MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 6554-6562
DOI: 10.12659/MSM.915845

Received: 2019.02.22
Accepted: 2019.04.29
Published: 2019.09.01

Phosphatidylinositol-3,4,5-Trisphosphate Dependent Rac Exchange Factor 1 (PREX1) is a Novel Predictor of Prognosis for Breast Cancer Patients: A Retrospective Case Series

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AE 1 Ying Zhong
C 2 Jing Zhang
BD 1 Yidong Zhou
C 1 Feng Mao
D 1 Yan Lin
E 1 Yali Xu
B 1 Jinghong Guan
F 1 Songjie Shen
C 1 Bo Pan
D 1 Changjun Wang
B 1 Li Peng
C 1 Xin Huang
B 1 Yan Li
E 1 Xi Cao
ABG 1 Qiang Sun

1 Department of Breast Disease, Peking Union Medical College Hospital, Beijing, P.R. China
2 Department of Pathology, Peking Union Medical College Hospital, Beijing, P.R. China

Corresponding Author: Qiang Sun, e-mail: bakenfish@163.com
Source of support: This work was supported by Beijing Science and Technology Commission 2016: Science and Technology Project (Optimization of Breast Cancer Screening Program for the Right Age Women in Beijing)

Background: In previous studies, higher expression of PREX1 (PtdIns (3,4,5)P3-dependent Rac exchanger 1) has been detected in some subsets of breast cancer, and activation of PREX1 has been associated with tumor progression *in vivo*. However, an association between PREX1 and breast cancer prognosis has not been examined.

Material/Methods: In this study, we investigated the expression and correlation of PREX1 with important clinical factors and prognosis of patients with breast cancer. Immunohistochemical staining was performed for 121 tumor tissue specimens obtained from primary breast cancer lesions.

Results: We found that 55 tissues exhibited positive staining for PREX1. Moreover, tumors positive for PREX1 were found to have significant association with recurrence rate (P=0.000) and metastasis rate (P=0.001). Univariate and multivariate regression analyses also identified PREX1 expression as an independent variable of disease-free survival. Our analyses indicate that high levels of PREX1 expression were related to longer disease-free survival in patients with breast cancer (P=0.013).

Conclusions: PREX1 is a favorable variable of prognosis for breast cancer patients, these study results need to be confirmed in larger research studies.

MeSH Keywords: **3-Phosphoinositide-Dependent Protein Kinases • Breast Neoplasms • Prognosis**

Abbreviations: **IDC** – invasive ductal carcinoma; **TNBC** – triple-negative breast cancer; **N/A** – not available; **A** – anthrocycline; **T** – taxane; **CMF** – cyclophosphamide, methotrexate, and 5-fluorouracil; **MRM** – modified radical mastectomy; **BCS** – breast-conserving surgery

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/915845

1839 3 4 24

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

Breast cancer is a malignant tumor that seriously threatens women's health. It is the most common malignant tumor in women. Worldwide, there are approximately 1.6 million new breast cancer patients each year, and more than 500 000 deaths [1]. Despite the availability of chemotherapy, radiation therapy, hormone therapy, and trastuzumab as treatment options for breast cancer patients, there are a subset of patients still experiencing tumor recurrence or metastasis.

Rac1, Rac2, and Rac3 represent members of the Rho-GTPase family of proteins which are associated with the morphology, motility, and invasion of cancer cells that form distant metastases [2–4]. The most popular mechanism identified for overactivation of Rac in human cancers involves the imbalance of Rac-guanine nucleotide exchange factor (GEF) activity. In particular, PtdIns (3,4,5)P3-dependent Rac exchanger 1 (PREX1) is a subgroup of the Dbl family of Rho-GEFs and has been shown to promote chemotactic agents to stimulate neutrophil chemotaxis and formation of reactive oxygen species [5–7]. When PREX1 is ectopically expressed *in vitro*, it promotes cell migration, viability, and invasion [8,9]. Similarly, targeting of *PREX1* with short-hairpin RNA in breast cancer cells that are positive for ErbB receptors has been reported to lead to a reduction in cell migration, proliferation, and the growth of xenograft tumors [10,11]. In estrogen receptor (ER)-positive luminal breast tumors, both mRNA and protein levels of PREX1 are upregulated, while expression of PREX1 is not detected in normal breast tissue [8,10]. In addition, *PREX1* has been found to be amplified in primary breast tumors, while 58% of breast cancers are reported to be positive for PREX1 by immunohistochemistry [10]. Thus, *PREX1* has been identified as a putative oncogene [10–14]. Clinically, PREX1 has also been found to be related to poor prognosis in various human cancers, including malignant myeloid diseases [15], ovarian cancer [16], pancreatic endocrine tumors [17], and hereditary prostate cancer [18].

Despite convincing evidence that in some breast cancer subtypes, PREX1 expression is increased and that PREX1 activation is associated with tumor progression *in vivo* [11], very few data are available regarding the relationship between PREX1 expression and breast cancer prognosis. Therefore, the aim of this study was to retrospectively analyze PREX1 expression in 121 breast cancer tissue samples and investigate a possible correlation between PREX1 expression and breast cancer prognosis.

Material and Methods

Patients with breast cancer and tumor samples

We obtained 121 tumor samples from breast cancer patients. All patients (aged 13–81 years) underwent surgery and other treatments between 2000 and 2007 at Peking Union Medical College Hospital (PUMCH, Beijing, China). The median follow-up time was 29 months. Treatment after surgery included a combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), or capecitabine, paclitaxel, anthracycline, radiotherapy, tamoxifen, or aromatase inhibitors. Some patients received a combination of agents for their treatment. In our study, recurrence was the presence of nodules in the chest wall, and metastatic sites were defined as bone, liver, lung, brain, supraclavicular lymph nodes, and contralateral breast.

Ethics approval and consent to participate

Peking Union Medical College Hospital ethics committee reviewed the study protocol and deemed the study exempt from full review (approval no. S-K609, dated November 5, 2018). All patients in our study provided written informed consent for participation.

Availability of data and materials

The datasets generated during and/or analyzed in the current study are not publicly available but are available from the corresponding author on reasonable request.

Immunohistochemical (IHC) staining and analysis

Collected tissues were paraffin embedded after fixing in neutral buffered formalin (10%) and tumor sections (4 um thickness) were accomplished by adhesion slides. According to normal protocols, immunohistochemical (IHC) staining was performed with standard autostaining protocols (Ventana Benchmark XT autostainer system). Isotype antibody and control tissue were included in positive and negative controls, according to the manufacturer's recommendations. Two pathologists evaluated each IHC slide respectively.

IHC analyses of ER, progesterone (PR), and human epidermal growth factor receptor 2 (HER2) were analyzed in the clinical laboratory at PUMCH. The sections were cut at 5 μm thickness and mounted on silicified slides. The expression of ER, PR, and HER2 were determined according to routine methods. All the samples were stained with hematoxylin and eosin, and histological analyses were performed according to classifications established by the World Health Organization [19,20].

From pathological reports, tumor size and number of metastatic lymph nodes were derived. Metastases were confirmed by biopsy and the locations were detected by imaging examinations. In IHC staining, negative expression of ER, PR, and HER2 were defined as basal-like features. If at least 1% of tumor cells were stained, ER and PR expression were considered positive. If >30% of the invasive tumor cells were stained in

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1. Baseline clinicopathological characteristics and treatments of the cohort.

Characteristics	Values	
Age at diagnosis		
Median range (years)	50	(13-81)
<40	18	(14.9%)
40~59	67	(55.4%)
≥60	36	(29.6%)
Surgery		
MRM	109	(90.1%)
BCS	9	(7.4%)
Others	3	(2.5%)
Histology subtype		
IDC	102	(84.4%)
Others	19	(18.6%)
Tumor size, cm		
≤2	41	(33.9%)
2~5	64	(52.9%)
>5	16	(13.2%)
Lymph node involvement		
LN(–)	24	(19.8%)
LN(+)	97	(80.2%)
Number of positive lymph nodes		
0	24	(19.8%)
1~3	38	(31.4%)
4~9	29	(24.0%)
≥10	30	(24.8%)
Stage		
I	12	(9.9%)
II	48	(39.7%)
III	61	(50.4%)
Lymphovascular invasion		
No	0	(100%)
Yes	121	(0%)
Molecular subtype		
Basal-like TNBC	30	(24.8%)
Non basal-like TNBC	91	(75.2%)
Chemotherapy		
No	2	(1.7%)
Yes	119	(98.3%)
Chemotherapy regimen		
None	2	(1.7%)
A-based	12	(9.9%)
AT-based	71	(58.7%)
Capecitabine-based	9	(7.4%)
CMF	7	(5.8%)
Others	20	(16.5%)
Radiation		
No	45	(37.2%)
Yes	60	(49.6%)
NA	16	(13.2%)
Hormone therapy		
No	65	(53.7%)
Yes	46	(38.0%)
NA	10	(8.3%)

MRM – modified radical mastectomy; BCS – breast-conserving surgery; IDC – invasive ductal carcinoma; NA – not available; A – anthrocycline;T – taxanes.

intense membrane by IHC, more than 6 *HER-2* gene copies per nucleus were revealed by fluorescence *in situ* hybridization (FISH), or HER2 signal compared to chromosome 17 signal was >2.2 with FISH ratio, HER-2 expression was considered positive.

Statistical analyses

Statistical analyses were performed by SPSS software (version 21.0). The χ^2 test and Mann-Whitney U test were applied to IHC results and various clinicopathologic parameters. The latter were also evaluated in relation to disease-free survival (DFS) with Mann-Whitney U test, χ^2 test, and logistic regression. The log-rank test was used to determine the significance of associations observed between PREX1 and DFS in Kaplan-Meier survival analyses. All of the statistical tests performed were 2-sided and *P*-values less than 0.05 were considered significant.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

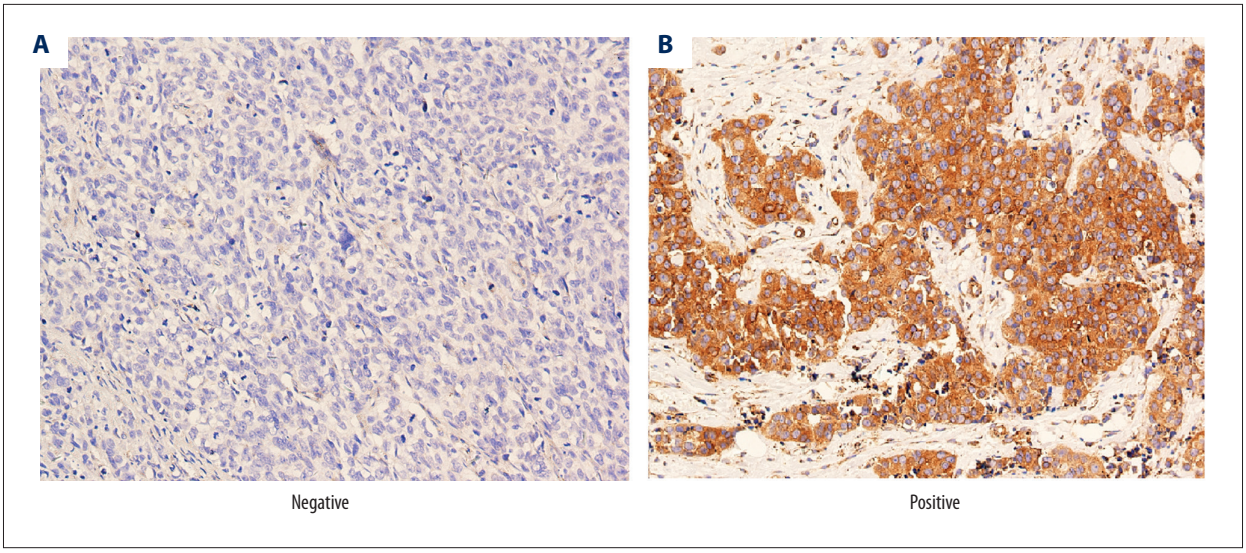

Figure 1. Immunohistochemical staining of PREX1 in representative breast tumor sections. Negative (**A**) and positive (**B**) staining for PREX1 are shown at 400× magnification.

Results

Clinicopathological characteristics and survival data

A total of 121 breast cancer patients were examined in this study (Table 1). Most cases involved invasive breast ductal carcinoma (102 out of 121 cases, 84.4%) and 109 out of 121 patients (90.1%) underwent modified radical mastectomy. The median age of this cohort at the time of surgery was 50 years (range, 13–81 years). Postsurgical treatment included CMF, or various combinations of anthracycline, paclitaxel, tamoxifen, aromatase inhibitors, or radiotherapy. Among the cases with adjuvant treatment information available, 98.3% (119 out of 121 cases) included chemotherapy and 49.6% (61 out of 121 cases) included radiation. The median follow-up time was 29 months (range, 2–91 months) and the DFS 5-years was 40.4%.

IHC detection of PREX1

Consequently, total PREX1 expression was analyzed in 121 human breast cancer tissue sections. Representative negative and positive IHC staining for PREX1 are shown in Figure 1. IHC staining results of epithelial cells, and nonstromal cells, were classified as: 3+ (tumor cells were stained positive at least 50%), 2+ (tumor cells were stained positive in 10–50%), 1+ (tumor cells were stained positive in 1–10%), and negative (tumor cells were stained positive <1%).

Associations of PREX1 with clinicopathologic features of breast cancer patients

Table 2 summarizes the associations identified between the clinicopathological characteristics of our cohort and PREX1 expression. No significant associations were detected between PREX1 expression and patient age, histology subtype, tumor size, lymph node involvement, or pathologic stage. In contrast, PREX1-negative tumors were significantly associated with tumor recurrence (P=0.000) and metastasis (P=0.001). Associations between DFS and tumor size, basal-like features, and PREX1 status were also examined (Table 3). In univariate regression analyses, basal-like features, hormone therapy, and PREX1 expression exhibited significant associations with DFS. In multivariate regression analyses, PREX1 expression, and hormone therapy were identified as independent predictors of DFS.

Associations of PREX1 expression with metastasis and recurrence

The rate of metastasis or recurrence was 53.7% among the 121 patients examined. The associations between PREX1-positive tumors with both recurrence rate (P=0.000; Figure 2) and metastasis rate (P=0.001; Figure 3) were significant. Kaplan-Meier survival curves for DFS versus PREX1 expression are shown in Figure 4. PREX1 expression exhibit a significant association with DFS (P=0.013).

Discussion

In recent studies, PREX1 has been shown to be an important mediator of tumor cell migration [8–10], the human *PREX1* gene has been related with poor prognosis in cancer [11,21], and hypomethylation of the *PREX1* promoter was identified as a prognostic marker of poor patient survival [22]. In the present study, PREX1 expression was not found to be significantly related to tumor size, pathological stage, hormone receptor (HR) expression,

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 2. Relationships between PREX1 cells with clinicopathologic features.

All cases	PREX1 expression in tumor cells				P
	Negative		Positive		
Age					0.061
<40	13	(19.7%)	5	(9.1%)	
40~59	37	(56.1%)	30	(54.5%)	
≥60	16	(24.2%)	20	(36.4%)	
Histology subtype					0.856
IDC	56	(84.8%)	46	(83.6%)	
Others	10	(15.2%)	9	(16.4%)	
Tumor size					0.686
≤2	22	(33.3%)	19	(34.5%)	
2~5	34	(51.5%)	30	(54.5%)	
>5	10	(15.2%)	6	(10.9%)	
Lymph node involvement					0.340
LN(–)	11	(16.7%)	13	(23.6%)	
LN(+)	55	(83.3%)	42	(76.4%)	
Number of positive lymph nodes					0.020
0	11	(16.7%)	13	(23.6%)	
1~3	16	(24.2%)	22	(40.0%)	
4~9	18	(27.3%)	11	(20.0%)	
≥10	21	(31.8%)	9	(16.4%)	
Stage					0.057
I	6	(9.1%)	6	(10.9%)	
II	21	(31.8%)	27	(49.1%)	
III	39	(59.1%)	22	(40.0%)	
Basal-like features					0.267
Present	19	(28.8%)	11	(20.0%)	
Absent	47	(71.2%)	44	(80.0%)	
Recurrence					0.000
Absent	21	(51.2%)	36	(83.7%)	
Present	20	(48.8%)	7	(16.3%)	
Metastasis					0.001
Absent	21	(45.7%)	36	(75.0%)	
Present	25	(54.3%)	12	(25.0%)	

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 3. Univariate and multivariate analyses of various predictors of disease-free survival.

Variable	No.patients	No.events (%)	Univariate analysis	Multivariate analysis
			P	P
Age				
<40	18	8 (44.4%)	0.145	
40~59	67	35 (52.2%)		
≥60	36	23 (63.9%)		
Operation method				
MRM	109	60 (55.0%)	0.427	
BCS	9	3 (33.3%)		
Others	3	3 (100.0%)		
Tumor size				
≤2	41	18 (43.9%)	0.165	
2~5	64	39 (60.9%)		
>5	16	9 (56.3%)		
Lymph node involvement				
LN(–)	24	13 (54.2%)	0.967	
LN(+)	97	53 (54.6%)		
Number of positive lymph nodes				
0	24	13 (54.2%)	0.672	
1~3	38	20 (52.6%)		
4~9	29	15 (51.7%)		
≥10	30	18 (60.0%)		
Pathologic stage				
I	12	7 (58.3%)	0.641	
II	48	24 (50.0%)		
III	61	35 (57.4%)		
HR				
(–)	56	34 (60.7%)	0.208	
(+)	65	32 (49.2%)		
Chemotherapy				
No	2	2 (100.0%)	0.195	
Yes	119	64 (53.8%)		
Radiation				
No	45	25 (55.6%)	0.608	
Yes	60	34 (56.7%)		
NA	16	7 (43.8%)		

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 3 continued. Univariate and multivariate analyses of various predictors of disease-free survival.

Variable	No.patients	No.events (%)	Univariate analysis	Multivariate analysis
			P	P
PREX1				
Negative	66	47 (71.2%)	0.000	0.000
Positive	55	19 (34.5%)		
Basal-like feature				
Present	30	22 (73.3%)	0.018	0.174
Absent	81	44 (48.4%)		
Hormone therapy				
No	65	44 (67.7%)	0.001	0.009
Yes	46	20 (43.5%)		
NA	10	2 (20.0%)		

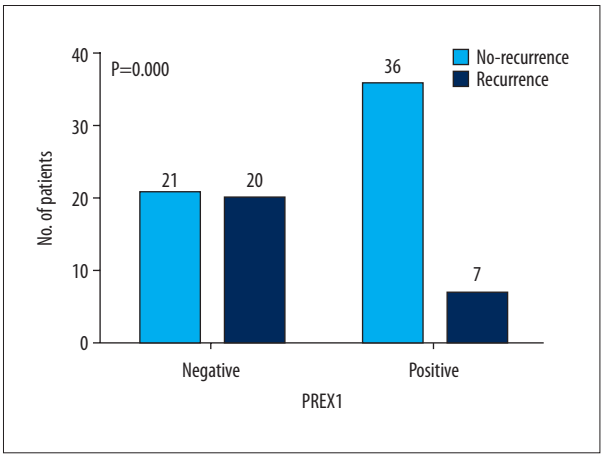

Figure 2. Relationship between PREX1 expression and recurrence. The number of patients with and without recurrence according to PREX1 expression. *P*-values are indicated.

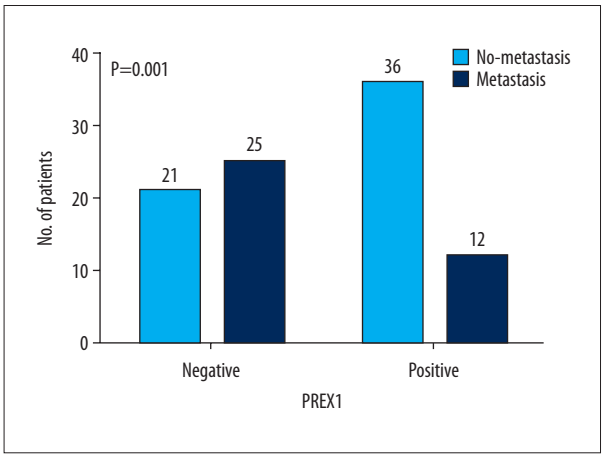

Figure 3. Relationship between PREX1 expression and metastasis. The number of patients with and without metastasis according to PREX1 expression. *P*-values are indicated.

or basal-like features. These results are inconsistent with previous findings that PREX1 are upregulated in estrogen receptor positive breast tumors [8,10] and that PREX1 expression is highest in ER+ breast tumors compared with other cancer subtypes [8]. In contrast, the significant association that was identified between PREX1 and tumor recurrence in the present study is inconsistent with the results of previous *in vitro* and *in vivo* studies [10,11]. Moreover, univariate and multivariate regression analyses revealed that PREX1 is an independent predictor of DFS, and according to Kaplan-Meier survival curves, higher expression of PREX1 was associated with longer DFS in breast cancer.

In a recent study, PREX1-Rac-GEF activity was shown to be critical for cell growth and the growth of xenograft tumors. Thus, PREX1, Rac, and GEF are likely to be therapeutic targets for breast cancers with high expression of PREX1 [23]. In another study, a significant association between levels of phosphorylated Rex1 (P-Rex1) in human luminal breast cancer and poor prognosis was observed [21].

Downregulation of phosphorylated Rex1 (P-Rex1) was also reported to increase sensitivity of prostate tumors to bevacizumab [21]. Accordingly, VEGF/VEGFR-targeted therapy in combination with inhibition of P-Rex1 or Rac1 may improve the efficacy of these therapies significantly [24]. Overall, downregulation or upregulation of PREX1 has been found to reduce or promote the proliferation, migration, and invasive capacity of breast cancer cells, respectively [8–11]. The results of the

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

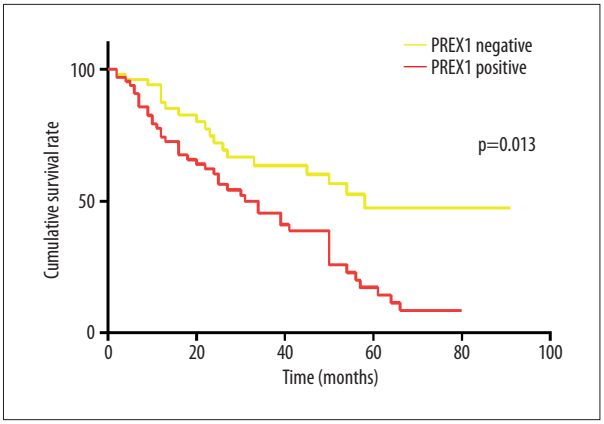

Figure 4. Disease free survival according to PREX1 expression.

present study indicate that lower levels of PREX1 expression are associated with poor prognosis in breast cancer patients, which is contrary to previous research conclusions. Our results remain to be confirmed in a larger study.

There were several limitations associated with the present study. First, the retrospective and single-institution samples analysis each represented limitations. Evaluation of PREX1 expression without standard method is also a disadvantage in this present study. Furthermore, multicollinearity existed between tumor size, number of metastatic lymph nodes, and TNM stage among the clinicopathological information, although these features were analyzed independently with regression models. Finally, we observed that PREX1 is associated with breast cancer recurrence and metastasis, and PREX1 was identified as an independent prognostic factor of DFS. It is possible that the short follow-up time and limited sample size of the present study account for this inconsistency with other research. Accordingly, a prospective multi-institutional study with larger number of patient samples are needed to prove the prognostic role of PREX1. Given the importance of PREX1 in breast cancer, it is additionally possible that PREX1 represents a valuable target in diagnosis and treatment for breast cancer.

Conclusions

The present study demonstrated that PREX1 expression was associated with recurrence rate and metastasis rate. Univariate and multivariate regression analyses also identified PREX1 expression as an independent predictor of DFS. While the present findings remain to be verified in a studies with a larger number of samples, our results suggested that PREX1 expression is an independent favorable predictor for breast cancer patients.

Acknowledgements

We would like to thank all of our patients for participating in this study and everyone who contributed towards the article.

Conflict of interests

None.

References:

1. Torre LA, Bray F, Siegel RL et al: Global cancer statistics, 2012. Cancer J Clin, 2015; 65(2): 87–108
2. Jaffe AB, Hall A: Rho GTPases: Biochemistry and biology. Ann Rev Cell Dev Biol, 2005; 21: 247–69
3. Orgaz JL, Herraiz C, Sanz-Moreno V: Rho GTPases modulate malignant transformation of tumor cells. Small GTPases, 2014; 5: e29019
4. Sadok A, Marshall CJ: Rho GTPases: Masters of cell migration. Small GTPases, 2014; 5: e29710
5. Welch HC, Coadwell WJ, Ellson CD et al: P-Rex1, a PtdIns(3,4,5)P3- and Gbetagamma-regulated guanine-nucleotide exchange factor for Rac. Cell, 2002; 108(6): 809–21
6. Welch HC, Condliffe AM, Milne LJ et al: P-Rex1 regulates neutrophil function. Curr Biol, 2005; 15(20): 1867–73
7. Lawson CD, Donald S, Anderson KE et al: P-Rex1 and Vav1 cooperate in the regulation of formyl-methionyl-leucyl-phenylalanine-dependent neutrophil responses. J Immunol, 2011; 186(3): 1467–76
8. Dillon LM, Bean JR, Yang W et al: P-REX1 creates a positive feedback loop to activate growth factor receptor, PI3K/AKT and MEK/ERK signaling in breast cancer. Oncogene, 2015; 34(30): 3968–76
9. Campbell AD, Lawn S, McGarry LC et al: P-Rex1 cooperates with PDGFRbeta to drive cellular migration in 3D microenvironments. PLoS One, 2013; 8(1): e53982
10. Sosa MS, Lopez-Haber C, Yang C et al: Identification of the Rac-GEF P-Rex1 as an essential mediator of ErbB signaling in breast cancer. Mol Cell, 2010; 40(6): 877–92
11. Montero JC, Seoane S, Ocana A, Pandiella A: P-Rex1 participates in Neuregulin-ErbB signal transduction and its expression correlates with patient outcome in breast cancer. Oncogene, 2011; 30(9): 1059–71
12. Fine B, Hodakoski C, Koujak S et al: Activation of the PI3K pathway in cancer through inhibition of PTEN by exchange factor P-REX2a. Science, 2009; 325(5945): 1261–65
13. Lindsay CR, Lawn S, Campbell AD et al: P-Rex1 is required for efficient melanoblast migration and melanoma metastasis. Nat Commun, 2011; 2: 555
14. Barrio-Real L, Kazanietz MG: Rho GEFs and cancer: Linking gene expression and metastatic dissemination. Sci Signal, 2012; 5(244): pe43
15. Asimakopoulos FA, Green AR: Deletions of chromosome 20q and the pathogenesis of myeloproliferative disorders. Br J Haematol, 1996; 95(2): 219–26
16. Larramendy ML, Lushnikova T, Bjorkqvist AM et al: Comparative genomic hybridization reveals complex genetic changes in primary breast cancer tumors and their cell lines. Cancer Genet Cytogenet, 2000; 119(2): 132–38
17. Stumpf E, Aalto Y, Hoog A et al: Chromosomal alterations in human pancreatic endocrine tumors. Genes Chromosomes Cancer, 2000; 29(1): 83–87
18. Berry R, Schroeder JJ, French AJ et al: Evidence for a prostate cancer-susceptibility locus on chromosome 20. Am J Hum Genet, 2000; 67(1): 82–91
19. Hammond ME, Hayes DF, Dowsett M et al: American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). Arch Pathol Lab Med, 2010; 134(7): e48–72
20. Wolff AC, Hammond ME, Hicks DG et al: Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol, 2013; 31(31): 3997–4013

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

21. Barrio-Real L, Wertheimer E, Garg R et al: Characterization of a P-Rex1 gene signature in breast cancer cells. Oncotarget, 2016; 7(32): 51335–48
22. Barrio-Real L, Benedetti LG, Engel N et al: Subtype-specific overexpression of the Rac-GEF P-REX1 in breast cancer is associated with promoter hypomethylation. Breast Cancer Res, 2014; 16(5): 441
23. Liu HJ, Ooms LM, Srijakotre N et al: PtdIns(3,4,5)P3-dependent Rac exchanger 1 (PREX1) Rac-guanine nucleotide exchange factor (GEF) activity promotes breast cancer cell proliferation and tumor growth via activation of extracellular signal-regulated kinase 1/2 (ERK1/2) signaling. J Biol Chem, 2016; 291(33): 17258–70
24. Goel HL, Pursell B, Shultz LD et al: P-Rex1 promotes resistance to VEGF/VEGFR-targeted therapy in prostate cancer. Cell Rep, 2016; 14(9): 2193–208

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]