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Original Article

Clinical impact and prognostic value of CD147 and MMP-7 expression in patients with pancreatic ductal adenocarcinoma

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Abstract: Aim: Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease with short overall survival. It is of great significance to identify new biomarkers to predict prognosis of PDAC patients after surgery. Methods: In this study, we examined the expression of CD147 and MMP-7 in 90 PDAC neoplastic tissues and paired non-neoplastic tissues from patients who underwent surgery and followed-up for as long as 87 months by immunohistochemistry staining. X^2 test, Kaplan-Meier and log-rank test were used to analysis the correlation between CD147, MMP-7 expression and clinicopathological features. Prognostic analysis was carried out by using multivariate Cox regression models. Results: Our results showed that expression of both CD147 and MMP-7 were increased in neoplastic tissue ($P<0.001$). MMP-7 expression in neoplastic tissue positively correlated with lymph node metastasis ($P<0.05$). Both CD147 and MMP-7 expression in neoplastic tissue had significantly impact on overall survival in patients with PDAC ($P<0.05$). More importantly, MMP-7 expression was correlated with the expression of CD147 in PDAC patients. Of 81 analyzed specimen, concurrent expression of CD147 and MMP-7 was found in 29 patients and had significantly negative impact on overall survival. Multivariate analysis determined that co-expression of CD147 and MMP-7 was an independent factor for prognosis. Conclusion: Our results indicate that CD147 and MMP-7 expression is associated with overall survival in PDAC patients and concurrent expression of CD147 and MMP-7 could better predict the prognosis after surgery. The conclusion of this study can help physicians to make better follow-up decision to monitor the disease progression in PDAC patents.

Keywords: Pancreatic ductal adenocarcinoma, CD147, MMP-7, prognosis, overall survival

Introduction

Pancreatic ductal adenocarcinoma (PDAC), also well-known as pancreatic cancer, is a lethal disease with an overall 5-year survival rate less than 10% [1]. In China, it is estimated that the incidence of pancreatic cancer is 90.1 per thousands, and the mortality is 79.4 per thousands in 2015 [2]. Until now, the most curative treatment is surgery. However, due to the insidiously appearance in early stage, diagnosis often occurs in later stages [3]. The recurrence after surgery is the major obstacle to improve patient survival time after surgery.

Since 1981, Carbohydrate 19-9 (CA19-9), which was discovered in colon cancer patient, have been widely used in diagnosis of PDAC in clinical practice [4]. However, there are limitations to use CA19-9 to screen and predict prognosis due to its poor sensitivity and specificity in Chinese patients. To date, assessment of patient with PDAC is largely relies on tumor grade and clinical stage [5]. Therefore identification of biomarkers, which can predict prognosis after surgery and help physicians to make follow-up decision, is of great significance.

HAb18G/CD147 is a member of immunoglobulin superfamily. It is also known as extracellular matrix metalloproteinase inducer (EMMPRIN) [6]. CD147 played an important role in some physiological processes, including spermato-

Table 1. Patient characteristics

Features	No. of tumor specimens (%)
Age, year	
Mean, media (range)	61.2, 62.0 (36~85)
Gender	
Male	50 (61.7%)
Female	31 (38.3%)
Tumor size, cm	
Mean, media (range)	4.5, 4.0 (0.5~14.0)
Survival status	
Survival	29 (35.8%)
Death	52 (64.2%)
Survival time, month	
Mean, media (range)	27.0, 15.0 (0~87)
T stage	
T1	5 (6.2%)
T2	61 (75.3%)
T3	15 (18.5%)
N stage	
N0	53 (65.4%)
N1	28 (34.6%)
Clinical stage	
I	36 (44.4%)
II	42 (51.9%)
III	1 (1.2%)
IV	2 (2.5%)

genesis, implantation, and lymphocyte responsiveness [7, 8]. Previous study had found that HAb18G/CD147 expression was also involved in variety of cancers [9]. It promotes tumor growth, invasion and metastasis by regulating tumor microenvironment [10-12]. And inhibition of CD147 expression by siRNA could reduce the malignant behavior of tumor cells [13, 14]. More importantly, our previous studies indicated that CD147 antibody could reduce the HCC recurrence after liver transplantation and [131]I CD147 targeted treatment might yield prevention of HCC recurrence after radiofrequency ablation [15, 16].

One of the key steps for tumor invasion and metastasis is the degradation of the extracellular matrix components and the basement membrane. Matrix metalloproteinase (MMP) is the downstream factor regulated by CD147, and plays a significant role in degrading the matrix and basement membrane [17]. MMP-7 is one of MMPs involved in the progression of the malignancy, and has been confirmed in many types of tumors [18-20]. It was reported that MMP-7 was potentially involved in metastasis process stimulated by TGF-β [21, 22]. Activated MMP-7 could also induce the expression of other metalloproteinase such as MMP-2 and MMP-9, which play important role in invasion [23].

Despite plenty of researches on CD147 and MMP-7 in many malignancies, whether these two markers are co-expressed in PDAC and its clinical significance is still unclear. The aim of our present study was to investigate the expression of CD147 and MMP-7 in PDAC, and analyze the association of these markers with the clinical pathological characteristics and the prognosis of the patients with PDAC.

Materials and methods

Ethics statement

The design and protocols of this study were approved by the Institutional Ethic Review Board of Fourth Military Medical University.

Patient samples and tissue microarray

A total of 90 neoplastic tissues and paired non-neoplastic tissues of PDAC patients were collected from patients who underwent surgery or biopsy between September 2004 and December 2011 and were preserved in laboratory pathological department. All the samples were diagnosed as PDAC through pathological analysis by two independent experienced pathologists. The last follow-up time was December, 2011. The information collected by follow-up includes survival status, date of death or the last follow-up time. Among the 90 cases, 9 patients lack of complete follow-up information and received previous treatment was excluded from the study. Finally 81 patients' tissue samples were used to construct tissue microarray (TMA) for immunohistochemistry and analysis.

Immunohistochemistry

Tissue samples resected from the patients were retrieved from tissue bank of our laboratory and then were made into tissue microarray for further experiment. Briefly, the TMA was deparaffinized with xylene and rehydrated for further peroxidase (DAB) immunohistochemistry staining using a HRP-Polymeranti-mouse/

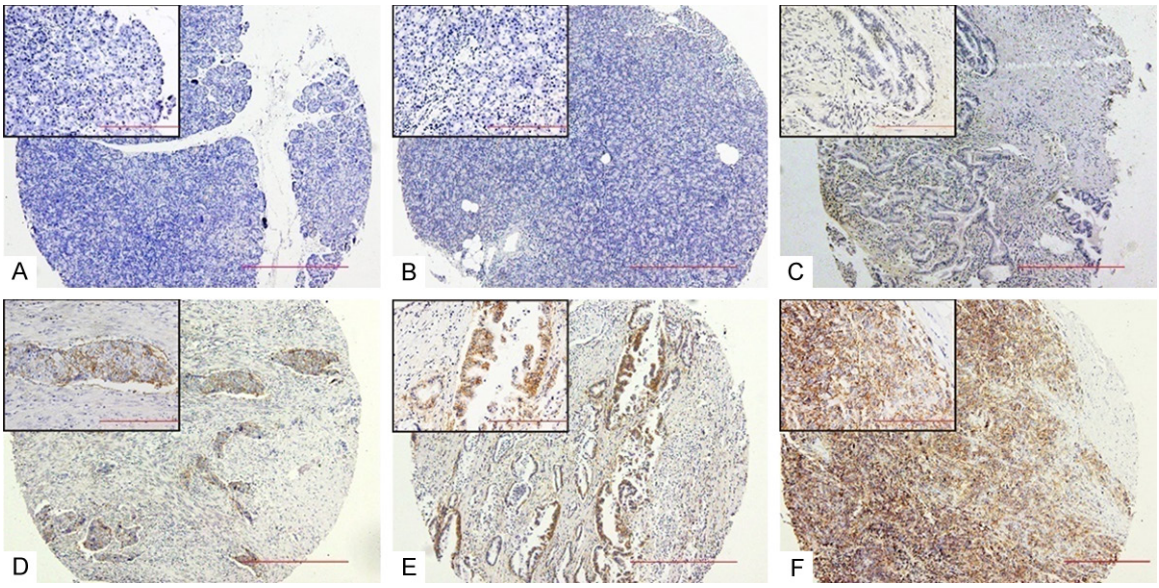

Figure 1. Expression of CD147 detected by immunohistochemistry in pancreatic ductal adenocarcinoma or paired non-neoplastic tissue. (A) Negative control, (B) non-neoplastic tissue, (C) negative expression in tumor cells, (D) weak expression in tumor cells, (E) moderate expression in tumor cells, and (F) strong expression in tumor cells. Magnification is 200× for large image and 400× for upper right.

Rabbit IHC kit (Zhongshan Jinqiao, Co., Beijing, China). Deparaffinized sections were treated with methanol containing 3% hydrogen peroxide for 12 minutes. After washing with PBS, blocking serum was applied for 30 min. The sections were incubated with the anti-CD147 (Abcam, Cambridge, UK), MMP-7 (Abcam, Cambridge, UK) monoclonal antibody for 2.5 hours at 35°C. A biotin-marked secondary antibody was applied for 20 min at 35°C, followed by a peroxidase marked streptavidin for an additional 20 min. After washing, substrate-chromogen was used to visualize the staining of the targeted proteins, and the nuclei were counterstained with hematoxylin. Then the TMA were examined manually under the microscope (Olympus). Positive and negative immunohistochemistry controls were routinely used.

Tissue microarray immunohistochemistry scoring

The TMA immunohistochemistry result was analyzed by three independent experienced pathologists, who were blinded to the cases involved in this experiment. The intensity and density of positive cells in the tissues were key factors considered in the scoring. Five fields of vision were randomly selected under ×400 magnification. The color of the positive cells was scored for the intensity of the positive cells, and was valued into four levels: non-staining scored as 0, yellow scored as 1, claybank as 2, brown as 3. The results of immunohistochemistry were defined as negative expression (no staining at all); weak expression (1+ staining regardless of positive cell percentages or 2+ staining of ≤30% of cells); moderate (2+ staining of >30% of cells or 3+ staining of ≤50% of cells); and strong (3+ staining of >50% of cells). The frequency of cell staining and semi-quantitative analysis of positive tumor cells was calculated for statistical analysis.

Statistical analysis

The statistical analyses in this study were carried out in SPSS 19.0 software (Chicago, USA). The correlation between CD147, MMP-7 expression and clinical characteristics were analyzed by χ^2 test. Overall survival (OS) was defined as the duration time between date of surgery and the date of death or last follow-up. OS was calculated in Kaplan-Meier method and log-rank test. Prognostic analysis was carried out by using multivariate Cox regression models. $P<0.05$ was considered to be significant in this study.

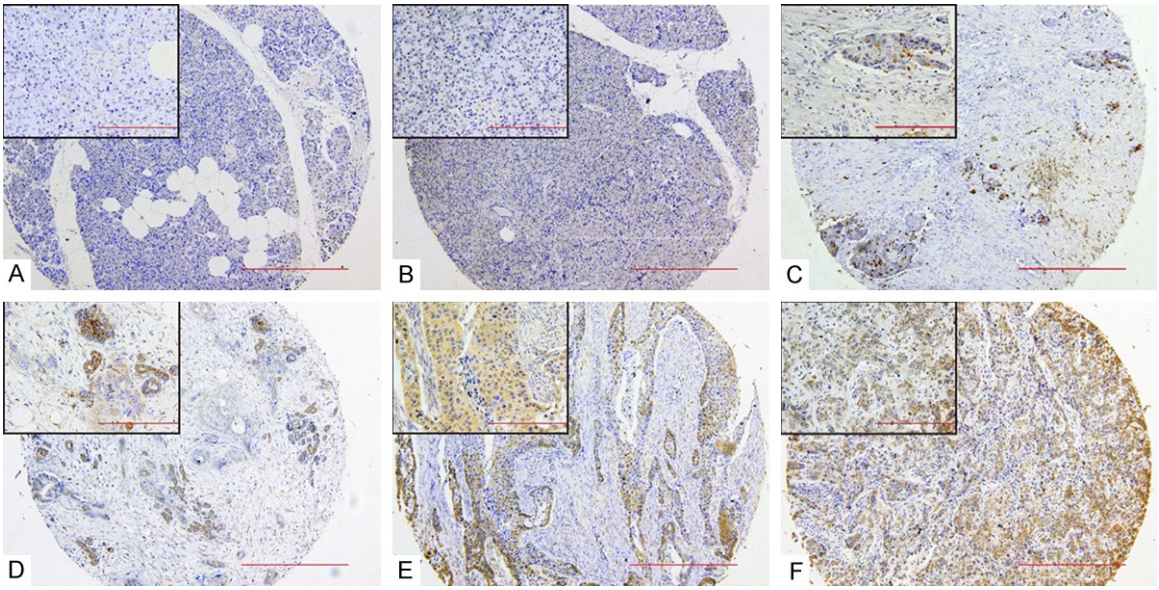

Figure 2. Expression of MMP-7 detected by immunohistochemistry in pancreatic ductal adenocarcinoma or paired non-neoplastic tissue. (A) Negative control, (B) non-neoplastic tissue, (C) negative expression in tumor cells, (D) weak expression in tumor cells, (E) moderate expression in tumor cells, and (F) strong expression in tumor cells. Magnification is 200× for large image and 400× for upper right.

Table 2. CD147 and MMP-7 expression in non-neoplastic and neoplastic tissues

CD147 expression	CD147		MMP-7	
	Neoplastic tissue (%)	Non-neoplastic tissue (%)	Neoplastic tissue (%)	Non-neoplastic tissue (%)
Negative	39 (48.1%)	75 (92.6%)	36 (44.4%)	37 (45.7%)
Weak	19 (23.5%)	6 (7.4%)	31 (38.3%)	29 (35.8%)
Moderate	16 (19.8%)	0	12 (14.8%)	12 (14.8%)
Strong	7 (8.6%)*	0	2 (2.5%)	3 (3.7%)

*P<0.001 *vs.* non-neoplastic tissue.

Results

Patient characteristics

The detailed characteristics of patient were summarized in **Table 1**. There were 50 male and 31 female, with a median age of 61.2 (range from 36 to 85) years old. During the follow-up period, 52 patients (64.2%) were died of pancreatic ductal adenocarcinoma with the median survival time of 15 (range from 0 to 87) months. Of all the patients, 5 (6.2%), 61 (75.3%) and 15 (18.5%) patient had T1, T2 and T3 primary tumor respectively at the time of diagnosis, with an average tumor size 4.5 cm. The tumor had invaded to lymph nodes in 28 (34.6%) patients at the time of operation. Of the patients, 44.4%, 51.9%, 1.2% and 2.5% of patients were presented with AJCC clinical stage I to IV respectively.

Expression of CD147 and MMP-7 in PDAC

Immunohistochemistry was performed to investigate the expression of CD147 and MMP-7 in 81 pairs of PDAC tissues. As shown in **Figure 1**, CD147 was mainly localized on membrane of pancreatic cancer cells. There was a significant difference (P<0.001) in CD147 expression between neoplastic tissue and non-neoplastic tissue. 42 (51.9%) tumors had positive staining with weak, moderate or strong expression of CD147 (23.5%, 19.8% and 8.6%, respectively). Conversely, non-neoplastic tissue mostly (92.6%) had negative staining and none showed moderate or high level of CD147. MMP-7, on the other hand, was largely stained in the cytoplasm of cells (**Figure 2**). Among 81 patients, 17.3% had intermediate or high MMP-7 expression, which was similar to the expression in paired non-neoplastic tissues. As summarized in **Table 2**, no statistical significant difference of MMP-7 expression was observed in neoplastic tissue and non-neoplastic tissue.

Table 3. Correlation of CD147 or MMP-7 expression with clinical pathological features

Features	CD147		*P* value	MMP-7		*P* value
	Positive	Negative		Positive	Negative	
Age, year						
≤60	17	21	0.233	17	21	0.067
>60	25	18		28	15	
Gender						
Male	25	25	0.047	31	19	0.142
Female	17	14		14	17	
Tumor size, cm						
≤2 cm	3	1	0.348	3	1	0.428
>2 cm	39	38		42	35	
T stage						
T1, T2	35	31	0.661	38	28	0.449
T3, T4	7	8		7	8	
N stage						
N0	27	26	0.825	22	31	0.001*
N1	15	13		23	5	

*p<0.001.

Table 4. Co-expression of CD147 and MMP-7

Group	Specimens (%)
$CD147^+MMP7^+$	29 (35.8%)
$CD147^+MMP7^-$	13 (16.0%)
$CD147^-MMP7^+$	16 (19.8%)
$CD147^-MMP7^-$	23 (28.4%)

Pearson r=0.282, P=0.011, *p<0.05.

Correlation between CD147 and MMP-7 expression and clinicopathological features in PDAC

In 81 tumor specimens, 42 (51.9%) and 45 (55.6%) showed positive staining of CD147 and MMP-7, respectively. CD147 and MMP-7 expression were summarized in **Table 3**, according to clinicopathological features. CD147 showed no correlation with patient age, gender, tumor size, T stage or lymph node invasion. Similar association between MMP-7 expression and age, gender, tumor or T stage was also observed in PDAC. However, MMP-7 showed significant association with lymphatic invasion stage (P< 0.001). Among 28 cases with N1 stage of lymph node invasion, most (82%) patients showed MMP-7 positive expression.

Co-expression of CD147 and MMP-7 in PDAC and its clinical significance

Co-expression of CD147 and MMP-7 are shown in **Table 4** and **Figure 4**. In 42 patients with positive expression of CD147, 69% had positive expression of MMP-7, and 31% had negative expression. Meanwhile, among 39 CD147 negative patients, 59% of tumors showed negative expression of MMP-7. Of 81 specimens, concurrent expression of CD147 and MMP-7 was found in 52 (64.2%) neoplastic tissue, including 29 (35.8%) concurrent positive expression and 23 (28.4%) concurrent negative expression. These results indicate that MMP-7 expression was highly associated with CD147 expression level (Spearman r=0.282, P=0.011). Correlation between co-expression of CD147 and MMP-7 and its clinicopathological features were also analyzed and summarized in **Table 5**. Concurrent expression of the two markers significantly correlated with lymph node metastasis (P=0.036), but not with age, gender, tumor size or T stage. In 28 patients with lymph node metastasis, 89.3% had double positive (46.4%) or single positive (42.9%) expression of CD147 and MMP-7.

Prognostic significance of CD147 and MMP-7

For further analysis, we explored the clinical significance of CD147 and MMP-7 expression in PDAC. Firstly, we analyzed the correlation between CD147, MMP-7 expression and survival time respectively in the PDAC patients using Kaplan-Meier analysis. As showed in **Figure 3A**, patient with negative expression of CD147 had a significant longer median survival time of 36 months (range from 6 to 87 months) compared with 9.5 months (range from 0 to 86 months) for patients with positive expression. For MMP-7, the median survival time of MMP-7 negative expression in neoplastic tissue patients was 36 weeks (range from 7 to 87 weeks), which is significant longer than those with positive expression patients 10 weeks, (range from 0 to 86 weeks). These data indicated that patient with positive expression of CD147 (P<0.001, HR=2.512, 95% CI=1.40 to 4.51) or MMP-7 (P<0.001, HR=2.39, 95% CI=1.35 to 4.22) tended to have a poorer prognosis than those with negative expression.

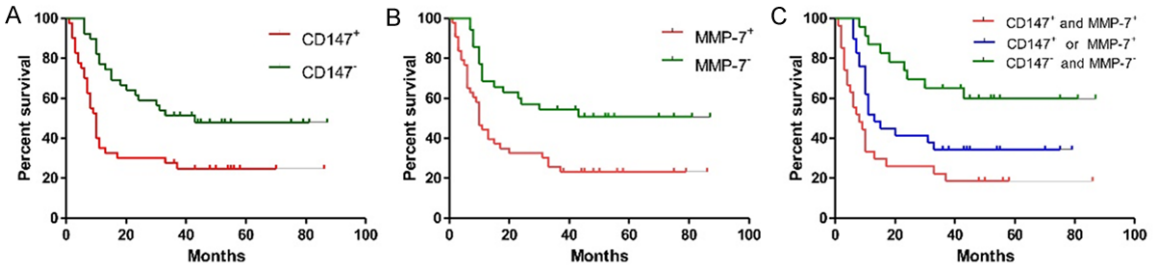

Figure 3. Overall survival curve of 81 patients with pancreatic ductal adenocarcinoma. A. Overall survival comparing CD147 positive expression and negative expression groups by Keplan-Meier analysis. B. Overall survival comparing MMP-7 positive expression and negative expression groups by Keplan-Meier analysis. C. Overall survival analysis based on CD147 and MMP-7 expression (red), CD147 or MMP-7 expression (blue) and both negative expression (green).

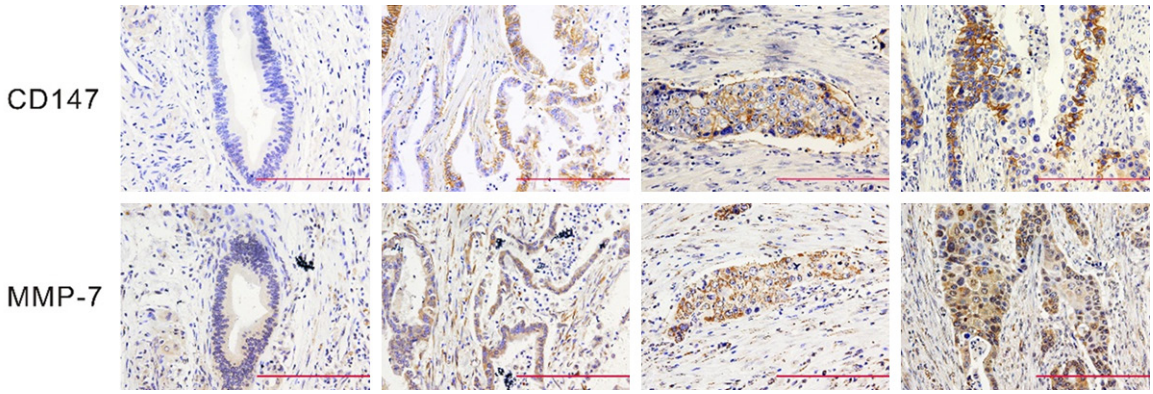

Figure 4. Co-expression of CD147 and MMP-7 in successive sections of patient with pancreatic ductal adenocarcinoma detected by immunohistochemistry. CD147 upper line and MMP-7 below, negative to strong expression from left to right. Magnification: 400×.

Table 5. Correlation between CD147, MMP-7 co-expression and clinical pathological features

Features	$CD147^+MMP\text{-}7^+$ n=29	$CD147^+$ or $MMP\text{-}7^+$ n=29	$CD147^-MMP\text{-}7^-$ n=23	*P* value
Age, year				
≤60	11	12	15	0.111
>60	18	17	8	
Gender				
Male	19	18	13	0.802
Female	10	11	10	
Tumor size, cm				
≤2 cm	3	0	1	0.189
>2 cm	26	29	22	
T stage				
T1, T2	24	25	17	0.513
T3, T4	5	4	6	
N stage				
N0	16	17	20	0.036*
N1	13	12	3	

*$p<0.05$.

To determine the clinical prognostic significance of concurrent expression of CD147 and MMP-7, patients were divided into three subgroups, CD147 and MMP-7 double positive, single positive and double negative. Cox's proportional hazards model was used to analyze the correlation with patient survival, which provided a further prognostic value of patients with pancreatic cancer. Patients with tumor negative expression of CD147 and MMP-7 had the best prognosis, with a median survival time of 43 months, compared with the patients with positive exp-

ression of single (median survival time, 13 months) or double markers (median survival time 7 months) (P<0.001, log-rank test, **Figure 3C**). And more importantly, multivariate analysis determined that co-expression of CD147 and MMP-7 was an independent factor for prognosis.

Discussion

Pancreatic cancer remains a lethal disease with 5-year survival less than 10%, which is also the sixth leading cause of cancer deaths in China [1, 2]. Pancreatic ductal adenocarcinoma is the most common type of pancreatic cancer. The patients involved in this study mostly are early stage (≤II stage) and underwent surgery or biopsy. The most important reason for mortality is the high recurrent after surgery in patient with PDAC. It is of great importance to identify a biomarker, which could well predict the prognosis after surgery to help physicians make better follow-up decision in clinic.

In our study, we focus on the overexpression of CD147 and MMP-7 in neoplastic tissues and their correlation with clinical prognosis. In contrast to non-neoplastic tissue, CD147 was significantly overexpressed in pancreatic tissue. However, MMP-7 expression showed no difference in neoplastic and non-neoplastic tissues. In further analysis, MMP-7 overexpression in neoplastic tissue highly correlated with the N stage, suggesting that MMP-7 played an important role in lymph node invasion. Although CD147 and MMP-7 were not correlated with other clinical features such as clinical stage and tumor size, they both showed significant values in prognosis of overall survival in a relatively long time follow-up in PDAC patients.

In previous study, CD147 was reported to promote pancreatic cancer development through CD44s-pSTAT3 signaling pathway [24]. Further results also suggested that silencing CD147 via RNAi could improve the chemosensitivity and suppress the pancreatic cancer cell invasion both *in vivo* and *in vitro* models [14, 25]. All these studies supported that CD147 is a potential therapeutic target in PDAC. And whether targeting CD147 therapy after surgery can improve the prognosis in PDAC patient needs further basic and clinical investigation.

Since MMPs are important molecular regulated by CD147 in most malignancies, we investigated the expression of MMP-7 in pancreatic cancer patients [26-28]. Immunohistochemistry results suggest that the expression of MMP-7 is not significantly different in neoplastic and non-neoplastic tissue. However, the expression of MMP-7 in cancer cell is significantly correlated with the overall survival in PDAC patients. The expression of MMP-7 in the non-neoplastic tissue might due to its involvement in inflammation response [29]. Further analysis indicated that the expression of CD147 and MMP-7 is associated in neoplastic tissues. The successive section immunohistochemistry results also confirm it to some degree, and the neoplastic tissue with stronger expression of CD147 showed more frequent MMP-7 overexpression. Seldom studies investigated that CD147 and MMP-7 is concurrent expression in PDAC. Recent study revealed that CD147/STAT3 signaling pathway plays an important role in pancreatic cancer initiation and progression, and STAT3 enforces MMP-7 expression in PDC cells [24, 28]. Studies also reported that CD147 induced epithelial-mesenchymal transition of hepatocytes through TGF-β signaling, [30, 31] which could stimulate the MMP-7 expression in tumor cell [22]. However, whether CD147 could induce MMP-7 and its mechanism should be further investigated. More importantly, when we divided the patient into three groups based on CD147 and MMP-7 expression status, survival analysis showed that PDAC patient with both CD147 and MMP-7 negative expression showed prolonged survival time compared to the other two groups. This result suggests that combinational detecting CD147 and MMP-7 could provide new strategy to better monitor the prognosis of patients with PDAC, and patients with both CD147 and MMP-7 should be closed followed.

In summary, our study revealed that CD147 and MMP-7 were both overexpressed in PDAC. High level of MMP-7 was correlated with lymph node invasion and both CD147 and MMP-7 expression in cancer cell was correlated with PDAC patient overall survival. Combination of CD147 and MMP-7 expression may serve as an efficient biomarker and improve the prediction of PDAC prognosis significantly. Taken together, CD147 and MMP-7 had significant value in

prognosis and might be potential therapeutic targets in PDAC.

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Disclosure of conflict of interest

None.

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