

## Original Article

# Association of pancreatic adenocarcinoma up-regulated factor expression in ovarian mucinous adenocarcinoma with poor prognosis

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**Abstract:** Pancreatic adenocarcinoma up-regulated factor (PAUF) expression is elevated in both ovarian tumors and pancreatic adenocarcinoma. However, PAUF expression in ovarian tumors according to histologic subtype and grade has not been investigated. In this study, we examined various clinicopathologic features of 24 patients with mucinous cystadenoma (MCA), 36 with mucinous borderline tumors (MBTs), and 46 with mucinous adenocarcinomas (MACs) according to PAUF expression status assessed using immunohistochemistry. We found that MACs more frequently stained positive for PAUF than did MCAs and MBTs ( $P < 0.0001$ ). Although there was no significant differences with respect to other clinicopathologic characteristics of MACs according to PAUF expression status, patients with PAUF-weakly positive and PAUF-strongly positive MACs tended to have a shorter overall survival (OS) than those with PAUF-negative MAC, determined using a Kaplan–Meier analysis ( $P = 0.1885$ ). After adjusting for various clinicopathologic parameters, PAUF positivity of MACs was a significant predictive factor for disease-free survival (DFS) (negative vs. weakly positive:  $P = 0.045$ , hazard ratio [HR] = 57.406, 95% confidence interval [CI]: 1.090-3022.596; and negative vs. strongly positive:  $P = 0.034$ , HR = 97.890, 95% CI: 1.412-6785.925). In conclusion, PAUF was more frequently expressed in MAC than in its benign and borderline counterparts, and was associated with a poor OS and DFS in MAC patients. Therefore, we suggest that PAUF may be a practical biomarker for histopathological categorization and a prognostic marker for patients with an ovarian mucinous tumor.

**Keywords:** Mucinous tumor, ovary, PAUF, prognostic factor

## Introduction

Ovarian mucinous neoplasm is a common ovarian epithelial tumor. It is categorized as benign mucinous cystadenoma (MCA), mucinous borderline tumor (MBT) of intermediate grade, and malignant mucinous adenocarcinoma (MAC) based on its biological behavior [1, 2]. Of these, MCA is the most common ovarian mucinous neoplasm, accounting for 14% of all ovarian tumors and approximately 80% of all primary ovarian mucinous tumors [3]. MBTs, which are associated with an excellent prognosis and have a survival rate of > 90%, are the most common type of borderline ovarian tumor in Asia and the second most common in North America and Europe [4-8]. In contrast, ovarian

MAC accounts for 3-4% of all primary ovarian carcinomas and is known to have an aggressive behavior, often recurring early and showing resistance to chemotherapy and radiotherapy [9, 10]. It is therefore important to distinguish between these tumor subtypes; however, there are no suitable biomarkers to that can help to differentiate between intermediate and malignant mucinous tumors.

Pancreatic adenocarcinoma up-regulated factor (PAUF) is a novel, tumor-specific protein [11]. It is known to play an important role in cancer progression and metastasis in pancreatic ductal adenocarcinoma [11, 12]. In addition, Kim *et al.* demonstrated that PAUF was also highly expressed in colon and ovarian tumors using

## PAUF-positive ovarian mucinous adenocarcinoma

**Table 1.** Clinicopathologic features of ovarian mucinous neoplasms

	Mucinous cystadenoma	Mucinous borderline tumor	Mucinous adenocarcinoma	P-value
Number of cases	24	36	46	
Age at diagnosis (years, mean ± SD)	49.25 ± 3.632	44.36 ± 2.502	43.26 ± 2.122	0.2951
Stage (%)				< 0.0001
Localized	-	34 (94.44)	22 (47.83)	
Regional	-	2 (5.56)	14 (30.43)	
Distant	-	0	10 (21.74)	
Histologic subtype (%)				
Intestinal	-	30 (83.33)	-	
Endocervical	-	6 (16.67)	-	
Invasion pattern (%)				
Expansile	-	-	37 (80.43)	
Infiltrative	-	-	9 (19.57)	
PAUF expression (%)				< 0.0001
Negative	16 (66.67)	27 (75.00)	10 (21.74)	
Weakly positive	7 (29.17)	5 (13.89)	19 (41.30)	
Strongly positive	1 (4.17)	4 (11.11)	17 (36.96)	

SD, standard deviation.

Northern blot analysis [11]. However, the expression profiles of PAUF in ovarian neoplasms according to histologic subtype or malignant potential are not known. In this study, we evaluated PAUF expression status according to the histologic grade of ovarian mucinous neoplasms and investigated its potential as a prognostic biomarker.

### Materials and methods

#### Case selection and tumor samples

The study cohort consisted of 24 patients with MCA, 36 patients with MBT, and 46 patients with MAC who had undergone surgery and were diagnosed at Yonsei University Medical Center between 2001 and 2012. This retrospective study was approved by the institutional review board of Yonsei University Medical Center (IRB no. 4-2014-0034). The following clinical parameters were recorded: age at diagnosis, tumor stage, follow-up duration, and survival. We grouped cases of mucinous neoplasms using the International Federation of Gynecology and Obstetrics (FIGO) staging criteria at diagnosis. These groups were a localized stage including FIGO stages IA and IB, a regional stage including FIGO stages IC and II, and a distant stage including FIGO stages III and IV.

Tissue samples were fixed in 10% buffered formalin and embedded in paraffin. Archival tis-

ues stained with hematoxylin and eosin (H&E) were reviewed by two obstetrics and gynecology pathologists (SK Kim and NH Cho). A representative area was selected on an H&E-stained slide and the corresponding area was marked on the formalin-fixed paraffin-embedded (FFPE) tissue block to make a tissue microarray (TMA), with 5 mm tissue cores. The pathologic parameters included the histologic subtype of MBT, invasion patterns of MAC, PAUF expression, estrogen receptor (ER) expression, and Ki-67 labeling index (LI).

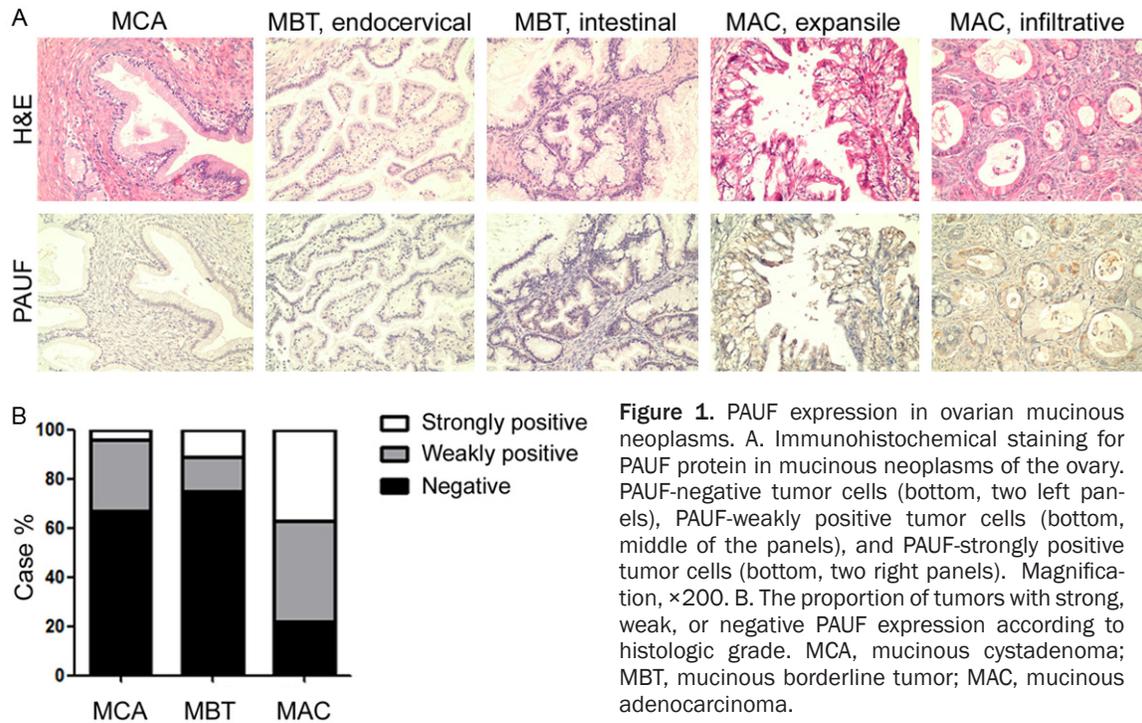
#### Immunohistochemistry

We used an anti-recombinant human PAUF (antirhPAUF) polyclonal antibody (pAb) which was kindly provided by Dr. Sun A Kim [11]. Immunohistochemistry was performed using 5- $\mu$ m-thick sections cut from a TMA block using a microtome. These were transferred onto adhesive slides and dried at 70°C for 30 min. Immunohistochemistry with anti-rhPAUF pAb (diluted 1:200), ER antibody (Thermo Scientific, diluted 1:100), and Ki-67 (Abcam, diluted 1:1000) was performed using a Dako Envision Kit following the manufacturers' instructions.

#### Interpretation of immunohistochemical staining

We divided ovarian mucinous tumors into three groups based on the immunostaining intensity

## PAUF-positive ovarian mucinous adenocarcinoma



**Figure 1.** PAUF expression in ovarian mucinous neoplasms. A. Immunohistochemical staining for PAUF protein in mucinous neoplasms of the ovary. PAUF-negative tumor cells (bottom, two left panels), PAUF-weakly positive tumor cells (bottom, middle of the panels), and PAUF-strongly positive tumor cells (bottom, two right panels). Magnification,  $\times 200$ . B. The proportion of tumors with strong, weak, or negative PAUF expression according to histologic grade. MCA, mucinous cystadenoma; MBT, mucinous borderline tumor; MAC, mucinous adenocarcinoma.

of PAUF: 0 (negative), 1 (weakly positive) and 2 (strongly positive). The proportion of PAUF-stained cells was scored as 0 (negative), 1 ( $< 10\%$ ) and 2 ( $> 10\%$ ). The final score for each tumor was calculated by multiplying the immunostaining intensity by the proportion of stained cells, and was then categorized as follows: 0-1, negative; 2, weakly positive; and 4, strongly positive.

A cut-off value of  $> 1\%$  of nuclei that were strongly stained was used to define ER expression [13]. To establish the cutoff Ki-67 LI, we analyzed the Ki-67 LI of ovarian mucinous tumors using receiver operator characteristic (ROC) curves according to PAUF positivity and determined that 1.167% (sensitivity: 70.4%, 1 - specificity: 84.8%) was the optimal cutoff value.

### Statistics

Statistical analyses were performed using GraphPad Prism 5 software, version 5.01 (GraphPad Software, Inc., La Jolla, CA, USA) and SPSS for Windows, version 12.0 (SPSS Inc., Chicago, IL, USA). For the analysis of age at diagnosis, a significant difference between means was determined by analysis of variances (ANOVA). Follow-up durations of patients

with MBT and MAC were compared using a t-test. FIGO stage, histologic subtypes, invasion patterns, and the expressions of PAUF, ER, and Ki-67 LI were compared using the chi-square and Fisher's exact test. Kaplan-Meier survival curves and log-rank statistics were employed to evaluate overall survival (OS) and disease-free survival (DFS). Univariate and multivariate regression analyses were performed using the Cox proportional hazards model. All reported *P*-values are two-sided, and *P*-values  $< 0.05$  were considered statistically significant.

### Results

#### *Clinicopathologic features of ovarian mucinous neoplasms*

Ovarian mucinous neoplasms are categorized as benign, intermediate, or malignant based on their pathologic features, and are referred to as MCA, MBT, and MAC, respectively [2]. We selected 24 cases of MCA, 36 cases of MBT, and 46 cases of MAC and compared the clinicopathologic features of these ovarian mucinous neoplasms (**Table 1**).

There was no significant difference in the median age at diagnosis of patients with MCA ( $49.25 \pm 3.632$  years), MBT ( $44.36 \pm 2.502$  years),

## PAUF-positive ovarian mucinous adenocarcinoma

**Table 2.** Clinicopathologic features of 36 MBTs according to PAUF expression status

	PAUF expression			P-value
	Negative	Weakly positive	Strongly positive	
Number of cases	27 (75.00)	5 (13.89)	4 (11.11)	
Age at diagnosis (years, mean ± SD)	45.96 ± 2.864	46.40 ± 7.954	31.00 ± 2.273	0.1697
Stage				
Localized	25	5	4	
Regional	2	0	0	
Distant	0	0	0	
Histologic subtype				0.1466
Intestinal	24	4	2	
Endocervical	3	1	2	
ER status				0.1466
Negative	24	4	2	
Positive	3	1	2	
Ki-67 LI				*0.0863
< 1.167%	4	1	3	
≥ 1.167%	23	4	1	

SD, standard deviation. \*We calculated P-value using Fisher's exact test after grouping PAUF weakly positive and strongly positive MBTs together as PAUF-positive MBTs and compared them with PAUF-negative MBTs, because the chi-square calculation is not valid when all expected values are < 1.

**Table 3.** Clinicopathologic features of 46 MACs according to PAUF expression status

	PAUF expression			P-value
	Negative	Weakly positive	Strongly positive	
Number of cases	10	19	17	
Age at diagnosis (years, mean ± SD)	40.40 ± 3.933	39.58 ± 2.838	49.06 ± 3.957	0.1095
Follow-up (months, mean ± SD)	69.10 ± 12.96	53.74 ± 8.538	37.53 ± 5.829	0.0696
Overall survival (%)	10/10 (100.000)	14/19 (73.684)	13/17 (76.471)	0.1885
Disease-free survival (%)	9/10 (87.500)	13/19 (60.014)	12/17 (63.995)	0.3732
Stage				0.2205
Localized	3	10	9	
Regional	3	4	7	
Distant	4	5	1	
Invasion pattern (%)				0.5464
Expansile	8	14	15	
Infiltrative	2	5	2	

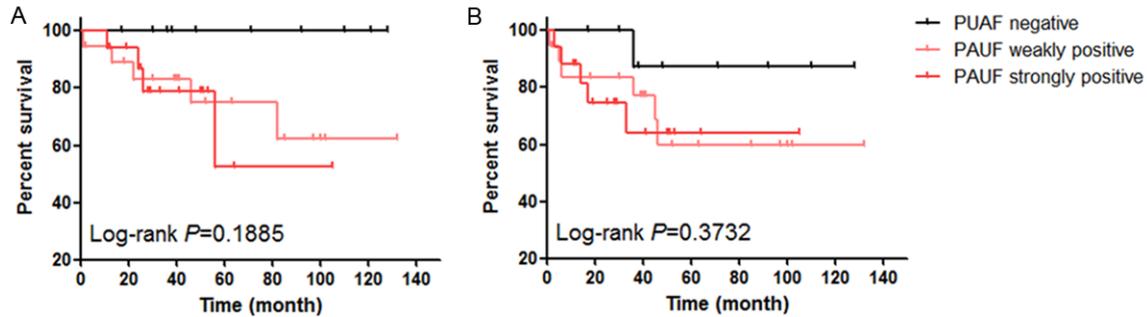
SD, standard deviation.

and MAC (43.26 ± 2.122,  $P = 0.2951$ ). We grouped cases of MBTs and MACs based on FIGO stage and categorized them as being localized, regional, or distant. Most MBT cases were at a localized stage, whereas most MCA cases were at a regional or distant stage ( $P < 0.0001$ ).

For a more detailed analysis, we subdivided MBTs into two groups according to the histologic features of their epithelial component:

intestinal type or endocervical type [2]. According to the most recent World Health Organization classification of female reproductive organs, endocervical-type MBTs are considered a subset of seromucinous tumors, referred to as seromucinous borderline tumors [14]. However, to date, seromucinous borderline tumors have been reported as endocervical-type MBTs and compared with other intestinal-type MBTs. Therefore, we included endocervical-type MBTs (seromucinous border-

## PAUF-positive ovarian mucinous adenocarcinoma



**Figure 2.** Survival analysis of patients with ovarian mucinous adenocarcinoma according to PAUF expression. A. Overall survival of MAC patients according to PAUF expression status. B. Disease-free survival of MAC patients according to PAUF expression status.

line tumors) in this study to clarify the clinicopathological features of intestinal-type MBTs. Thirty of the 36 MBTs (83.33%) had an epithelial component resembling intestinal epithelium, and the other six cases (16.67%) exhibited mucinous epithelial cells resembling endocervical epithelium. This finding is similar to those of previous reports, in which the intestinal type accounted for 85-90% of MBTs and the endocervical type for 10-15% [7, 15-17].

MACs were subdivided into expansile and infiltrative types according to their invasion patterns, rather than a grading system, because it is well established that the current grading system for mucinous carcinoma can predict neither tumor behavior nor treatment response [15, 16, 18]. However, infiltrative stromal invasion has proved to be more biologically aggressive than expansile invasion [2]. We found infiltrative invasion growth in nine out of 46 MACs (19.57%) and an expansile invasion pattern in 37 out of 46 MACs (80.43%).

### *PAUF expression status according to subtypes of ovarian mucinous tumors*

We performed immunohistochemical staining with antiPAUF pAb on FFPE tissue of ovarian mucinous neoplasms, and interpreted PAUF reactivity as negative, weakly positive, or strongly positive as described above (**Figure 1A**). Interestingly, MACs most frequently demonstrated weak PAUF positivity (19 of 46 cases, 41.30%) and strong PAUF positivity (17 of 46 cases, 36.96%), in contrast to MCAs (weakly positive: 29.17%, strongly positive: 4.17%) and MBTs (weakly positive: 13.89%, strongly positive: 8.33%; **Table 1** and **Figure 1B**,  $P < 0.0001$ ).

Thus, strongly positive PAUF staining was more common in ovarian mucinous tumors with more aggressive behavior.

### *Clinicopathologic features of MBTs according to PAUF expression status*

We next compared the clinicopathologic features of MBTs according to their PAUF expression status (**Table 2**). Although only four of 36 MBTs were strongly positive for PAUF, these cases tended to occur 10 years earlier ( $31.00 \pm 2.273$  years) than their PAUF negative ( $45.96 \pm 2.864$  years) or weakly positive PAUF ( $46.40 \pm 7.954$  years) equivalents, although these differences were not statistically different ( $P = 0.1697$ ). Differences in tumor stage according to PAUF expression status could not be statistically analyzed because most MBTs were at a localized stage, except for two cases at a regional stage.

Chi-square calculations are usually only valid when all expected values are  $> 1$ , and this condition was not met when we assessed the pathologic features of MBTs according to PAUF expression status. Therefore, we combined MBTs that were either weakly or strongly positive for PAUF as a single PAUF-positive group ( $n = 9$ ) and compared their pathologic parameters with those of the PAUF-negative group ( $n = 27$ ) using Fisher's exact test. This revealed no statistically significant differences with respect to histologic subtype or ER status. However, all of the endocervical MBTs were ER positive, as they are known [19]. There were also no significant differences between PAUF-positive and negative MBTs with respect to the Ki-67 LI, a marker of proliferative activity.

## PAUF-positive ovarian mucinous adenocarcinoma

**Table 4.** Univariate analysis for overall survival and disease-free survival

Parameter	Overall survival			Disease-free survival		
	P-value	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI
Age	0.002	1.097	1.034-1.164	0.001	1.090	1.038-1.146
Stage	0.014			0.009		
Localized vs. regional	0.808	0.741	0.067-8.256	0.385	2.213	0.369-13.263
Localized vs. distant	0.016	7.099	1.431-35.206	0.006	9.175	1.899-44.334
Invasion						
Expansile vs. infiltrative	0.091	3.117	0.835-11.636	0.088	2.724	0.863-8.599
PAUF	0.960			0.425		
Negative vs. weakly positive	0.948			0.230	3.655	0.440-30.369
Negative vs. strongly positive	0.947			0.197	4.134	0.480-35.618

**Table 5.** Multivariate analysis for overall survival and disease-free survival

Parameter	Overall survival			Disease-free survival		
	P-value	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI
Age	0.042	1.116	1.004-1.240	0.044	1.083	1.002-1.170
Stage	0.024			0.080		
Localized vs. regional	0.378	0.313	0.024-4.131	0.882	1.159	0.164-8.184
Localized vs. distant	0.021	23.365	1.605-340.079	0.037	9.941	1.142-86.496
Invasion						
Expansile vs. infiltrative	0.640	0.626	0.088-4.450	0.823	1.218	0.216-6.884
PAUF	0.809			0.099		
Negative vs. weakly positive	0.941			0.045	57.406	1.090-3022.596
Negative vs. strongly positive	0.937			0.034	97.890	1.412-6785.925

MAC PAUF expression is associated with shorter OS and DFS

As described above, MACs more frequently stain positive for PAUF than other ovarian mucinous tumors. We therefore compared the clinicopathologic features of MACs according to PAUF expression (Table 3). There was no significant difference in age at diagnosis, tumor stage, and invasion pattern in MACs with respect to PAUF expression.

When we compared the OS and DFS of MAC patients according to PAUF expression status using a Kaplan-Meier analysis, patients with MACs staining weakly or strongly for PAUF tended to have a shorter OS than those negative for PAUF (Figure 2,  $P = 0.1885$ ). We conducted a statistical analysis to identify predictive factors for survival of ovarian MAC patients using a Cox regression assay (Table 4). In univariate analysis, age at diagnosis ( $P = 0.002$ , hazard ratio [HR] = 1.097, 95% confidence interval [CI]: 1.034-1.164), tumor stage (localized vs. dis-

tant,  $P = 0.016$ , HR = 7.099, 95% CI: 1.431-35.206), and invasion pattern (expansile vs. infiltrative,  $P = 0.091$ , HR = 3.117, 95% CI: 0.835-11.636) affected the OS of MAC patients. Age at diagnosis ( $P = 0.001$ , HR = 1.090, 95% CI: 1.038-1.146), tumor stage (localized vs. distant,  $P = 0.006$ , HR = 9.175, 95% CI: 1.899-44.334), and invasion pattern (expansile vs. infiltrative,  $P = 0.088$ , HR = 2.724, 95% CI: 0.863-8.599) also affected the DFS of MAC patients. There was a tendency towards a shorter DFS in patients with MACs that stained strongly for PAUF than that in those with PAUF-negative MACs ( $P = 0.197$ , HR = 4.134, 95% CI: 0.480-35.618). When we adjusted various parameters by multivariate analysis, older age at diagnosis and a distant tumor stage were associated with a shorter OS and DFS amongst MAC patients (Table 5). In particular, PAUF expression in MACs was an independent predictive factor for DFS (negative vs. weakly positive PAUF staining,  $P = 0.045$ , HR = 57.406, 95% CI: 1.090-3022.596 and negative vs. strongly positive PAUF staining,  $P =$

0.034, HR = 97.890, 95% CI: 1.412-6785.95), although there was no statistical difference in DFS according to PAUF expression status using Kaplan-Meier survival analysis.

### Discussion

PAUF, a novel tumor-specific protein, is known to be associated with cancer progression and metastasis in pancreatic ductal adenocarcinoma and ovarian tumors [11, 12]. MBTs are the most common type of borderline ovarian tumor and generally have an excellent prognosis. In contrast, MACs, although far less common, show an aggressive behavior [4-10]. We therefore hypothesized that PAUF expression status might be different between MBTs and MACs.

As expected, we found that MACs were more frequently positive for PAUF expression than other ovarian mucinous tumors, with an increasing frequency of strong PAUF staining in MCA, MBT, and MAC tumor types. This suggests that PAUF could be a sensitive and specific biomarker for distinguishing between intermediate and malignant mucinous tumors of the ovary.

We also failed to find any significant differences in PAUF expression status of MBTs with respect to a range of clinicopathological features, which might reflect the generally low PAUF expression in these tumors. However, for MACs, PAUF expression tended to be higher in patients with a shorter OS. When we adjusted for possible confounders using multivariate Cox regression analysis, weak or strong PAUF expression in MAC was associated with a shorter DFS.

Our findings indicate that PAUF expression can help categorize ovarian mucinous tumors, and predicts shorter OS and DFS amongst MAC patients. Thus, PAUF could act as a prognostic and diagnostic biomarker for patients with an ovarian mucinous tumor.

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### Disclosure of conflict of interest

None.

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