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High cytoplasm HABP1 expression as a predictor of poor survival and late tumor stage in pancreatic ductal adenocarcinoma patients

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ABSTRACT

Background: Hyaluronan-binding protein 1 (HABP1) overexpression has been confirmed in different malignancies and found to be strongly associated with tumor development and progression. The aim of the present study was to explore the impact of HABP1 in pancreatic ductal adenocarcinoma (PDAC) patients.

Method: HABP1 expression was evaluated in 89 PDAC specimens.

Results: The expression of HABP1 was significantly higher in tumor tissues than that in adjacent normal tissues. High nucleus HABP1 expression and high cytoplasm HABP1 expression were both detected in PDAC tissues. Overall survival analysis by optical density showed that the mean survival was similar between patients with low and high optical density values of HABP1 expression ($P = 0.312$). The similar result was also found between patients with low-moderate or high nucleus HABP1 expression ($P = 0.275$). However, the mean survival was significantly poorer in patients with cytoplasm HABP1 overexpression ($P < 0.001$). High cytoplasm HABP1 expression was strongly correlated with late tumor stages, arterial involvement, lymph node metastasis and carbohydrate antigen 19-9 levels.

Conclusion: High cytoplasm HABP1 expression may prove to be a predictor of poor survival and late tumor stage in PDAC patients. HABP1 could serve as a promising biomarker to identify subsets of PDAC patients with high malignant clinical behavior.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignant tumors [1] with a median survival of 3–6 months and a 5-year survival rate of less than 6% [2–5]. According to the Chinese Cancer Registry Annual Report 2012, the crude incidence rate of pancreatic cancer in registration areas is 7.28 per 100000 [6]. Although some breakthrough improvements have been made in the treatment of PDAC in recent years, PDAC continues to have a dismal prognosis [7].

Hyaluronan-binding protein 1 (HABP1/p32/gC1qR) is a novel hyaluronan-binding protein [8,9]. It is mainly distributed in mitochondria [10,11], but can also be detected on the cell surface and in the nucleus of different cells [12,13]. HABP1 was originally thought to act as a plasmalemmal receptor for C1q, playing a critical role in inflammatory responses [14]. In malignant tumors, HABP1 plays an important role in hyaluronan-mediated cellular events such as cell adhesion [8], tumor invasion [15], tumorigenesis and progression [16,17]. HABP1 overexpression was reported to be associated with unfavorable prognosis in breast cancer [16,18,19] and endometrial cancer [17]. During the process of tumor progression, HABP1 was required for tumor cells to maintain oxidative phosphorylation [20] and the HABP1 cellular surface receptor was found to regulate lamellipodia formation in cancer cells [21]. siRNA targeting of HABP1 was reported to inhibit cell proliferation, and the treated cells became more sensitive to chemotherapeutic drugs [22]. It has also been discovered that HABP1 can enhance migration through EGF-induced cancer cell chemotaxis and regulate the activity of

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protein kinase C ζ (a key regulator of cell polarity and migration), implicating its role in cell metastasis [23]. However, the association between HABP1 and PDAC is rarely reported. The aim of the present study was to investigate the expression level of HABP1 in PDAC tissue and find whether HABP1 expression was associated with tumor malignancy and survival of PDAC patients. In addition, HABP1 expression levels in test and validation cohorts were detected and the possible correlation between variables and overall survival (OS) was analyzed, in an attempt to elucidate the prognostic impact of HABP1 on PDAC.

Patients and methods

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Shanghai Medical College of Fudan University (Shanghai, China), and conducted in accordance with the Declaration of Helsinki and internationally accepted ethical guidelines. The use of human tissue samples and clinical data was approved by the Clinical Research Ethics Committee of Huashan Hospital affiliated to Fudan University. All donors provided written informed consent to donate their samples. All methods were taken in accordance with the approved guidelines of Shanghai Medical College of Fudan University.

Patients

This retrospective study involved 89 consecutive PDAC patients admitted to our hospital between 2010 and 2012. The inclusion criteria were patients (a) aged 18–75 years; (b) without other organ metastasis; (c) diagnosed as having resectable tumors; (d) with an Eastern Cooperative Oncology Group score of 0–2; and (e) definitively diagnosed with PDAC by postoperative pathology. The exclusion criteria were patients with (a) a previous history of treatment; (b) other malignant tumors or extra-pancreatic metastases; (c) multi-organ dysfunction; (d) a history of drug abuse or in pregnancy; and (e) contradictions for pancreatic surgery. Within one week before pancreatic surgery, all patients underwent a baseline assessment of serum white blood cell count, serum levels of alanine aminotransferase, total bilirubin, albumin; serum levels of carcinoembryonic antigen, carbohydrate antigen (CA)125, and CA 19-9. Intra- and peri-operative data including tumor diameter, operation time, blood loss, tumor stage, lymph node (LN) metastasis and arterial involvement were collected. Patients were staged according to 7th edition AJCC criteria [24].

RNA extraction and qRT-PCR

Total RNA was isolated from the PDAC and adjacent normal specimens using TRIzol reagent (Invitrogen, Carlsbad, CA, USA) and subjected to reverse transcription with Oligo (dT) and M-MLV Reverse Transcriptase (Thermo Fisher Scientific). GAPDH was used as a reference gene and primers of GAPDH were: 5′-GGAGCGAGATCCCTCCAAAAT-3' (forward), and 5′-GGCTGTTGTCATACTTCTCATGG-3' (reverse). Primers of HABP1 were as follows: 5′-ATCAACTCCCAATTTCGTGGTT-3' (forward), and 5′-GGTGGTCATAAAGGCCCAGT-3' (reverse) [25].

Immunohistochemistry and evaluation

Paraformaldehyde-fixed paraffin-embedded tissue sections (5 μm) were prepared using a rabbit monoclonal immunoglobulin IgG specific for HABP1 (1:200, Abcam, USA, ab131284), which was incubated with the sections overnight at 4 °C. After incubation with secondary antibodies, the sections were developed with diaminobenzidine and counterstained with haematoxylin [26].

Staining for HABP1 was determined in a series of 10 randomly selected high-power fields, which were believed to represent the mean size of the tumors at ×200 magnification. HABP1 expression levels were semiquantitatively classified by combining the proportion and intensity of positively stained tumor cells [16,27]. In addition, optical density (OD) was used for quantitative detection of HABP1 (ImagePro® Plus Version 6.0, MediaCybernetics). Cytoplasmic and nucleus HABP1 protein expression was evaluated by immunohistochemistry: no staining; weak = light yellow; moderate = yellow brown and strong = brown.

Western blot

Tissues lysates were electrophoresed in SDS-PAGE and transferred onto PVDF membranes (Millipore, Bedford, MA, U.S.A.). The membranes were blocked with 5% skim milk and the primary antibodies (anti-HABP1; 1: 1000; Cell Signaling Technology, Beverly, MA, U.S.A, 5734) were used for incubation overnight at 4 °C. Membrane was incubated with horseradish peroxidase-conjugated secondary antibodies for 1 h after washing. Immunoreactive bands were quantitatively analyzed with ImageJ software (http://imagej.nih.gov/ij/) [26].

Cytoplasmic and nucleus HABP1 protein extraction was performed using NE-PER™ Nucleus and Cytoplasmic Extraction Reagents (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions.

Statistical analysis

SPSS 21.0 (IBM, Chicago, USA) was used to perform statistical analysis, and $P < 0.05$ was defined as the threshold of statistical significance. Normally distributed data were expressed as mean ± standard deviation (SD), and asymmetrically distributed data were expressed as median (range). Differences in outcomes between high and low/moderate expressions of HABP1 were assessed for significance using independent-samples t tests. ROC curve was used to determine the sensitivity and specificity of prediction of HABP1 for PDAC diagnosis. Kaplan–Meier method was used to calculate survival curves, and the significance was analyzed by log-rank test. Multivariate survival analysis was performed by Cox proportional hazards model.

Results

Altogether 89 PDAC patients who were eligible for the inclusion criteria were enrolled in the present study. The baseline characteristics of these patients are shown in Table 1. All 89 patients underwent radical pancreatectomy and were diagnosed as PDAC based on postoperative pathological evidence.

HABP1 expression is significantly higher in PDAC tissue than that in adjacent normal tissues

Differences in HABP1 mRNA expression were first detected between PDAC and adjacent normal tissues. It was found that the expression level of HABP1 mRNA in PDAC tissue was significantly higher than that in adjacent normal tissue (Fig. 1A). Subsequently, immunohistochemistry was performed to find pathological evidence of HABP1 expression in PDAC and adjacent normal tissues. It was found that the OD value in PDAC tissue was significantly higher than that in adjacent normal tissue (1.88 ± 1.21 vs. 0.95 ± 0.56, $P < 0.001$) (Fig. 1B).

Table 1
Baseline characteristics of the included patients with pancreatic adenocarcinoma.

Index	Pancreatic adenocarcinoma patients (n = 89)
Male, n (%)	58 (65.2%)
Age, years	62.08 ± 9.09
Diabetes, n (%)	13 (14.6%)
Leukocyte, 10^9/L	5.56 ± 1.46
Albumin, g/L	38.61 ± 4.20
Total bilirubin, μmol/L	17.90 (12.00–41.15)
Alanine Transaminase, U/L	45.00 (20.50–104.50)
Carcinoembryonic antigen, μg/L	2.67 (1.67–4.14)
Carbohydrateantigen 125, U/ml	10.14 (0.00–19.30)
Carbohydrateantigen 19-9, U/ml	149.00 (51.00–271.00)
Tumor diameters, cm	3.92 ± 1.34
Tumor stage I, n (%)	26 (29.2%)
Tumor stage II, n (%)	45 (50.6%)
Tumor stage III, n (%)	18 (20.2%)
Lymph node metastasis, n (%)	34 (38.2%)
Artery involvement, n (%)	18 (20.2%)
Time, minutes	450.42 ± 82.89
Blood loss, ml	400.00 (300.00–650.00)
Hospital stay, days	19.26 ± 5.78

High nucleus HABP1 expression and high cytoplasm HABP1 expression in tumor tissues

Our initial literature review showed that HABP1 was mainly distributed in mitochondria, although it could also be detected in multiple cellular compartments. It was found in the present study that HABP1 was mainly expressed in the nucleus and cytoplasm. In some PDAC specimens, HABP1 was mainly located in the cytoplasm (Fig. 1C), and results of Western blot analysis had the same trend as immunohistochemistry results (Fig. 1D). In other PDAC specimens, HABP1 was mainly located in the nucleus (Fig. 1E), the same trend could be seen in the Western blot analysis (Fig. 1F).

Cytoplasm HABP1 overexpression predicts poor survival in PDAC patients

Previous immunohistochemistry analysis revealed that HABP1 was overexpressed in PDAC, suggesting that HABP1 expression may have some clinical value. For this reason, we conducted a survival analysis to verify the prognostic value of HABP1. However, we

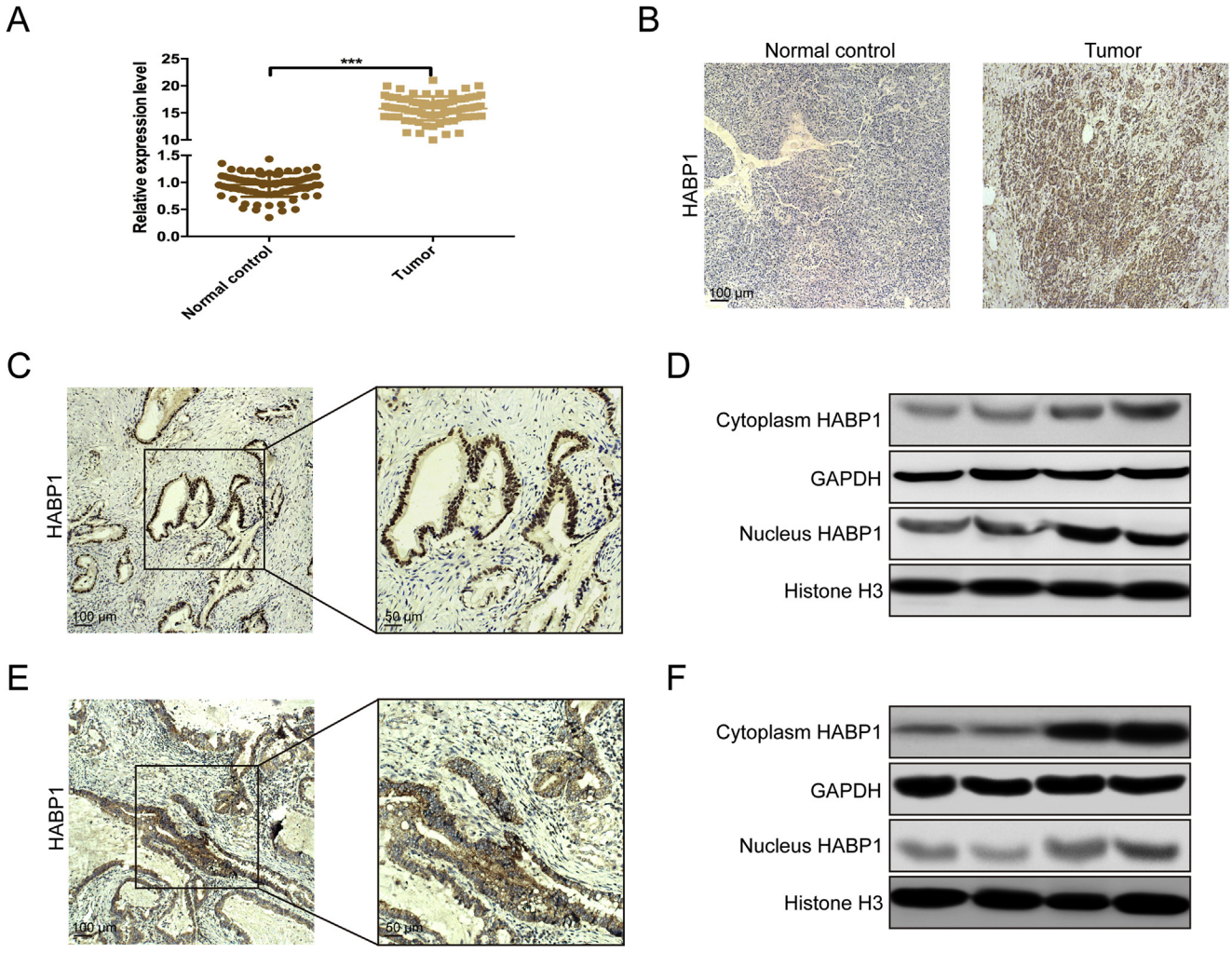

Fig. 1. HABP1 expression in pancreatic ductal adenocarcinoma.
1A. HABP1 mRNA levels in malignant and adjacent normal tissues.
1B. Immunohistochemical findings in pancreatic ductal adenocarcinoma and adjacent normal tissues. Scale bars, 100 μm.
1C. Cytoplasm HABP1 expression in pancreatic ductal adenocarcinoma. Scale bars, 100 μm, zoom scale bars, 50 μm.
1D. The levels of cytoplasm HABP1 protein in pancreatic ductal adenocarcinoma.
1E. Nucleus HABP1 expression in pancreatic ductal adenocarcinoma. Scale bars, 100 μm, zoom scale bars, 50 μm.
1F. The levels of nucleus HABP1 protein in pancreatic ductal adenocarcinoma.

found that the mean survival was similar between patients with a low OD value of HABP1 expression and those with a high OD value of HABP1 expression (26.2 ± 2.8 months vs. 24.6 ± 3.5 month, P = 0.312) (Fig. 2A). Similarly, there was no significant difference in the mean survival between patients with low/moderate or high nucleus HABP1 expression (22.5 ± 2.4 months vs. 28.7 ± 3.9 month, P = 0.275) (Fig. 2B). However, cytoplasm HABP1 overexpression was found to be a predictor of poor survival in PDAC patients (patients with cytoplasm HABP1 overexpression: 9.3 ± 1.4 months; patients with low/moderate cytoplasm HABP1 expression: 29.4 ± 2.6 months, P < 0.001) (Fig. 2C) (Table 2).

Table 2
Prognostic value of HABP1 expression.

Index	Patients, n	Mean survivals, months	P value
Optical density value of HABP1 expressions			
Low	48	26.2 ± 2.8	0.312
High	41	24.6 ± 3.5	
Nucleus HABP1 expressions			
Low to moderate	56	22.5 ± 2.4	0.275
High	33	28.7 ± 3.9	
Cytoplasm HABP1 expressions			
Low to moderate	71	29.4 ± 2.6	<0.001
High	18	9.3 ± 1.4	

Cytoplasm HABP1 expression predicts late tumor stage

Using Logistic regression mode, we made a correlation analysis between cytoplasm HABP1 expression and the clinical features of the patients, and found that high cytoplasm HABP1 expression was strongly correlated with late tumor stages (P = 0.002), LN metastasis (P = 0.030), arterial involvement (P = 0.001) and CA 19-9 level (P = 0.026) (Table 3).

Table 3
The clinical value of cytoplasm HABP1 expression.

Index	Logistics regression mode analysis		
	Hazard ratio	95% Confidence interval	P value
Tumor stage			
Stage I	3.923	1.634-9.420	0.002
Stage II			
Stage III			
Lymph node metastasis			
No	3.280	1.125-9.562	0.030
Yes			
Artery involvement			
No	6.889	2.163-21.945	0.001
Yes			
Carbohydrateantigen 19-9			
≤200 U/ml	3.462	1.161-10.321	0.026
>200 U/ml			

Related factors associated with overall survival

Factors significantly affecting OS were identified first using univariate analysis followed by multivariate analysis (Supplement Table 1). Multivariate analysis showed that the following risk factors emerged as significant: an advanced pathological stage [hazard ratio (HR) = 2.652, 95% confidence interval (CI) 1.202 to 5.852, P = 0.016], LN metastasis (HR = 2.578, 95% CI 1.375 to 4.834, P = 0.003), arterial involvement (HR = 4.756, 95% CI 1.305 to 17.340, P = 0.018), a high CA 19-9 level (HR = 2.593, 95% CI 1.439 to 4.672, P = 0.002), and high cytoplasm HABP1 expression (HR = 4.105, 95% CI 2.011 to 8.380, P < 0.001).

To investigate whether patients with the above risk factors had a poor survival outcome, we conducted survival analysis using Kaplan–Meier curves and found that patients with an early tumor stage had significantly longer survival (mean survival: stage I, 40.6 ± 3.9 months; stage II, 21.6 ± 2.4 month; stage III, 6.9 ± 0.4 month; P < 0.001) (Supplement Fig. 1A). Survival was significantly poor in patients with LN metastasis (mean survival: 11.6 ± 1.1 months vs. 32.9 ± 3.0 month, P < 0.001) (Supplement Fig. 1B), arterial involvement (mean survival: 6.9 ± 0.5 months vs. 29.9 ± 2.6 month, P < 0.001) (Supplement Fig. 1C), and a CA 19-9 level higher than 200 U/ml (mean survival: 14.1 ± 1.8 months vs. 32.8 ± 3.1 month, P < 0.001) (Supplement Fig. 1D) (Supplement Table 2).

Receiver operating characteristic curve of HABP1 for the diagnosis of PDAC

Furthermore, receiver operating characteristic (ROC) curve was used to determine the sensitivity and specificity of prediction of HABP1 OD level for diagnosis of PDAC. We found the area under the curve was 0.755 (95%CI 68.2%–82.7%, P < 0.001) for HABP1 level to predict PDAC diagnosis (Fig. 3).

Discussion

PDAC accounts for 90% of all pancreatic malignancies and the incidence of PDAC is increasing rapidly in the last 5 year [28]. Current therapeutic approaches for PDAC mainly include pancreatic surgery, cytotoxic medication and radiation therapy [29]. However, survival of PDAC patients remains unsatisfied.

In the present study, we found that the expression of HABP1 was higher in PDAC tissue than that in adjacent normal tissue, which is

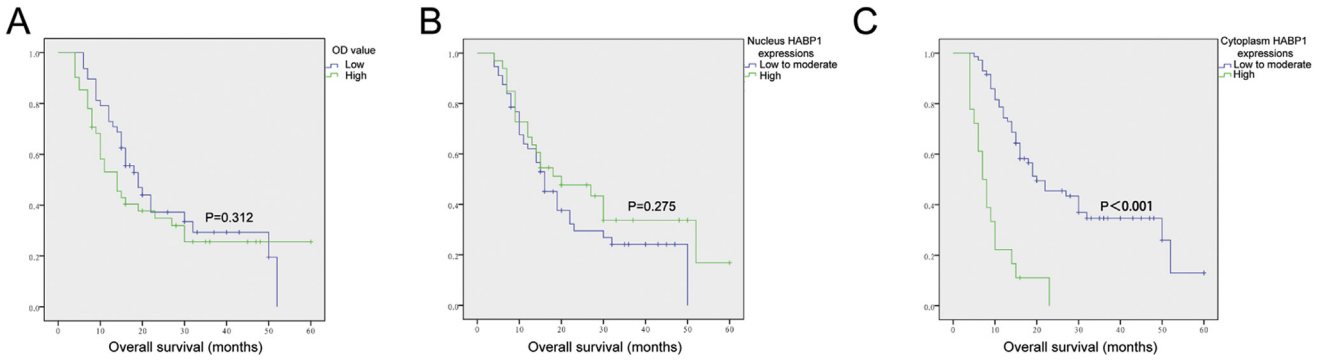

Fig. 2. Survival analysis of PDAC patients with different HABP1 expressions.

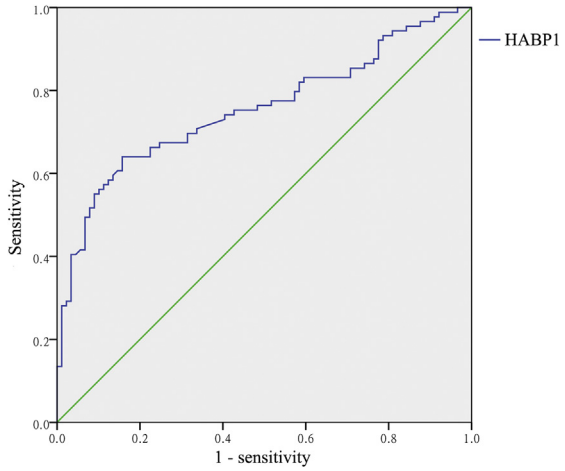

Fig. 3. Receiver operating characteristic curve of HABP1 levels for the diagnosis of PDAC.

consistent with the finding in other adenocarcinomas such as breast cancer [19] and endometrial cancer [17]. We carefully examined the adjacent normal specimens with high HABP1 expression and found that all these specimens were affected by severe inflammatory cell infiltration. Likewise, increased HABP1 expression also occurred in benign inflammatory and proliferative lesions [30]. Persistent inflammation is the pre-stage of a malignant tumor. The high HABP1 expression in adjacent normal specimens in our study may suggest that these high expression areas had a high risk to have malignant transformation. Furthermore, we found that HABP1 was mainly expressed in the nucleus and cytoplasm in PDAC. In some PDAC specimens, HABP1 was located in the cytoplasm, while in some other PDAC specimens, HABP1 expression was detected in the nucleus. This is not surprising because this protein displays considerable multifunctional activities, including inflammatory response, oxidative phosphorylation, tumor invasion [19] and cell apoptosis [31].

HABP1 displays interactions with numerous proteins, which seem to have key functions in different cellular processes at different sub-cellular locations [32]. In cytoplasm, mitochondrial HABP1 protein played an important role in tumor metabolism that knocking down HABP1 expression in human cancer cells strongly shifts their metabolism from oxidative phosphorylation to glycolysis [20]. Fogal V et al. showed that high level of Myc in malignant brain cancers correlated with high cytoplasm HABP1 expression and attenuation of HABP1 expression reduced growth rate of glioma cells expressing Myc and impaired tumor formation *in vivo* [33]. Additionally, cytoplasmic HABP1 has interactions with alternative reading frame (ARF) and inhibit ARF induced type II autophagic cell death [34]. Therefore, the increasing expression of cytoplasmic HABP1 may affect the above cellular processes to promote tumor progression. HABP1 located in nucleus could interact with multiple transcription factors such as CBF/NF-y [35], FOXC1 [36], p58 [37] and SF2/ASF [38]. The mainly functions of nucleus HABP1 including controls RNA splicing [38] and acts as a linker between the nucleus membrane and intra nucleus spliceosomal substructures [37].

Large numbers of studies have shown that high HABP1 expression is associated with poor OS in breast cancer patients [16,18,39], endometrial cancer patients [17] and prostate cancer patients [11]. In our study, we found that cytoplasm HABP1 overexpression predicted poor survival in PDAC patients. However, there was no significant survival difference between patients with low-moderate and high nucleus HABP1 expressions. In addition, high cytoplasm HABP1 expression was correlated with late tumor stage and arterial involvement. These lines of evidence give rise to the intriguing possibility that HABP1 may affect PDAC progression. HABP1 overexpression was reported to be closely correlated with lymphatic metastasis and malignant neoplasm invasion [11,27,40,41]. In our research, we also found the similar result. As report, an interactome analysis revealed that HABP1 was associated with ductal carcinoma cancer cell chemotaxis and metastasis [23].

Similar to our findings, Peerschke et al. [42] found that soluble HABP1 in the blood and body fluid of PDAC patients was higher than that in healthy individuals. Moreover, the serum level of sgC1qR was increased in patients with metastatic pancreatic cancer as compared with that in healthy controls. However, they did not provide the survival outcomes of the patients. Nevertheless, their study provides us with the information that combined detection of soluble HABP1 in blood and body fluid and HABP1 expression in specimens may help better assess tumor development and progression. The significance of HABP1 in cancer suggests the possibility of HABP1 as a potential target for anticancer therapies. Kim et al. [43] reported that the anti-HABP1 antibody could prevent the formation of growth factor-stimulated lamellipodia, cell migration and focal adhesion kinase activation by inactivating receptor tyrosine kinases in various cancer cells. Nevertheless, the antibody neutralization of cell-surface HABP1 also inhibited angiogenesis. These findings suggest that HABP1 may be a potential therapeutic target for PDAC.

The biggest limitation of our study is the small sample size. We plan to collect more cases to conduct further investigations on the role of HABP1 in PDAC. In addition, further investigations are also required to confirm whether HABP1 protein may potentially be used alone or in combination with other markers as a predictive marker of clinical progression in PDAC. Furthermore, the detailed mechanism of PDAC metastasis caused by increased HABP1 expression is still unclear. Thus, the correlation between increased HABP1 expression and migration or invasion by PDAC cells will be examined in further study with a larger sample size.

In conclusion, high cytoplasm HABP1 expression may prove to be a predictor of poor survival in PDAC patients, and HABP1 may serve as a marker to identify subsets of PDAC patients with high malignant clinical behavior.

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Competing interests

The authors disclose no conflicts of interest.

Consent for publication

Written informed consent was obtained from all patients.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2018.09.020.

References

[1] Siegel R, et al. Cancer statistics. CA A Cancer J Clin 2014;64:9–29. 2014.
[2] Ryan DP, et al. Pancreatic adenocarcinoma. N Engl J Med 2014;371:2140–1.
[3] Zell JA, et al. Race, socioeconomic status, treatment, and survival time among pancreatic cancer cases in California. In: Cancer epidemiology, biomarkers & prevention: a publication of the american association for cancer research, cosponsored by the american society of preventive oncology, vol. 16; 2007. p. 546–52.
[4] Lau MK, et al. Incidence and survival of pancreatic head and body and tail cancers: a population-based study in the United States. Pancreas 2010;39:458–62.
[5] Quaresma M, et al. 40-year trends in an index of survival for all cancers combined and survival adjusted for age and sex for each cancer in England and Wales, 1971-2011: a population-based study. Lancet 2015;385:1206–18.
[6] He J, Chen W. Chinese cancer Registry annual report 2012. Beijing: Press of Military Medical Sciences; 2012. p. 68–71.
[7] Vincent A, et al. Pancreatic cancer. Lancet 2011;378:607–20.
[8] Gupta S, Datta K. Possible role of hyaluronectin on cell adhesion in rat histiocytoma. Exp Cell Res 1991;195:386–94.
[9] Deb TB, Datta K. Molecular cloning of human fibroblast hyaluronic acid-binding protein confirms its identity with P-32, a protein co-purified with splicing factor SF2. Hyaluronic acid-binding protein as P-32 protein, co-purified with splicing factor SF2. J Biol Chem 1996;271:2206–12.
[10] Dedio J, et al. The multiligand-binding protein gC1qR, putative C1q receptor, is a mitochondrial protein. J Immunol 1998;160:3534–42.
[11] Amamoto R, et al. Mitochondrial p32/C1QBP is highly expressed in prostate cancer and is associated with shorter prostate-specific antigen relapse time after radical prostatectomy. Cancer Sci 2011;102:639–47.
[12] Kamal A, Datta K. Upregulation of hyaluronan binding protein 1 (HABP1/p32/gC1qR) is associated with Cisplatin induced apoptosis. Apoptosis: Int J Program Cell Death 2006;11:861–74.
[13] Soltys BJ, et al. Localization of P32 protein (gC1q-R) in mitochondria and at specific extramitochondrial locations in normal tissues. Histochem Cell Biol 2000;114:245–55.
[14] Ghebrehiwet B, et al. gC1q-R/p33, a member of a new class of multifunctional and multicompartmental cellular proteins, is involved in inflammation and infection. Immunol Rev 2001;180:65–77.
[15] Das S, et al. Multifunctional activities of human fibroblast 34-kDa hyaluronic acid-binding protein. Gene 1997;190:223–5.
[16] Yu H, et al. Elevated expression of hyaluronic acid binding protein 1 (HABP1)/P32/C1QBP is a novel indicator for lymph node and peritoneal metastasis of epithelial ovarian cancer patients. Tumour Biol: J Int Soc Oncodevelopmental Biol Med 2013;34:3981–7.
[17] Zhao J, et al. Overexpression of HABP1 correlated with clinicopathological characteristics and unfavorable prognosis in endometrial cancer. Tumour Biol: J Int Soc Oncodevelopmental Biol Med 2015;36:1299–306.
[18] Niu M, et al. Elevated expression of HABP1 is correlated with metastasis and poor survival in breast cancer patients. Am J Canc Res 2015;5:1190–8.
[19] Wang J, et al. Elevated expression of HABP1 is a novel prognostic indicator in triple-negative breast cancers. Tumour Biol: J Int Soc Oncodevelopmental Biol Med 2015;36:4793–9.
[20] Fogal V, et al. Mitochondrial p32 protein is a critical regulator of tumor metabolism via maintenance of oxidative phosphorylation. Mol Cell Biol 2010;30:1303–18.
[21] Kim KB, et al. Cell-surface receptor for complement component C1q (gC1qR) is a key regulator for lamellipodia formation and cancer metastasis. J Biol Chem 2011;286:23093–101.
[22] McGee AM, et al. The mitochondrial protein C1qbp promotes cell proliferation, migration and resistance to cell death. Cell Cycle 2011;10:4119–27.
[23] Zhang X, et al. Interactome analysis reveals that C1QBP (complement component 1, q subcomponent binding protein) is associated with cancer cell chemotaxis and metastasis. Mol Cell Proteomics: MCP 2013;12:3199–209.
[24] Edge S, et al. AJCC cancer staging manual, vol. 7. New York: Springer; 2010.
[25] Klionsky DJ, et al. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). Autophagy 2016;12:1–222.
[26] Huang W, et al. A non-synonymous single nucleotide polymorphism in the HJURP gene associated with susceptibility to hepatocellular carcinoma among Chinese. PLoS One 2016;11:e0148618.
[27] Yu G, Wang J. Significance of hyaluronan binding protein (HABP1/P32/gC1qR) expression in advanced serous ovarian cancer patients. Exp Mol Pathol 2013;94:210–5.
[28] Biankin AV, et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. Nature 2012;491:399–405.
[29] Kleeff J, et al. Pancreatic cancer. Nature reviews Disease primers 2016;2:16022.
[30] Dembitzer FR, et al. gC1qR expression in normal and pathologic human tissues: differential expression in tissues of epithelial and mesenchymal origin. J Histochem Cytochem: Offic J Histochem Soc 2012;60:467–74.
[31] Itahana K, Zhang Y. Mitochondrial p32 is a critical mediator of ARF-induced apoptosis. Cancer Cell 2008;13:542–53.
[32] Saha P, Datta K. Multi-functional, multicompartmental hyaluronan-binding protein 1 (HABP1/p32/gC1qR): implication in cancer progression and metastasis. Oncotarget 2018;9:10784–807.
[33] Fogal V, et al. Mitochondrial p32 is upregulated in Myc expressing brain cancers and mediates glutamine addiction. Oncotarget 2015;6:1157–70.
[34] Reef S, et al. The autophagic inducer smARF interacts with and is stabilized by the mitochondrial p32 protein. Oncogene 2007;26:6677–83.
[35] Chattopadhyay C, et al. Human p32, interacts with B subunit of the CCAAT-binding factor, CBF/NF-Y, and inhibits CBF-mediated transcription activation in vitro. Nucleic Acids Res 2004;32:3632–41.
[36] Huang L, et al. Human p32 is a novel FOXC1-interacting protein that regulates FOXC1 transcriptional activity in ocular cells. Invest Ophthalmol Vis Sci 2008;49:5243–9.
[37] Simos G, Georgatos SD. The lamin B receptor-associated protein p34 shares sequence homology and antigenic determinants with the splicing factor 2-associated protein p32. FEBS Lett 1994;346:225–8.
[38] Petersen-Mahrt SK, et al. The splicing factor-associated protein, p32, regulates RNA splicing by inhibiting ASF/SF2 RNA binding and phosphorylation. EMBO J 1999;18:1014–24.
[39] Chen YB, et al. Increased expression of hyaluronic acid binding protein 1 is correlated with poor prognosis in patients with breast cancer. J Surg Oncol 2009;100:382–6.
[40] Prakash M, et al. Hyaluronan-binding protein 1 (HABP1/p32/gC1qR) induces melanoma cell migration and tumor growth by NF-kappa B dependent MMP-2 activation through integrin alpha(v)beta(3) interaction. Cell Signal 2011;23:1563–77.
[41] Sengupta A, et al. Golgi localization and dynamics of hyaluronan binding protein 1 (HABP1/p32/C1QBP) during the cell cycle. Cell Res 2005;15:183–6.
[42] Peerschke EI, et al. Soluble gC1qR in blood and body fluids: examination in a pancreatic cancer patient cohort. Int J Canc Res Mol Mech 2015:1.
[43] Kim BC, et al. Antibody neutralization of cell-surface gC1qR/HABP1/SF2-p32 prevents lamellipodia formation and tumorigenesis. Oncotarget 2016;7:49972–85.