Pathol. Oncol. Res. (2016) 22:541–547
DOI 10.1007/s12253-015-0036-3

ORIGINAL ARTICLE

Loss of Protein Tyrosine Phosphatase Receptor J Expression Predicts an Aggressive Clinical Course in Patients with Esophageal Squamous Cell Carcinoma

Dongfeng Qiao[1] · Ming Li[2] · Juan Pu[1] · Wanwei Wang[1] · Weiguo Zhu[3] · Haiyan Liu[4]

Received: 16 October 2015 / Accepted: 15 December 2015 / Published online: 23 December 2015

Abstract Protein Tyrosine Phosphatase Receptor J (PTPRJ) has been reported to be a tumor suppressor in various human cancers. The aim of this study was to investigate the clinical significance of PTPRJ in ESCC patients and its effects on biological behaviors of ESCC cells. PTPRJ expression, at mRNA and protein levels, were respectively detected by quantitative real-time PCR, western blot and immunohistochemistry, based on 106 newly diagnosed ESCC patients. The associations between PTPRJ expression and clinicopathological characteristics of ESCC patients were statistically analyzed. Then, the effects of PTPRJ in migration and invasion were determined by wound healing and transwell assays based on ESCC cell line transfected with siRNA or expression vector of PTPRJ. Expression of PTPRJ at mRNA and protein levels were both significantly lower in ESCC tissues than those in normal esophageal mucosa. Immunohistochemistry showed that PTPRJ protein was localized in the cytoplasm of cancer cells in ESCC tissues. In addition, PTPRJ downregulation was found to be closely correlated with advanced tumor stage ($P = 0.01$) and poor differentiation ($P = 0.03$). Moreover, knockdown of PTPRJ in KYSE510 cells could significantly promote cell migration and invasion (both $P < 0.05$), which were reversed by the restoration of PTPRJ expression *in vitro* (both $P < 0.05$). Our data offer the convincing evidence that loss of PTPRJ expression may predict an aggressive clinical course in ESCC patients. PTPRJ may function as a tumor suppressor and play an important role in the regulation of ESCC cell motility, suggesting its potentials as a therapeutic agent for human ESCC.

Keywords Protein tyrosine phosphatase receptor J · Esophageal squamous cell carcinoma · Progression · Migration · Invasion

Dongfeng Qiao and Ming Li contributed equally in this study.

✉ Weiguo Zhu
jshazwg@126.com

✉ Haiyan Liu
lhyjsha@hotmail.com

[1] Department of Radiotherapy Pathology, People's Hospital of Lianshui County, Lianshui 223400, China

[2] Department of Radiotherapy Pathology, People's Hospital of Xuyi County, Xuyi 211700, China

[3] Department of Radiotherapy Oncology, Huai'an First People's Hospital, Nanjing Medical University, Huai'an 223300, China

[4] Department of Pathology, Huai'an First People's Hospital, Nanjing Medical University, Huai'an 223300, China

Introduction

Esophageal squamous cell carcinoma (ESCC) represents one of the most aggressive malignancy with the highest incidence and poor prognosis [1]. Due to early lymphatic and hematogenous metastases, ESCC is usually diagnosed locally at an advanced stage or with lymph node metastases. Despite improvements in prevention, early detection, surgical removal and chemo-radiotherapy for ESCC have been achieved, its morbidity and mortality have changed little over recent decades [2]. Accumulating studies suggest that it is a multistep process of the tumorigenesis of ESCC from esophagitis to metastasis [3]. Therefore, the clarification of the molecular mechanisms that drive the aggressive tumor progression is of great clinical significance to develop novel and efficient diagnostic methods, and treatment strategies of ESCC.

Protein Tyrosine Phosphatase Receptor J (PTPRJ, also recognized as DEP-1, HPTPg or CD148) belongs to a type III receptor-like protein tyrosine phosphatase (RPTP) with an

extracellular receptor containing eight fibronectin type III-like domains, a transmembrane region and a single phosphatase catalytic domain [4]. PTPRJ maps at chromosome 11p11.2, a region implicated in human tumors through loss of heterozygosity [5]. Substrates of PTPRJ include proteins which belong to the family of tyrosine kinase receptors (PDGFR, EGFR, VEGFR2, HGFR and RET) as well as those involved in cell adhesion (c-Src, p120-catenin and ZO-1), thus, PTPRJ can control multiple signaling pathways of cell growth, proliferation, adhesion and angiogenesis [6]. Of particular note, several lines of evidence have shown that PTPRJ expression may be downregulated in a vast majority of human epithelial cancers and cancer cell lines (i.e. thyroid, mammary, lung, pancreatic and colon cancers), and function as a tumor suppressor [7–10]. For example, Ortuso et al. [7] reported that PTPRJ agonist peptides could effectively inhibit in vitro cancer cell proliferation and tube formation; Smart et al. [8] found that PTPRJ regulated the differentiation of normal mammary epithelia and that dysregulation of protein localization might be associated with tumorigenesis. In contrast, Spring et al. [9] identified a new role for PTPRJ as a mediator of an invasive cell program implicating Src activation and the promotion of breast cancer progression. These findings suggest that PTPRJ might play different roles depending on the cancer types.

However, the role of PTPRJ in ESCC remains unclear. To address this problem, we here detected the expression of PTPRJ, at mRNA and protein levels, respectively, by quantitative real-time PCR, western blot and immunohistochemistry, based on 106 newly diagnosed ESCC patients. Then, the associations between PTPRJ expression and clinicopathological characteristics of ESCC patients were statistically analyzed. After that, the effects of PTPRJ in migration and invasion were determined by wound healing and transwell assay based on ESCC cell line transfected with siRNA or expression vector of PTPRJ.

Materials and Methods

Patients and Tissue Samples

The Ethics Commitee of People's Hospital of Lianshui County, People's Hospital of Xuyi County and Huai'an First People's Hospital approved the current study. All patients agreed to the procedure and signed consent forms.

A total of 106 patients with ESCC were diagnosed by endoscopic biopsy pathology between 2006 and 2012 at People's Hospital of Lianshui County, People's Hospital of Xuyi County and Huai'an First People's Hospital. There were 78 men and 28 women ranging in age from 38 to 82 years (median age 50 years). The histological grade and clinical stage of the tumors were defined based on the International Union Against Cancer (UICC) in 2009. Of the 106 patients with ESCC, 16, 30 and 60 cases were I ~ II, III and IV, respectively; 26, 30 and 50 cases were well, moderately and poorly differentiated, respectively. The clinicopathologic characteristics of 106 EOC patients are summarized in Table 1. Twenty cases from normal esophageal mucosa were used as a control group. All the specimens were collected from endoscopic biopsy immediately, snap-frozen in liquid nitrogen and maintained at −80 °C until use.

Cell Culture and Transfection

The human ESCC cell line KYSE510 was purchased from Chinese Academy of Sciences (Shanghai, China) and was cultured in Roswell Park Memorial Institute (RPMI)-1640 (GibCo BRL, Grand Island, NY, USA) supplemented with 10 % fetal bovine serum (FBS; Hyclone) and 100 U/ml penicillin/streptomycin (GibCo BRL, Grand Island, NY, USA) and was maintained in a humidified 5 % CO_2 atmosphere at 37 °C.

The PTPRJ-targeted small interfering RNA (si-PTPRJ)/negative control (si-con) and pCEFL-PTPRJ/pCEFL-empty vector (pCEFL-con) plasmids were synthesized by Sangon Biotech Co., Ltd. (Shanghai, China) and transfected by Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA) based on the manufacturer's instructions.

Quantitative Real-Time PCR

Quantitative real-time PCR was performed to detect the expression level of PTPRJ mRNA in ESCC tissues and normal

Table 1 Association of Protein Tyrosine Phosphatase Receptor J (PTPRJ) with different clinicopathological parameters of esophageal squamous cell carcinoma (ESCC) patients

Clinicopathological features	No. of cases	PTPRJ-high (n, %)	PTPRJ-low (n, %)	P
Age (years)				
<60	40	16 (40.0)	24 (60.0)	NS
≥60	66	34 (51.5)	32 (48.5)	
Gender				
Male	70	34 (48.6)	36 (51.4)	NS
Female	36	16 (44.4)	20 (55.6)	
Differentiation				
Well ~ moderate	56	35 (62.5)	21 (37.5)	0.03
Poor	50	15 (30.0)	35 (70.0)	
Tumor size (cm)				
<5	46	26 (56.5)	20 (43.5)	NS
≥5	60	24 (40.0)	36 (60.0)	
TNM stage				
I ~ II	16	15 (93.8)	1 (6.2)	0.01
III	30	20 (66.7)	10 (33.3)	
IV	60	15 (25.0)	45 (75.0)	

'NS' refers to the difference without statistical significance

esophageal mucosa according to the same protocol as our previous study [11]. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as an internal control. The quantitative PCR primers were used for PTPRJ: 5'- GTA TTA TCA TTG GTG GCT TGT TC -3' (forward) and 5'- CAT CTC CGT GGT GGT GAC -3' (reverse), and GAPDH: 5'- AGG TCG GTG TGA ACG GAT TTG -3' (forward) and 5'- GGG GTC GTT GAT GGC AAC A -3' (reverse). The threshold cycle (Ct) is defined as the fractional cycle number at which the fluorescence passes the fixed threshold. The relative expression of PTPRJ mRNA was normalized to the expression of GAPDH mRNA using the $2^{-\Delta\Delta Ct}$ method.

Western Blot Analysis

Western blot analysis was performed to detect the expression level of PTPRJ protein in ESCC tissues and normal esophageal mucosa. Proteins in tissues and cell lysates were extracted by using cell lysis buffer (Sigma-Aldrich, MO, USA) and separated by SDS-PAGE followed by electrotransferring onto nitrocellulose membrane which were blocked with nonfat dry milk at room temperature for 1 h. Subsequently, the membranes were incubated overnight at 4 °C with the primary antibodies against PTPRJ (1:1000 dilution, Sigma-Aldrich, MO, USA) and GAPDH (1:2000 dilution, Sigma-Aldrich, MO, USA), respectively. After that, the membranes were washed by TBST for several times and then incubated with horseradish peroxidase-conjugated secondary antibodies (1:3000, Sigma-Aldrich, MO, USA) at room temperature for 1 h. Immunoblots were visualized by the enhanced chemiluminescence detection system (Pierce Biotechnology, Rockford, IL).

Immunohistochemistry

Immunohistochemistry was performed to detect the expression pattern and subcellular localization of PTPRJ protein in ESCC tissues and normal esophageal mucosa. All tissue samples were fixed with 4 % formaldehyde, embedded in paraffin, and sectioned at 4 μm thickness. The sections were deparaffinized in xylene and rehydrated in graded ethanol. Endogenous peroxidase activity was blocked for 15 min with 3 % hydrogen peroxide in phosphate-buffered saline (PBS). The sections were incubated with primary antibody against PTPRJ (1:100 dilution, Sigma-Aldrich, MO, USA) overnight at 4 °C and then incubated with IgG-horseradish peroxidase (1:1000, Zhongshan, China) for 1 h at 37 °C. Immunostaining were performed using the avidin biotin peroxidase complex method and antigen-antibody reactions were visualized with the chromogen diaminobenzadine.

To evaluate the results of immunohistochemistry, the sections were observed under microscope by two different pathologists who were blinded with the clinicopathological characteristics of 106 patients with ESCC. The immunoreactive score (IRS) was calculated by multiplying the intensity score and the percentage score of immunostaining. The former was defined as strong (3), moderate (2), weak (1), or negative (0) and the latter was defined as <5 % of cells (0), 5–25 % (1), 26–50 % (2), 50–75 % (3), and >75 % (4) of cells. The median IRS value (3.0) of PTPRJ protein was used as a cutoff point to divide all 106 patients with ESCC into PTPRJ-high (n = 50) and PTPRJ-low (n = 56) groups.

Wound Healing Assay

Wound healing assay was performed to assess the migration ability of KYSE510 cells transfected with si-PTPRJ/si-con or pCEFL-PTPRJ/pCEFL-con plasmids. In brief, wounds were created in confluent cells (approximately 80 %) using a 100-μl pipette tip, at 48 h after transfection. Cell migration was assessed by measuring the movement of cells toward the scratch, and the wound healing was observed at different time points (0 h, 24 h and 48 h) within the scrape line.

Transwell Assay

Transwell assay was performed to assess the invasion ability of KYSE510 cells transfected with si-PTPRJ/si-con or pCEFL-PTPRJ/pCEFL-con plasmids. In brief, 1×10^5 cells were suspended with serum-free RPMI 1640 (GibCo BRL, Grand Island, NY, USA) and seeded in the upper chambers of the 24-well transwells (8 mm pore size) coated with matrigel (1 mg/ml, BD Biosciences, USA). The lower chamber was supplemented with RPMI 1640 containing 10 % serum (GibCo BRL, Grand Island, NY, USA) as a chemoattractant. Following incubation for 24 h, the invading cells on the underside of the membrane were fixed with 4 % formaldehyde, stained with 0.5 % crystal violet, and examined under an Olympus microscope in ten randomly selected fields.

Statistical Analysis

All statistical analyses in the current study were conducted by using the software of SPSS version 11.0 for Windows (SPSS Inc., IL, USA). Each experiment was performed in triplicate. Data were expressed as the mean ± standard error of three repeated assays. Differences between various groups were assessed using Student's t test. Fisher's exact test and Chi-square were performed to assess the associations between PTPRJ expression and different clinicopathological characteristics. Differences were considered statistically significant when p was less than 0.05.

Results

Decreased Expression of PTPRJ mRNA and Protein in Human ESCC Tissues

The mRNA expression levels of PTPRJ were detected in 106 ESCC tissues and 20 normal esophageal mucosa using quantitative real-time PCR. The relative expression of PTPRJ mRNA was significantly lower in the ESCC tissues than that in the normal esophageal mucosa ($P = 0.001$, Fig. 1a). Consistent with quantitative real-time PCR, western blot analysis revealed that PTPRJ protein expression was downregulated in the ESCC tissues compared to that of the normal esophageal mucosa ($P = 0.002$, Fig. 1b).

To further confirm the quantitative real-time PCR and western blot results, immunohistochemistry was performed to evaluate the expression pattern and subcellular localization of PTPRJ protein in paraffin wax slices of ESCC and normal esophageal mucosa. As shown in Fig. 1c, positive staining of PTPRJ protein was localized in the cytoplasm of cancer cells in ESCC tissues. Of the 106 ESCC tissues, 8 (7.5 %) were strongly positive for PTPRJ immunoreactivity, whereas 66 (62.3 %) showed a medium to low PTPRJ expression and 32 (26.4 %) were PTPRJ negative. In contrast, all of the normal esophageal mucosa were PTPRJ strongly positive. The statistical analysis showed that the IRS of PTPRJ in the ESCC tissues was significantly lower than that in the normal esophageal mucosa ($P < 0.001$, Fig. 1d), which was consistent with the results of quantitative real-time PCR and western blot analysis.

Decreased Expression of PTPRJ Protein Associates with Aggressive Progression of ESCC Patients

Table 1 summarized the association of PTPRJ protein expression with clinicopathological parameters of ESCC patients. There were significant associations of PTPRJ protein expression with clinicopathological parameters, such as age, gender or tumor size, respectively (all $P > 0.05$). Conversely, significant correlations were observed between PTPRJ protein expression, and tumor stage and differentiation of ESCC patients. The average IRS of PTPRJ protein for ESCC patients in early TNM stage was significantly lower than that in advanced TNM stage ($P = 0.01$, Table 1). Besides, we also observed the negative correlations of PTPRJ protein immunostaining with tumor differentiation of ESCC patients ($P = 0.03$, Table 1).

Decreased Expression of PTPRJ Protein Promotes ESCC Cell Migration and Invasion in Vitro

To investigate the function of PTPRJ in ESCC progression, PTPRJ siRNA was used to reduce the expression of PTPRJ in the human ESCC cell line KYSE510. Forty-eight hours after transfection, PTPRJ siRNA could dramatically reduce the expression of PTPRJ protein in KYSE510 cells ($P < 0.01$, Fig.

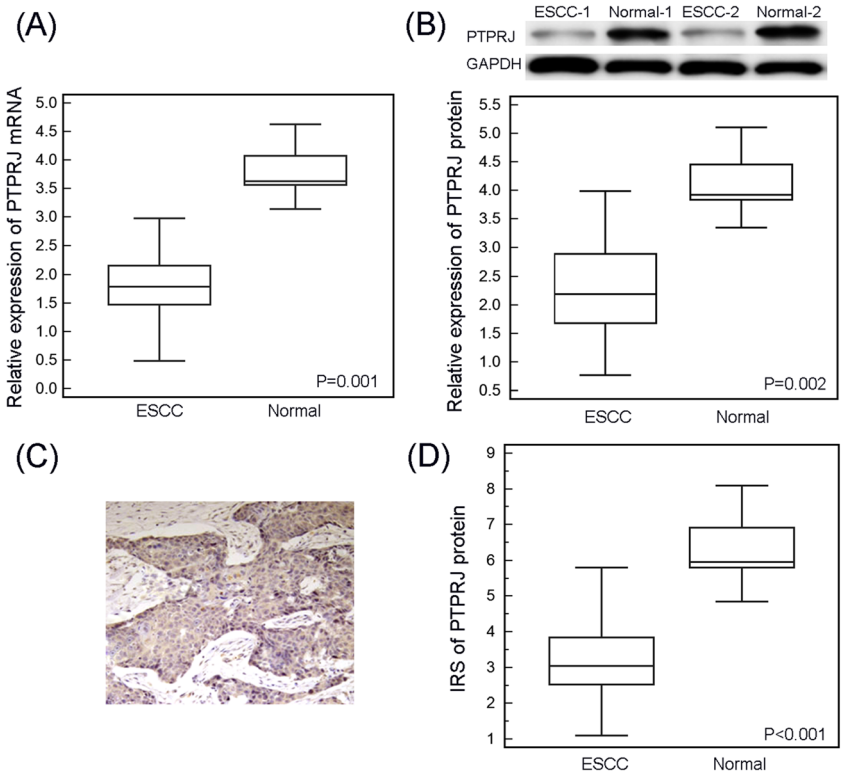

Fig. 1 Decreased expression of PTPRJ mRNA and protein in human ESCC tissues. **a** The relative expression of PTPRJ mRNA was significantly lower in the ESCC tissues than that in the normal esophageal mucosa ($P = 0.001$). **b** Western blot analysis revealed that PTPRJ protein expression was downregulated in the ESCC tissues compared to that of the normal esophageal mucosa ($P = 0.002$). **c** Positive staining of PTPRJ protein was localized in the cytoplasm of cancer cells in ESCC tissues. **d** Statistical analysis showed that the IRS of PTPRJ in the ESCC tissues was significantly lower than that in the normal esophageal mucosa ($P < 0.001$)

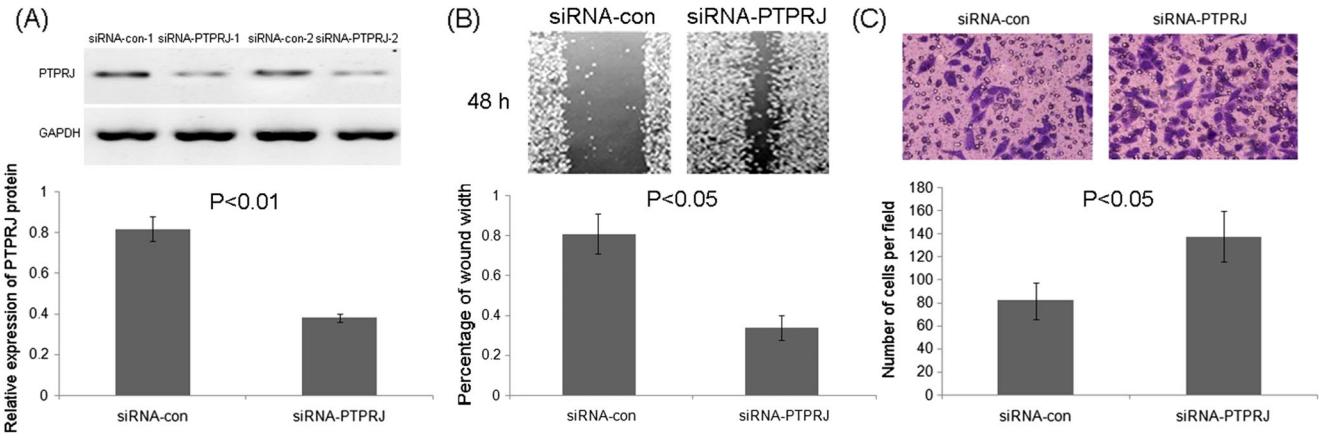

Fig. 2 Decreased expression of PTPRJ protein promotes ESCC cell migration and invasion in vitro. **a** PTPRJ siRNA could dramatically reduce the expression of PTPRJ protein in KYSE510 cells ($P < 0.01$). **b** and **c** Loss of PTPRJ protein promoted the migration and invasion of KYSE510 cells (both $P < 0.05$), respectively

2a). Then, the transfected cells were subjected to cell migration assay and invasion assay. As a result, we found that the loss of PTPRJ protein promoted the migration and invasion of KYSE510 cells (both $P < 0.05$, Fig. 2b and c).

Restoration of PTPRJ Expression Inhibited ESCC Cell Migration and Invasion in Vitro

To further evaluate whether PTPRJ upregulation could inhibit tumor migration and invasion, KYSE510 cells were transfected with pCEFL-PTPRJ plasmid which effectively increased the expression of PTPRJ as shown in Fig. 3a. Then, the transfected cells were subjected to cell migration assay and invasion assay. Compared to KYSE510 cells transfected with pCEFL-empty vector (pCEFL-con) plasmid, over-expression of PTPRJ significantly inhibited the migration and invasion abilities of KYSE510 cells (both $P < 0.05$, Fig. 3b and c).

Discussion

As the most common subtype of esophageal cancer in China, ESCC has an increase incidence of relapse and metastasis, and poor prognosis despite improvements in diagnostic and therapeutic techniques [12]. It is extremely necessary to identify factors underlying carcinogenesis, invasion and metastasis of ESCC. In the current study, our data first illustrated the expression patterns of PTPRJ in ESCC tissues, followed by demonstrating the association between the PTPRJ expression and clinicopathologic parameters based on 106 clinical samples, and finally discovered the role of PTPRJ in malignant phenotypes of ESCC cells. Differential expression of PTPRJ at both mRNA and protein levels had been measured among primary ESCC tissues and normal esophageal mucosa by quantitative real-time PCR, western blot and immunohistochemistry, which all showed the decreased expression of

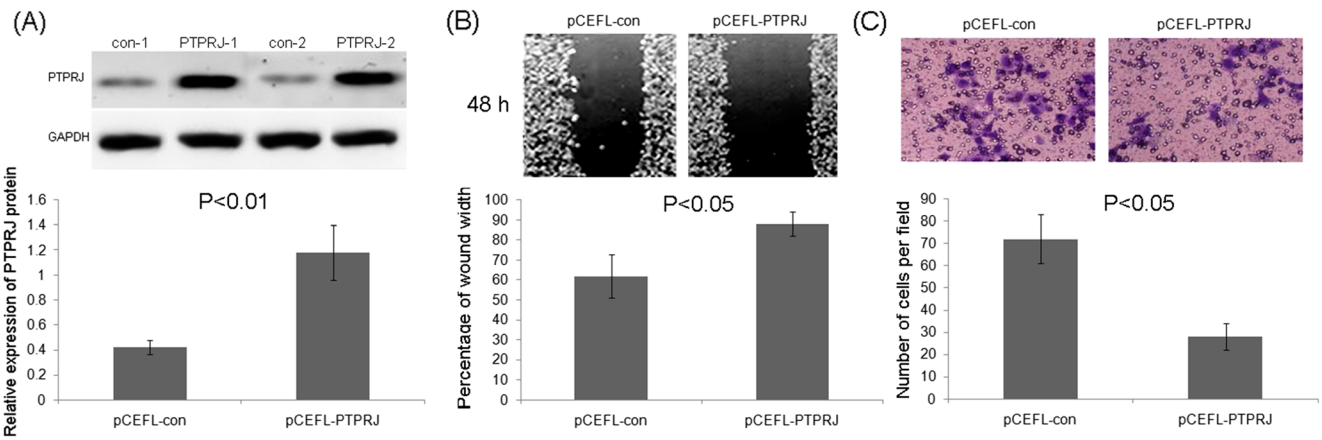

Fig. 3 Restoration of PTPRJ expression inhibited ESCC cell migration and invasion in vitro. **a** KYSE510 cells were transfected with pCEFL-PTPRJ plasmid which effectively increased the expression of PTPRJ protein. **b** and **c** Compared to KYSE510 cells transfected with pCEFL-empty vector (pCEFL-con) plasmid, over-expression of PTPRJ significantly inhibited the migration and invasion abilities of KYSE510 cells (both $P < 0.05$), respectively

PTPRJ in ESCC tissues compared with normal esophageal mucosa. Then, PTPRJ downregulation was found to be closely correlated with advanced tumor stage and poor differentiation. Further experiments presented here showed that KYSE510 cells interference of PTPRJ had a stronger migration and invasion abilities than that of normal control which were verified by wound healing and transwell assay. In contrast, the enforced expression of PTPRJ in KYSE510 cells led to the suppression of cell migration and invasion.

PTPRJ is one of receptor-like protein tyrosine phosphatases which function as crucial antagonists of tyrosine kinase-dependent signaling and are involved into various biological responses including cell development, transformation, proliferation and migration [13–15]. Among all protein tyrosine phosphatases, PTPRJ is of particular interest since accumulating studies have revealed that its expression is lower in several types of cancers, and the loss of PTPRJ plays important roles in carcinogenesis and cancer progression [7–10]. Consistent with the results of studies in other types of cancers, we here observed the obviously decreased expression of PTPRJ at the mRNA and protein levels compared to normal esophageal mucosa. Simultaneously, immunohistochemistry demonstrated that positive staining of PTPRJ was noted in the cytoplasm of the cancer cells, suggesting that PTPRJ might be a cytosolic protein, which is consistent with the previous studies. More importantly, our clinical evidence clearly supported that compared with different tumor stage and differentiation of ESCC, PTPRJ was lower expressed in later stage and poorly differentiated ESCC tissues, suggesting that PTPRJ might participate in ESCC progression.

Cancer cell motility has been recognized as a sign of invasiveness and an essential step during malignant metastasis [16, 17]. Moreover, cancer cell migration and invasion are also important characteristics of the molecular pathology of malignancies and are the main causes of cancer-related death [18]. Our study showed that the migration and invasion of ESCC cell line KYSE510, following transfection with siRNA-PTPRJ were obviously enhanced compared to the negative control cells, which could be effectively reversed by the transfection of expression vector of PTPRJ, implying that PTPRJ might be an important factor for suppressing migratory ability and invasiveness in ESCC progression.

In conclusion, our data offer the convincing evidence that loss of PTPRJ expression may predict an aggressive clinical course in ESCC patients. PTPRJ may function as a tumor suppressor and play an important role in the regulation of ESCC cell motility, suggesting its potentials as a therapeutic agent for human ESCC. Further studies should be required to elucidate the mechanisms underlying the functions of PTPRJ as a useful marker for ESCC.

Compliance with Ethical Standards

Conflict of Interest None.

References

1. Baba Y, Watanabe M, Yoshida N, Baba H (2014) Neoadjuvant treatment for esophageal squamous cell carcinoma. World J Gastrointest Oncol 6:121–128
2. Shang L, Wang M (2013) Molecular alterations and clinical relevance in esophageal squamous cell carcinoma. Front Med 7:401–410
3. Li JS, Ying JM, Wang XW, Wang ZH, Tao Q, Li LL (2013) Promoter methylation of tumor suppressor genes in esophageal squamous cell carcinoma. Chin J Cancer 32:3–11
4. Krüger J, Brachs S, Trappiel M, Kintscher U, Meyborg H, Wellnhofer E, Thöne-Reineke C, Stawowy P, Östman A, Birkenfeld AL, Böhmer FD, Kappert K (2015) Enhanced insulin signaling in density-enhanced phosphatase-1 (DEP-1) knockout mice. Mol Metab 4:325–336
5. Petermann A, Stampnik Y, Cui Y, Morrison H, Pachow D, Kliese N, Mawrin C, Böhmer FD (2015) Deficiency of the protein-tyrosine phosphatase DEP-1/PTPRJ promotes matrix metalloproteinase-9 expression in meningioma cells. J Neuro-Oncol 122:451–459
6. Spring K, Lapointe L, Caron C, Langlois S, Royal I (2014) Phosphorylation of DEP-1/PTPRJ on threonine 1318 regulates Src activation and endothelial cell permeability induced by vascular endothelial growth factor. Cell Signal 26:1283–1293
7. Ortuso F, Paduano F, Carotenuto A, Gomez-Monterrey I, Bilotta A, Gaudio E, Sala M, Artese A, Vernieri E, Dattilo V, Iuliano R, Brancaccio D, Bertamino A, Musella S, Alcaro S, Grieco P, Perrotti N, Croce CM, Novellino E, Fusco A, Campiglia P, Trapasso F (2013) Discovery of PTPRJ agonist peptides that effectively inhibit in vitro cancer cell proliferation and tube formation. ACS Chem Biol 8:1497–1506
8. Smart CE, Askarian Amiri ME, Wronski A, Dinger ME, Crawford J, Ovchinnikov DA, Vargas AC, Reid L, Simpson PT, Song S, Wiesner C, French JD, Dave RK, da Silva L, Purdon A, Andrew M, Mattick JS, Lakhani SR, Brown MA, Kellie S (2012) Expression and function of the protein tyrosine phosphatase receptor J (PTPRJ) in normal mammary epithelial cells and breast tumors. PLoS One 7:e40742
9. Spring K, Fournier P, Lapointe L, Chabot C, Roussy J, Pommey S, Stagg J, Royal I (2015) The protein tyrosine phosphatase DEP-1/PTPRJ promotes breast cancer cell invasion and metastasis. Oncogene In press
10. Yan CM, Zhao YL, Cai HY, Miao GY, Ma W (2015) Blockage of PTPRJ promotes cell growth and resistance to 5-FU through activation of JAK1/STAT3 in the cervical carcinoma cell line C33A. Oncol Rep 33:1737–1744
11. Chen G, Peng J, Zhu W, Tao G, Song Y, Zhou X, Wang W (2014) Combined downregulation of microRNA-133a and microRNA-133b predicts chemosensitivity of patients with esophageal squamous cell carcinoma undergoing paclitaxel-based chemotherapy. Med Oncol 31:263
12. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM (2010) Estimates of worldwide burden of cancer in 2008. Int J Cancer 127:2893–2917
13. Xu X, Lan W, Jin X, Wang B, Yan H, Chen X, Lai X, Zhang L, Zhang X, Li Z (2014) Regulated expression of PTPRJ by COX-2/PGE2 axis in endothelial cells. PLoS One 9:e114996
14. Dave RK, Dinger ME, Andrew M, Askarian-Amiri M, Hume DA, Kellie S (2013) Regulated expression of PTPRJ/CD148 and an antisense long noncoding RNA in macrophages by proinflammatory stimuli. PLoS One 8:e68306
15. Aya-Bonilla C, Green MR, Camilleri E, Benton M, Keane C, Marlton P, Lea R, Gandhi MK, Griffiths LR (2013) High-

resolution loss of heterozygosity screening implicates PTPRJ as a potential tumor suppressor gene that affects susceptibility to Non-Hodgkin's lymphoma. Genes Chromosom Cancer 52:467–479
16. Liotta LA, Kohn EC (2001) The microenvironment of the tumour-host interface. Nature 411:375–379
17. Wang W, Goswami S, Sahai E (2005) Tumor cells caught in the act of invading: their strategy for enhanced cell motility. Trends Cell Biol 15:138–145
18. Ridley AJ, Schwartz MA, Burridge K (2003) Cell migration: integrating signals from front to back. Science 302:1704–1709