition tumor stage (T) ($p = 0.001$, $p = 0.030$), the 8th edition node stage (N) ($p = 0.015$, $p = 0.035$), and the 8th edition tumor node metastasis stage (TNM) ($p = 0.021$, $p = 0.042$). In the validation set, Arpin expression was also related to tumor differentiation ($p = 0.014$).

The Kaplan-Meier analysis showed that patients with low intratumoral Arpin expression had worse OS and RFS than patients with high Arpin expression in the training set ($p < 0.001$, $p < 0.001$; Fig. 2A) and the validation set ($p < 0.001$, $p < 0.001$ Fig. 2B). A receiver operating characteristic (ROC) curve analysis was performed to evaluate the prognostic value of Arpin. The area under the curve (AUC) for Arpin expression associated with OS was 0.793 and 0.719 in the training set and the validation set, respectively. The AUC for Arpin expression associated with RFS was 0.739 and 0.709 in the training set and the validation set, respectively (Fig. 2C and D).

Low Arpin expression was an independent prognostic factor for patients with resectable PDAC

The univariate Cox regression analysis identified clinical factors significantly associated with OS in the training set and the validation set, and these factors were microvascular invasion ($p = 0.025$, $p = 0.014$), the 8th edition T stage ($p < 0.001$, $p < 0.001$), the 8th edition N stage ($p < 0.001$, $p < 0.001$), the 8th edition TNM staging system ($p < 0.001$, $p < 0.001$) and Arpin expression ($p < 0.001$, $p < 0.001$). Major factors significantly associated with RFS were microvascular invasion ($p = 0.049$, $p = 0.021$), the 8th edition T stage ($p = 0.001$, $p = 0.012$), the 8th edition N stage ($p < 0.001$, $p < 0.001$), the 8th edition TNM stage ($p < 0.001$, $p < 0.001$) and Arpin expression ($p < 0.001$, $p < 0.001$) in the training set and the validation set (Table 2).

The variables demonstrating a meaningful effect on the outcome of PDAC were included in the multivariate analysis (Table 2). The multivariate analysis revealed that the 8th edition TNM stage [$p < 0.001$, hazard ratio (HR) = 3.180; $p < 0.001$, $HR = 1.964$] and Arpin expression ($p = 0.003$, $HR = 2.640$; $p = 0.003$, $HR = 1.907$) were independent prognostic factors that were associated with OS in the training and the validation sets, respectively. In the same way, the multivariate analysis revealed that the 8th edition TNM stage ($p < 0.001$, $HR = 2.423$; $p < 0.001$, $HR = 1.954$) and Arpin expression ($p = 0.027$, $HR = 2.012$; $p < 0.001$, $HR = 2.247$) were independent prognostic factors associated with RFS in the two sets (Table 2).

The expression of the Arpin protein was decreased in metastasis tissue

Immunostaining was then performed on the metastasis set using 43 paired pathological sections containing primary tumor and metastasis tissue. We found that Arpin expression was lower in the metastasis tissue than in the primary tumor tissue ($p = 0.048$; Fig. 3; Supplementary Table 2). The percentage of negative Arpin

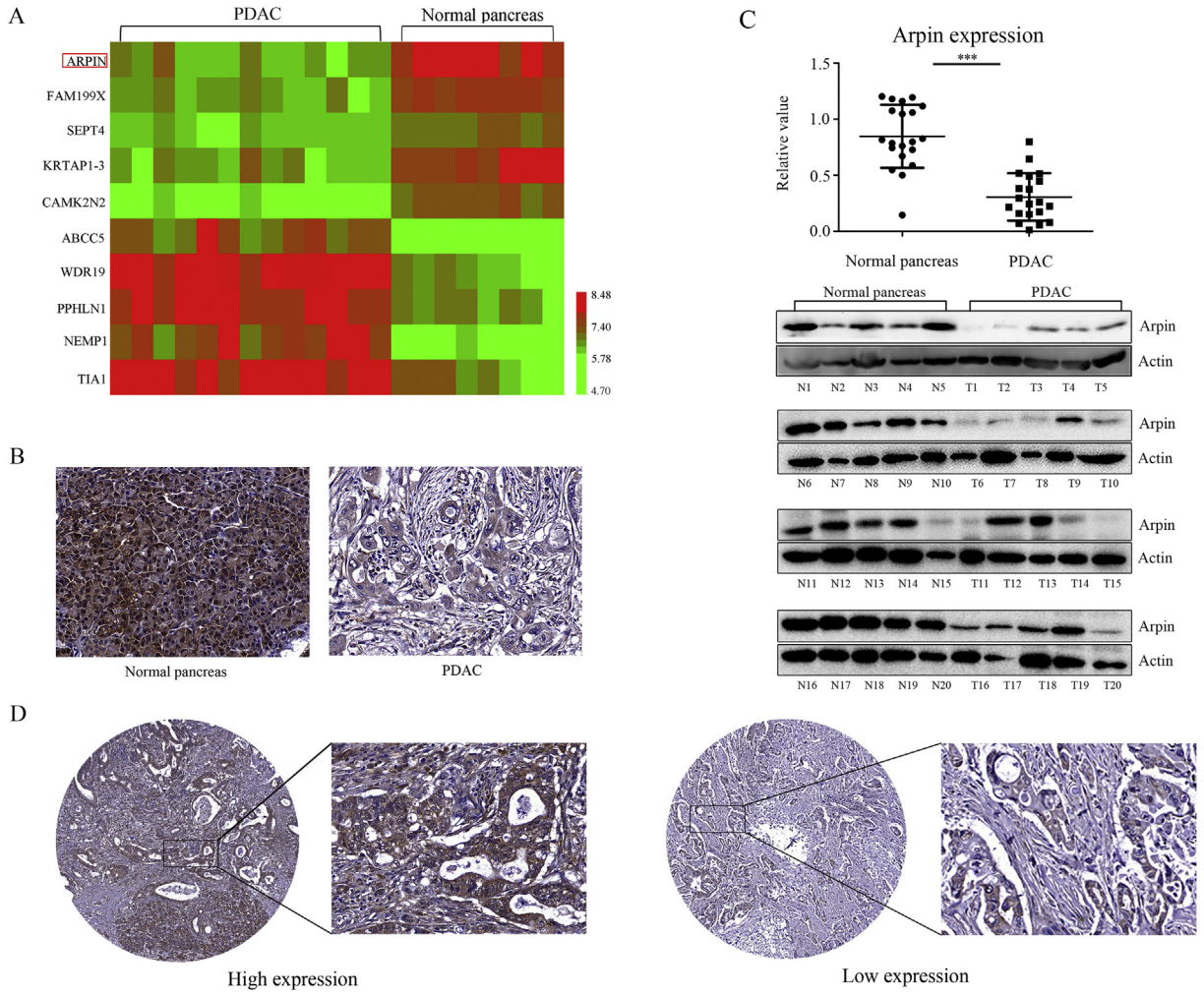

Fig. 1. Arpin expression in PDAC. (A) The gene expression of *ARPIN* was downregulated in PDAC tissue compared with that in the matched normal pancreatic tissue ($p = 6.85e^{-10}$; GSE71989); (B, C) The expression level was significantly downregulated in pancreatic cancer tissue compared to that in the adjacent noncancerous tissue (WB: $p < 0.01$). (D) The levels of Arpin expression were classified into low and high groups according to the scores from the IHC staining. Magnification = 400 ×. The positive staining appears brown.

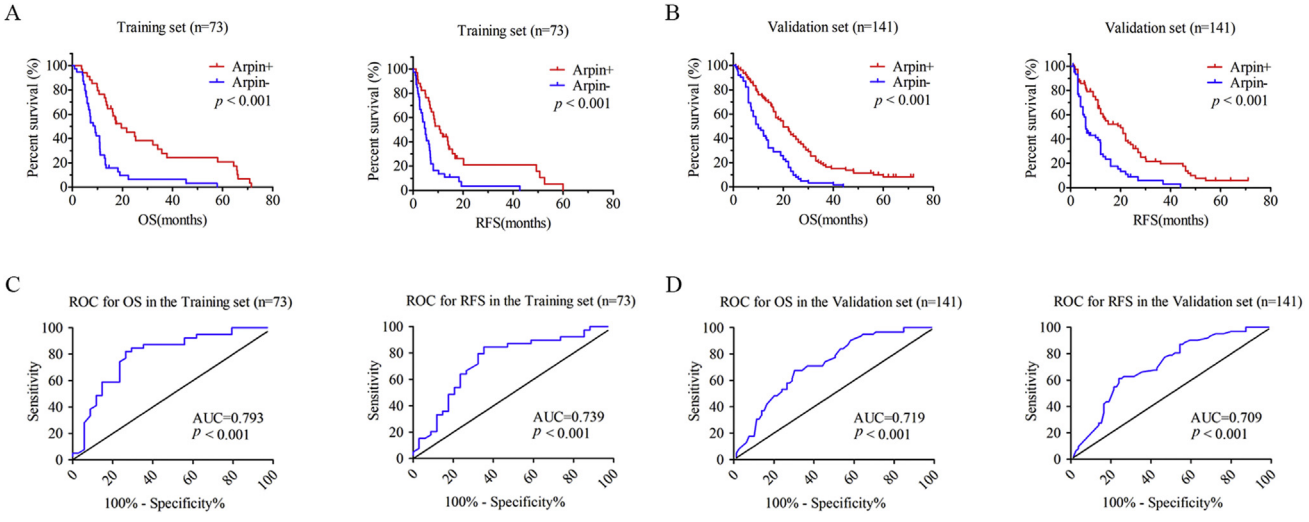

Fig. 2. Kaplan-Meier estimates of OS and RFS according to the expression of Arpin in patients with resectable PDAC. (A) Training set, OS ($p < 0.001$), RFS ($p < 0.001$); (B) Validation set, OS ($p < 0.001$), RFS ($p < 0.001$). ROC curve of Arpin. (C) Training set, OS (AUC = 0.793), RFS (AUC = 0.739); (D) Validation set, OS (AUC = 0.719), RFS (AUC = 0.709). AUC = area under the curve.

Table 2
Univariate Cox regression analyses of OS and RFS in the training, testing, and validation sets of patients with PDAC (continued).

Training set (n = 73)	OS				RFS			
	Univariate Analyses		Multivariate Analyses		Univariate Analyses		Multivariate Analyses	
Factors	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (>62 years/≤62 years)	1.001 (0.611−1.641)	0.996	1.209 (0.680−2.148)	0.518	1.014 (0.612−1.681)	0.955	0.959 (0.526−1.749)	0.893
Sex (male/female)	1.030 (0.633−1.676)	0.905	1.478 (0.858−2.547)	0.159	1.058 (0.645−1.735)	0.822	1.226 (0.715−2.102)	0.459
Tumor location (head/body, tail)	1.515 (0.933−2.461)	0.093	1.041 (0.588−1.843)	0.890	1.628 (0.998−2.657)	0.052	1.180 (0.662−2.105)	0.574
Neural invasion (yes/no)	1.131 (0.615−2.080)	0.692	1.489 (0.749−1.956)	0.256	0.892 (0.492−1.618)	0.708	1.088 (0.549−2.154)	0.890
Microvascular invasion (yes/no)	1.959 (1.088−3.524)	**0.025**	1.399 (0.668−2.929)	0.373	1.781 (0.992−3.197)	**0.049**	1.272 (0.591−2.740)	0.538
Tumor differentiation (well, moderate/poor)	1.424 (0.844−2.402)	0.186	1.535 (0.814−2.898)	0.186	1.541 (0.902−2.631)	0.114	1.391 (0.723−2.676)	0.323
Preoperative CA19-9 (U/mL, >37/≤37)	1.631 (0.867−3.070)	0.129	1.039 (0.504−2.142)	0.917	2.127 (1.041−4.343)	**0.038**	1.812 (0.891−4.009)	0.142
8th edition T classification (T1+T2/T3)	3.085 (1.855−5.131)	< **0.001**	−	**-**	2.273 (1.417−3.646)	**0.001**	−	**-**
8th edition N classification (N0/N1/N2)	3.211 (2.215−4.654)	< **0.001**	−	**-**	2.674 (1.869−3.827)	< **0.001**	−	**-**
8th edition TNM stage (I/II/III)	3.320 (2.171−5.087)	< **0.001**	3.180 (1.964−5.149)	< **0.001**	2.672 (1.748−4.085)	< **0.001**	2.423 (1.503−3.908)	< **0.001**
Arpin expression (High/Low)	3.280 (1.917−5.612)	< **0.001**	2.640 (1.392−5.008)	**0.003**	2.593 (1.538−4.373)	< **0.001**	2.012 (1.083−3.739)	**0.027**
Validation set (n = 141)	**OS Univariate Analyses**		**Multivariate Analyses**		**RFS Univariate Analyses**		**Multivariate Analyses**	
Factors	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (>62 years/≤62 years)	1.086 (0.773−1.526)	0.633	1.509 (0.742−1.513)	0.750	0.990 (0.685−1.430)	0.956	0.884 (0.602−1.298)	0.528
Sex (male/female)	0.925 (0.653−1.311)	0.663	1.041 (0.708−1.532)	0.837	1.064 (0.730−1.551)	0.747	1.273 (0.847−1.913)	0.245
Tumor location (head/body, tail)	1.042 (0.742−1.463)	0.812	0.995 (0.703−1.410)	0.979	0.909 (0.629−1.312)	0.609	0.861 (0.590−1.255)	0.439
Neural invasion (yes/no)	1.072 (0.738−1.558)	0.716	1.460 (0.957−2.226)	0.079	1.040 (0.690−1.570)	0.850	1.573 (0.993−2.492)	0.054
Microvascular invasion (yes/no)	1.616 (1.100−2.393)	**0.014**	1.635 (0.796−3.357)	0.181	1.641 (1.076−2.502)	**0.021**	1.950 (0.859−4.423)	0.110
Tumor differentiation (well, moderate/poor)	1.506 (1.050−2.161)	**0.026**	0.895 (0.457−1.749)	0.745	1.483 (0.996−2.209)	0.052	0.760 (0.327−1.526)	0.376
Preoperative CA19-9 (U/mL, >37/≤37)	1.662 (1.074−2.571)	**0.023**	1.220 (0.770−1.935)	0.397	1.281 (0.820−2.000)	0.276	0.915 (0.565−1.481)	0.717
8th edition T classification (T1+T2/T3)	1.978 (1.458−2.684)	< **0.001**	−	**-**	1.512 (1.097−2.086)	**0.012**	−	**-**
8th edition N classification (N0/N1/N2)	1.974 (1.556−2.503)	< **0.001**	−	**-**	1.778 (1.374−2.301)	< **0.001**	−	**-**
8th edition TNM stage (I/II/III)	2.166 (1.687−2.781)	< **0.001**	1.964 (1.499−2.574)	< **0.001**	1.831 (1.395−2.407)	< **0.001**	1.954 (1.498−2.571)	< **0.001**
Arpin expression (High/Low)	2.441 (1.701−3.502)	< **0.001**	1.907 (1.250−2.908)	**0.003**	2.432 (1.648−3.587)	< **0.001**	2.247 (1.531−3.530)	< **0.001**

Note: CI: confidence interval; HR: hazard ratio; OS: overall survival; RFS: recurrence-free survival; TNM: tumor node metastasis; CA19-9: carbohydrate antigen 19-9; *p*-value less than 0.05 marked in bold font shows statistically significant difference.

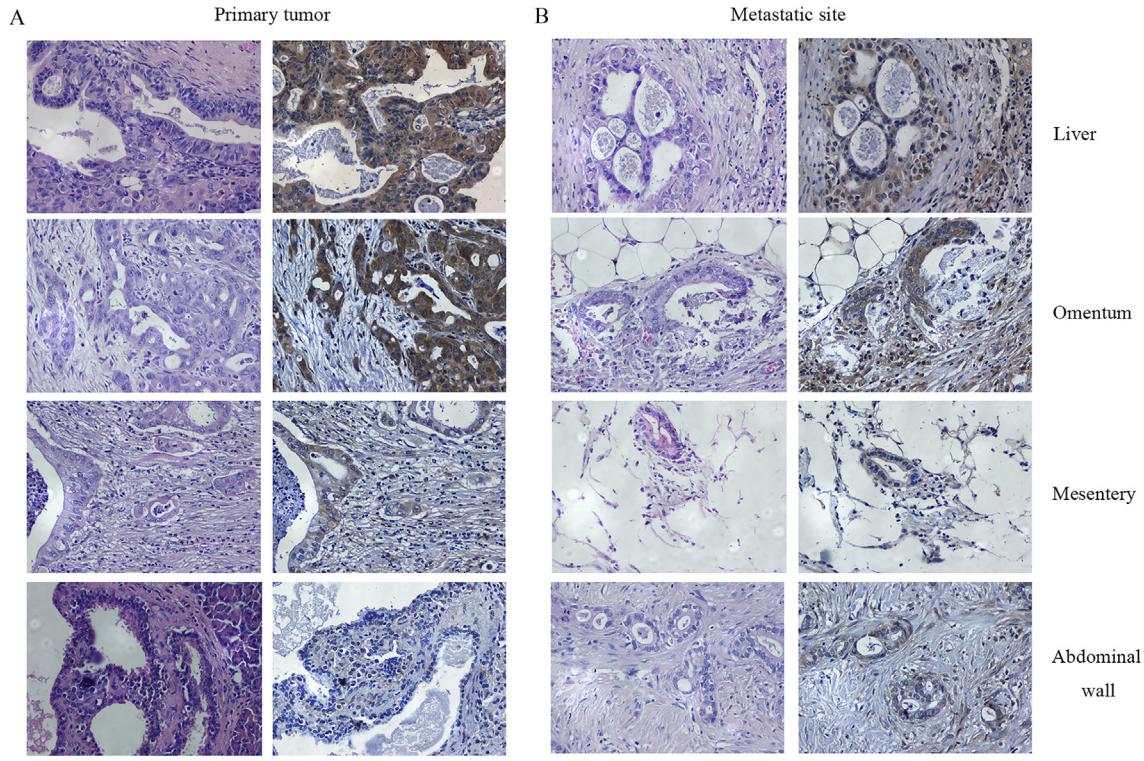

Fig. 3. Representative microphotographs of Arpin staining in the paired primary tumor and metastasis. (A) HE staining and immunostaining of Arpin in PDAC tissue; (B) HE staining and immunostaining of Arpin in paired metastatic sites; magnification = 400 ×. The positive staining appears brown.

expression in the metastasis tissue was as high as 83.8%. The expression of Arpin in the primary tumors of patients with metastases was lower than that in patients with resectable PDACs.

Discussion

In this study, we found that Arpin expression was low in the tumor tissue compared with the paracancerous normal pancreas and that the low expression of Arpin was predictive of poor post-surgical survival of patients with resectable PDAC. The Arpin protein level was also decreased in the metastasis tissues, and the percentage of negative Arpin expression was high. We used independent samples collected at different times (training set and validation set) in our research center to validate our results and collected numerous paired primary tumor and metastasis sites to explore the expression of Arpin in metastasis tissue.

Arpin is a conserved Arp2/3 inhibitory protein and is localized at the lamellipodium tip. The absence of Arpin can induce faster lamellipodia protrusions and cell migration [7]. In this study, we found that the Arpin protein level was significantly decreased in the tumor samples relative to the paired normal tissues. In the tumor tissue, low Arpin expression was associated with microvascular invasion and local lymph node metastases in patients with resectable PDAC. We found that low expression of Arpin in tumor tissue was closely associated with poor OS and RFS for patients with resectable PDAC and had high prognostic value. These results are consistent with studies addressing other cancers [10–12]. We further discovered that Arpin had lower expression in the metastatic site than in the primary tumor. These results suggest that due to the decreased expression of Arpin, tumor cells acquire the ability to invade and metastasize in PDAC. In addition, Arpin controls cell proliferation. In breast cancer [12], loss of Arpin expression is associated with enhanced cell growth and larger tumor size, which supported our results that low Arpin expression is related to T stage of PDAC. Altogether, these results suggest that loss of Arpin expression may be associated with the enhanced growth and migration of tumor cells, in line with the poor prognosis of PDAC patients after resection. However, the exact molecular events leading to cancer metastasis and poor prognosis have not yet been well elucidated, and further research is required.

The Arp2/3 complex is the sole machinery that generates branched actin networks. This machinery is activated at different locations of the cell by NPF [5,17]. Arp2/3 is activated at the leading edge of migrating cells by Wiskott–Aldrich syndrome protein (WASP)-family verprolin-homologous protein (WAVE, also known as SCAR), which can influence cell proliferation, migration and invasion in PDAC cells; Arpin inactivates Arp2/3 at the same location [5,7,18]. The WAVE complex is itself directly activated by the small GTPase Rac. Interestingly, Arpin is also under the control of the small GTPase Rac [7]. The coexistence of the Rac–Arpin–Arp2/3 inhibitory circuit with the Rac–WAVE–Arp2/3 activator circuit can induce and inhibit actin polymerization and generate an 'incoherent feed-forward loop', which can steer cell migration [7]. In this feedback system, the WAVE complex closes a positive feedback loop that maintains efficient directional migration over time, whereas Arpin closes a concurrent negative feedback loop, which induces braking and allows turning, similar to the "brake and accelerator" in cells. There are several reports that indicate aberrant activity of Rac in PDAC cells [19,20]. However, there are still no studies on the factors that can affect Rac to inhibit Arpin and to promote WAVE, then permanently influence this "circuitry" in the PDAC cell. In addition, the regulatory mechanism of Arpin in PDAC is still unknown. These are interesting problems that whether the unique microenvironment such as hypoxia influences Rac activation, and that whether the loss of Arpin function is associated with increased cell motility in the epithelial-mesenchymal transition during the

progression of cancer. We are conducting basic experiments in vivo and in vitro to demonstrate the potential mechanism of Arpin in PDAC.

The present study is the first to report on the clinical significance of Arpin expression in PDAC patients, but it has some limitations. First, because of the retrospective nature of the study, some details are not available for the two sets. Second, our results do not provide any information about the mechanism by which Arpin down-regulation affects the prognosis of patients with PDAC. Thus, these results need to be confirmed further in follow-up studies with larger sample sizes, and further experiments are needed to explore how Arpin is downregulated and influences tumor behavior in PDAC.

Conclusion

In summary, the present study showed that Arpin is decreased in PDAC tissues, and Arpin was demonstrated to be a potential marker to predict disease progression and patient outcomes. The findings of this study may aid in the management of patients in clinical practice and the development of novel treatment strategies in the future to control metastasis.

Disclosure

The authors declare no conflicts of interest in this study.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejso.2018.10.539.

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