RESEARCH ARTICLE

Low Expression of Tyrosine-protein Phosphatase Nonreceptor Type 12 is Associated with Lymph Node Metastasis and Poor Prognosis in Operable Triple-negative Breast Cancer

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Abstract

Background: Low tyrosine-protein phosphatase nonreceptor type 12 (PTPN12) expression may be associated with breast cancer growth, proliferation, and metastasis. However, the prognostic value of PTPN12 in breast cancer has not been clearly identified. Patients and Methods: 51 triple-negative breast cancer (TNBC) patients and 83 non-TNBC patients with a histopathology diagnosis from October 2001 to September 2006 were included in this study. Immunohistochemical staining for PTPN12 on tissue microarrays was conducted. Results: High PTPN12 expression was seen in 39.2% of TNBC and 60.2 % of non-TNBC cases. Low PTPN12 expression was associated with lymph node status ($p = 0.002$) and distant metastatic relapse ($p = 0.002$) in TNBC patients. Similarly, low PTPN12 expression in non-TNBC patients was significantly correlated with lymph node status ($p = 0.002$), stage ($p = 0.002$) and distant metastatic relapse ($p = 0.039$). The high PTPN12 expression group was associated with longer DFS and OS compared with low PTPN12 expression group only in TNBC cases ($p = 0.005$, $p = 0.015$), according to univariate Cox regression analysis. Conclusion: These findings provide evidence that low expression of PTPN12 is associated with worse prognosis and may be used as a potential prognostic biomarker in TNBC patients.

Keywords: Breast cancer - triple-negative breast cancer - PTPN12 - immunohistochemistry - prognosis

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Introduction

Breast cancer is the most common malignancy in female population worldwide and breast cancer rates are rising in Asian women in China (Kwong et al., 2009; DeSantis et al., 2011). Findings show that breast cancer has different prognoses for different subtypes (Carey et al., 2006). There are five subtypes in breast cancer, including luminal A (estrogen receptor (ER)+ and/or progesterone (PR)+, human epidermal growth factor receptor-2 (HER2)–), luminal B (ER+ and/or PR+, HER2+), basal-like (ER–, PR–, HER2–, cytokeratin (CK)5/6+, and/or epidermal growth factor receptor (EGFR)+), HER2 overexpressing (ER–, PR–, and HER2+), and unclassified (negative for all 5 markers). The basal-like is also known as triple-negative breast cancer (TNBC) (Carey et al., 2006) which is the most poorly understood and associated with shortest disease-free survival (DFS) and overall survival (OS) among all breast cancer subtypes (Nielsen et al., 2004). Thus, a large mount of research on TNBC has been focusing on the discovery of specific biomarker that could serve as prognostic factors and therapeutic target. Protein tyrosine phosphatases (PTPs) play a important role in signal transduction and regulation in all eukaryotic cells and in cancer (Hunter, 2009; Rhee et al., 2012). PTPs can also serve as antagonists to tyrosine kinase (TK) signaling, thereby playing a prominent role in tumor suppression (Hsu et al., 2003; Tonks, 2006). The identified role of PTPs is not clear. Tyrosine-potein phosphatase nonreceptor type 12 (PTPN12) is a ubiquitously expressed cytosolic PTP (Davidson et al., 2010) and a critical regulator of cell adhesion and migration (Zheng et al., 2011). Recently, many researches reported that low expression of PTPN12 is associated with cancer growth, proliferation, and metastasis, including breast cancer (Sun et al., 2011), colon cancer (Espejo et al., 2010), esophageal ovarian cancer (Villa-Moruzzi, 2011), and has been shown to be a useful prognostic marker in squamous cell carcinoma (Cao et al., 2012).

However, to our knowledge, the clinicopathologic and

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prognostic value of PTPN12 in breast cancer has been rarely documented. In this study, we have investigated the expression of PTPN12 in TNBC and non-TNBC by tissue microarray and immunohistochemistry and evaluated the value of PTPN12 for DFS and OS in TNBC and non-TNBC.

Materials and Methods

Patients and samples

We obtained 51 TNBC samples and 83 non-TNBC samples from 134 female patients who were diagnosed by histopathology diagnosis from October 2001 to September 2006. Specimens that were stored in the department of specimen and resource in Sun Yat-Sen University Cancer Center were obtained during the surgery and formalin-fixed and embedded in paraffin by standard methodology. IHC of ER, PR, HER2 status were performed in the pathology department of Sun Yat-Sen University Cancer Center. All the patients included in present study did not receive any chemotherapy and radiation therapy before, and their complete clinical data, including age, histologic type, lymph nodes status, tumor size, stage, local relapse, distant metastatic relapse, ER status, PR status, and HER2 status, were available and reviewed. Histologic type, reclassified according to the WHO classification (Bocker, 2002) and stage of tumor was based on the TNM staging system (American Joint Committee on Cancer classification) (Connolly, 2006). Follow-up was updated by review of records and telephone calls. The date of death and the date of relapse were used to calculate OS and DFS. The patients were grouped according to TN status, age, histologic type, lymph nodes status, tumor size, stage, local relapse, distant metastatic relapse, ER status, PR status, and HER2 status.

Our study was permitted by center's Ethnics Committee and informed consent was obtained from all patients.

Tissue microarray construction

Two experienced pathologists used hematoxylin and eosin-stained sections to select representative areas of tumor which were formalin-fixed and embedded in paraffin for creating tissue microarray (TMA). TMA block was constructed with MiniCore Control Station (ALPHELYS, Plaisir, France) and designed by TMADesigner tissue array design software (ALPHELYS, Plaisir, France). We used 1.0 mm core tissue biopsies and took tissues from paraffin-embedded tissue blocks to two new recipient blocks (one contained 51 TNBC samples, the other contained 83 non-TNBC samples) , one core per case was arrayed. The recipient blocks were cut and placed on slides for immunohistochemical staining.

Immunohistochemical staining and scoring

After deparaffnization and dehydration, the slides were soaked in a solution of 90 % methanol/3 % H2O2 for 15 min at room temperature to block endogenous peroxidases. Then, the slides were treated with 0.01 mol/L EDTA solution (pH = 8) and 96 °C 4 minutes in an autoclave for antigen retrieval. The following marker was used: anti-PTPN12 antibody (1:50, HPA007097, Sigma-Aldrich, St Louis, MO). We added antibody to the slides for overnight storage at 4 °C, and then incubated the slides at room temperature with secondary antibody. After staining, immunohistochemical staining was graded for intensity (0-negative, 1-weak, 2-moderate, and 3-strong) and percentage of positive cells (0, 1 (1–24%), 2 (25–49%), 3 (50–74%), and 4 (75–100%)) with discrepancies resolved by consensus. The grades were multiplied to determine a score. The scores of tumors were defined as the following rule: low expression (score = 0–3) and high expression (score ≥ 4) (Friedrichs et al., 1993; Galgano et al., 2006).

Statistical analysis

The association between the immunohistochemical staining of PTPN12 and other categorical factors potentially predictive of prognosis was analyzed using Pearson's chi-square test or Fisher's exact test, depending on the nature of the data.

Distribution of PTPN12 expression in relationship to TN status was performed using Pearson's chi-square test. DFS was defined as the time from diagnosis to disease progression or death, no matter which occurred first. Patients who were alive and disease free were censored at the date of last follow-up visit. OS was calculated from diagnosis to the date of death for any cause, and patients who were alive were censored at date of last follow-up visit. The Kaplan–Meier method was used to calculate survival curves, and Log Rank test was used to estimate the differences. Univariate and multivariate Cox proportional hazards regression analyses were performed to evaluate the impact of expression of PTPN12 and other categorical factors on DFS and OS. All the statistical analyses were evaluated using the Statistical Software Package for the Social Sciences (SPSS version 13.0, SPSS, USA), and all p values of less than 0.05 were considered as statistically significant.

Results

Expression of PTPN12 in TNBC and non-TNBC

The clinicopathologic characteristics of breast cancer patients are showen in Table 1. PTPN12 immunostaining in breast cancer tissues was located in the cytoplasm (Figure1). In all 134 breast cancer patients, high expression of PTPN12 was seen in 52.2% of patients. High expression of PTPN12 was seen in 39.2% of 51 TNBC patients and high expression of PTPN12 was seen in 60.2% of 83 non-TNBC patients (Table 2). There were differences in tumor expression of PTPN12 between TNBC and non-TNBC patients ($p = 0.018$) (Table 2).

Clinicopathologic association of PTPN12 expression in TNBC and non-TNBC

As shown in Table 1, we observed that PTPN12 expression in TNBC patients showed statistically significant differences according to lymph nodes status ($p = 0.002$), distant metastatic relapse ($p = 0.002$). Similarly, expression of PTPN12 in non-TNBC patients was significantly correlated with lymph nodes status ($p = 0.002$), stage ($p = 0.002$), distant metastatic relapse (p

Table 1. Clinicopathologic Variables and the Expression Status of PTPN12

Characteristics		TN				Non-TN			
		Total	PTPN12		*P*	Total	PTPN12		*P*
			Low	High			Low	High	
Age(years)	<50	29	21	8	0.051	53	19	34	0.333
	≥50	22	10	12		30	14	16	
Histologic type	Ductal	48	30	18	0.315	80	32	48	0.817
	Lobular	3	1	2		3	1	2	
LN	Not infiltrated	30	13	17	0.002*	50	13	37	0.002*
	Infiltrated	21	18	3		33	20	13	
Tumor size(CM)	≤2	18	11	7	0.972	20	6	14	0.306
	<2	33	20	13		63	27	36	
Stage	I, II	27	13	14	0.05	47	12	35	0.002*
	III	24	18	6		36	21	15	
Local relapse	Presenc	4	3	1	0.544	4	2	2	0.668
	Absence	47	28	19		79	31	48	
Distant metastatic relapse	Presenc	18	16	2	0.002*	16	10	6	0.039*
	Absence	33	15	18		67	23	44	
ER status	Positive					51	19	32	0.556
	Negative					32	14	18	
PR status	Positive					54	22	32	0.803
	Negative					29	11	18	
HER2 status	Positive					22	10	12	0.098
	Negative					61	40	21	

* $P<0.05$

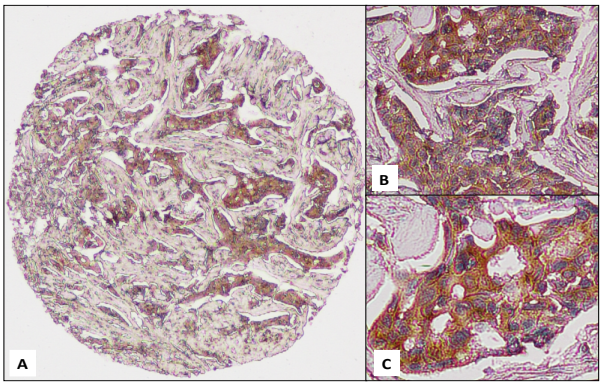

Figure 1. Immunohistochemical Expression of PTPN12 in Breast Carcinoma. Immunohistochemical staining for PTPN12 in breast cancer tissues: (A) high expression (×40); (B) high expression (×100); (C) high expression (×200)

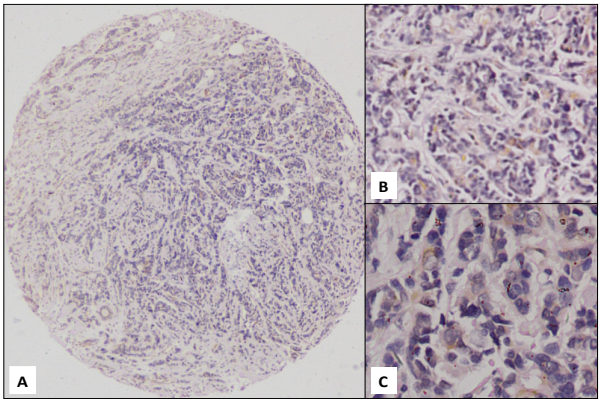

Figure 2. Immunohistochemical Expression of PTPN12 in Breast Carcinoma. Immunohistochemical staining for PTPN12 in breast cancer tissues: (A) low expression (×40); (B) low expression (×100); (C) low expression (×200)

= 0.039). Expression of PTPN12 showed no statistically significant association with other clinicopathologic factors.

Expression of PTPN12 in TNBC patients correlates with shorter DFS and OS

In TNBC patients, with a median follow-up of 74 months, recurrence or distant organs metastasis was observed in 18 patients and 15 patients died. In non-TNBC patients, with a median follow-up of 92 months, recurrence or distant organs metastasis was observed in 20 patients and 12 patients died. The end point of observing was the May 30, 2012.

As shown in Kaplan–Meier survival curves (Figure3), differences for survival existed between high expression group and low expression group. To find the impact of each variable on DFS and OS, univariate Cox regression was used. Univariate Cox regression was shown in Table 3. In TNBC patients, high expression of PTPN12 in tumor

Table 2. Distribution of PTPN12 Expression for Breast Carcinoma Patients in Relationship to TN Status

TN status	n	PTPN12 status		Percentage of PTPN12 within TN status
		PTPN12+	PTPN12-	
TN	51	20	31	39.20%
Non TN	83	50	33	60.20%
Total	134	70	64	52.20%

$P = 0.018$

tissues significantly correlated with longer DFS (HR = 0.223, 95 %CI 0.061–0.774, $p = 0.018$) (Table 3) and OS (HR = 0.166, 95 %CI 0.037–0.746, $p = 0.019$) (Table 3). Meanwhile, advanced tumor stage($p = 0.002$, $p = 0.002$), lymph nodes status($p = 0.005$, $p = 0.015$), were correlated with shorter DFS and OS in TNBC patients. However, in non-TNBC patients, only lymph nodes status ($p = 0.029$) were correlated with shorter DFS. High expression of PTPN12 in tumor tissues did not correlate with longer

Table 3. Univariate Cox Regression Analysis for Variables Considered for DFS and OS

Characteristics	DFS			OS	
	HR	95 %CI	*p*	HR	*P*
TN (n = 51)					
Stages 3 (vs 1 and 2)	5.837	1.906–17.877	0.002*	10.61	0.002*
PTPN12 high (vs low)	0.223	0.061–0.774	0.018*	0.166	0.019*
Size positive (vs negative)	2.056	0.675–6.260	0.205	2.445	0.167
Age positive (vs negative)	0.892	0.346–2.304	0.814	0.914	0.866
Lymph nodes status positive (vs negative)	4.061	1.519–10.857	0.005*	3.815	0.015*
Non-TN (n = 83)					
Stages 3 (vs 1 and 2)	2.549	0.814–7.987	0.108	3.521	0.154
PTPN12 high (vs low)	0.692	0.256–1.868	0.467	0.897	0.881
Size positive (vs negative)	1.132	0.365–3.512	0.829	1.159	0.853
Age positive (vs negative)	0.483	0.169–1.383	0.175	1.541	0.491
Lymph nodes status positive (vs negative)	3.541	1.141–10.988	0.029*	5.33	0.05

*$P<0.05$

Table 4. Multivariate Cox Regression Analysis for Variables Considered for DFS and OS

Characteristics	DFS			OS	
	HR	95 %CI	*p*	HR	*P*
TN (n = 51)					
PTPN12 high (vs low)	0.264	0.075–0.927	0.038*	0.199	0.039*
Stages 3 (vs 1 and 2)	5.208	1.680–16.145	0.004*	9.319	0.004*
Non-TN (n = 83)					
PTPN12 high (vs low)	0.667	0.260–1.712	0.4	0.526	0.312
Lymph nodes status positive (vs negative)	5.175	1.781–15.039	0.003*	7.005	0.015*

*$P<0.05$

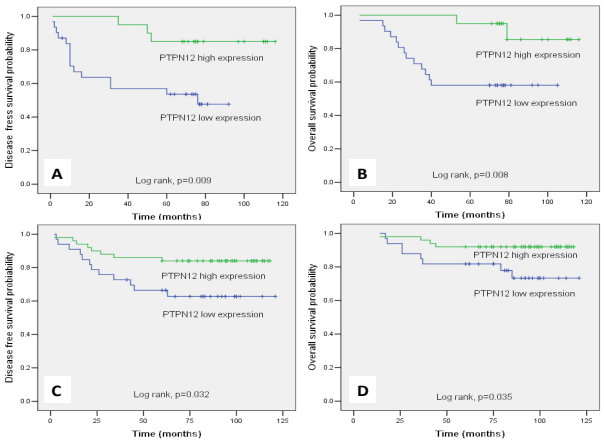

Figure 3. Kaplan–Meier Survival Curve of DFS and OS According to PTPN12 Expression. Kaplan–Meier estimate for (A) DFS; (B) OS according to PTPN12 expression in TNBC patients; Kaplan–Meier estimate for (C) DFS; (D) OS according to PTPN12 expression in non-TNBC patients

DFS (HR = 0.692, 95 %CI 0.256–1.868, $p = 0.476$) (Table 3) and OS (HR = 0.897, 95 %CI 0.218–3.698, $p = 0.881$) (Table 3).

Expression of PTPN12 in TNBC patients is a potential prognostic factor for DFS and OS

As demonstrated in Table 4, multivariate Cox regression, though, was used to analyze clinicopathologic variables, including PTPN12 status, tumor stage, size status, lymph nodes status and age status, only part of them had statistically significant association with DFS and OS. In TNBC patients, high expression of PTPN12 group had a significant longer DFS (HR = 0.264 95 %CI 0.075–0.927 $p = 0.038$) and OS (HR = 0.199 95 %CI 0.043–0.925 $p = 0.039$) to low expression of PTPN12 group. Meanwhile, advanced tumor stage ($p = 0.004$, $p = 0.004$) was correlated with shorter DFS and OS. However, in non-TNBC patients, only lymph nodes status ($p = 0.003$, $p = 0.015$) was correlated with shorter DFS and OS. High expression of PTPN12 group did not correlated with longer DFS (HR = 0.667 95 %CI 0.260–1.712 $p = 0.400$) and OS (HR = 0.526 95 %CI 0.151–1.830 $p = 0.312$) to low expression of PTPN12 group in non-TNBC patients. In summary, PTPN12 status was only associated with DFS and OS in TNBC patients and PTPN12 was a potential prognostic indicator for TNBC patients.

Discussion

In this study, we demonstrated that (a) high PTPN12 expression was seen in 39.2 % of TNBC patients and 60.2 % of non-TNBC patients. There were differences in tumor expression of PTPN12 between TNBC and non-TNBC patients ($p = 0.018$). (b) Expression of PTPN12 was associated with lymph nodes status ($p = 0.002$) and distant metastatic relapse ($p = 0.002$) in TNBC patients. Similarly, expression of PTPN12 in non-TNBC patients was significantly correlated with lymph nodes status ($p = 0.002$), stage ($p = 0.002$) and distant metastatic relapse ($p = 0.039$) (c) high PTPN12 expression group was associated with longer DFS and OS compared with low PTPN12 expression group in TNBC patients ($p = 0.038$, $p = 0.039$), according to univariate Cox regression analysis.

PTPN12 is a ubiquitously expressed protein that, together with PEP, PTP-HSCF, and BDP-1, forms a subfamily of cytoplasmic protein tyrosine phosphatases PTP family (Garton et al., 1997; Streit et al., 2006).

PTPN12 is also thought to play an important role in cell adhesion and motility, and is involved in cancer metastasis (Andersen et al., 2004; Streit et al., 2006; Hunter, 2009; Kwong et al., 2009; DeSantis et al., 2011; Rhee et al., 2012). To date, several researches reported that some oncogenes and cell adhesion molecules such like c-ABL, p130 (Cas), CAKbeta, and PSTPIP1 were associated with PTP family (Angers-Loustau et al., 1999; Andersen et al., 2004; Westbrook et al., 2008). Tingting Sun et al. reported that PTPN12 suppressed transformation by interacting with and inhibiting tyrosine kinase signaling, such as EGFR and HER2. PTPN12 also suppressed proliferation and metastasis of PTPN12-deficient breast cancer cells, and thus, PTPN12 could serve as a tumor suppressor in human breast cancer (Sun et al., 2011). Recently, Xun Cao et al. revealed that PTPN12 was a significant prognostic indicator for esophageal squamous cell carcinoma (Cao et al., 2012). To our knowledge, however, the status of PTPN12 expression and its prognostic value in breast cancer have not been fully elucidated. In the present study, we demonstrated that high PTPN12 expression was associated with longer DFS and OS in TNBC, indicating that PTPN12 could suppress the formation and proliferation of in TNBC. Besides, low PTPN12 expression was associated with lymph nodes metastasis, which was consistent with the evidence provided by Tingting Sun et al. (2011), suggesting that PTPN12 could suppress breast cancer metastasis, but more samples were needed to exclude the possibility of tissue specificity. In summary, with a lack of proper prognostic indicators in clinical application, further researches to clarify the function of PTPN12 are needed.

TNBC is one type of breast cancer. Till now, there is no effective therapy for TNBC (Anders et al., 2009; Ma et al., 2012). Although TNBC is sensitive to initial chemotherapy (Kaplan et al., 2009), it still shows a worse prognosis for DFS and OS than non-TNBC (Kim et al., 2006; Kaplan et al., 2008; Rakha et al., 2008). Thus, it is essential for researchers and clinicians to find a reliable prognostic factors and therapeutic target. In this study, we correlated PTPN12 expression with TN status and found that the number of high PTPN12 expression in non-TNBC were more than in TNBC, which was in accordance with the previous study (Sun et al., 2011). We also found that high PTPN12 expression correlated with longer DFS and OS only in TNBC but not in non-TNBC. The possibility is that PTPN12 may have different roles in different types of breast cancer and the expression of PTPN12 is also depending upon the breast cancer cell types. The results may indicate that PTPN12 can be a potential prognostic biomarker for TNBC which has no effect therapy methods currently. In addition, clinicians could select favorable prognosis patients from TNBC by PTPN12 status and TNBC patients could benefit from new therapy methods (Brady-West et al., 2011; He et al., 2012; Wu et al., 2012).

In conclusion, our study have demonstrated that low expression PTPN12 is associated with worse prognosis in TNBC and PTPN12 could be a potential prognostic biomarker for TNBC. Also, our findings have provided evidence that expression of PTPN12 is associated with lymph node metastasis both in TNBC and non-TNBC. Nevertheless, further studies and more samples will be required to investigate the prognostic role of PTPN12 in breast cancer.

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