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PECAM-1 is a Prognostic-Related Biomarker and Correlated with Immune Infiltrates in Breast Cancer

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Abstract:This study aims to analyze the expression and clinical significance of Platelet endothelial cell adhesion molecule 1 (PECAM-1) in breast cancer and the correlation between PECAM-1 and immune infiltrations. We performed a bioinformatic analysis of the prognostic value and immune infiltration correlation of PECAM-1 in breast cancer**.** The results showed that there were significant differences in PECAM-1 expression levels between breast invasive carcinoma tissues and adjacent normal tissues. The high expression of PECAM-1 was significantly related to favorable overall survival, progression-free survival and distant metastasis free survival in patients with breast cancer. There were significantly positive correlations with the levels of infiltrated B cell, CD4+T cells, CD8+ T cells, neutrophils, macrophages, and dendritic cells in breast cancer. In summary, the expression of PECAM-1 can serves as a prognostic biomarker in breast invasive carcinoma and is correlated with immune infiltrates.

Keywords: PECAM-1; Breast invasive Carcinoma; Prognosis Biomarker; Immune infiltration.

1. Introduction

Breast cancer is the most common malignancy in women and remain the second cancer-related death worldwide. Treatments have progressed substantially over the past years based on systemic and multidisciplinary treatment, while the overall outcomes remain rather unsatisfactory. Recently, immunotherapy targeting interactions between immune cells and tumor cells have been developed to reactivate adaptive and innate immune systems and create a robust antitumoral immune response[1]. It is urgent to identify biomarkers of immune interactions with breast cancer and explore new targets for immune-related therapies.

Platelet endothelial cell adhesion molecule 1 (PECAM-1), also known as CD31, is a member of the adhesion molecule in the immunoglobulin superfamily[2]. PECAM-1 is an adhesion molecule expressed by vascular endothelial cells, platelets, monocytes, neutrophils, natural killer cell and naive T lymphocytes[3]. PECAM-1 has been implicated in a number of important biological processes[4], leukocyte emigration at sites of inflammation, T cell activation, platelet aggregation and homeostasis, and the maintenance of vascular endothelial barrier function. Whether PECAM-1 expression in breast invasive carcinoma tissues is associated with tumor immune infiltrates and clinical outcomes are still unclear.

Here, we visualized the expression and the prognostic landscape of PECAM-1 in breast cancer using multiple databases. We then explored the potential relationships between PECAM-1 expression and immune infiltration levels using the TIMER database.

2. Methods

We used the online database Oncomine database (https://www.oncomine.org/ resource/login.htm);UALCAN (http://ualcan.path.uab.edu/) Kaplan-Meier Plotter (https://kmplot.com/); TIMER **database** (https://cistrome.shinyapps.io/timer/) to explore the prognosis of PECAM-1 in breast cancer.

3. Results

3.1 The mRNA and protein expression levels of PECAM-1 in breast cancer

The Oncomine database was used to analyze PECAM-1 mRNA levels in tumor tissues and normal tissues of various cancer types, the results revealed that PECAM-1 mRNA expression of breast cancer increased in 1 data set and decreased in 6 data sets compared to the normal tissues (Figure 1A). The TCGA RNA-sequencing date was used to further verify the PECAM-1 expression and the results showed that PECAM-1 expression was significantly lower in breast invasive carcinoma (BRCA) compared with adjacent normal tissues (Figure 1B). In addition, the results showed that the mRNA expression level were similar in the breast cancer subtypes. Next, we evaluated the protein expression of PECAM-1 in UALCAN database and the result revealed it was lowly expressed in tumor tissues (Figure 2).

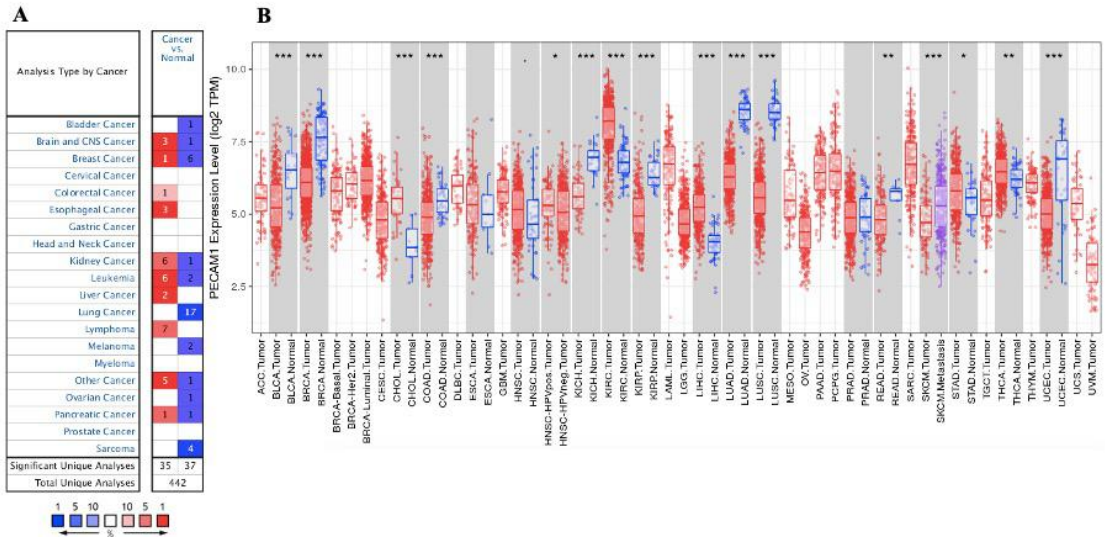

Figure 1. PECAM-1 expression levels in cancers. (A) the expression of PECAM-1 in different cancer tissues and normal tissues in Oncomine database. (B) Human PECAM-1 expression leaves in different cancer types from TCGA date in TIMER. *P < 0.05, **P < 0.01, ***P < 0.001.

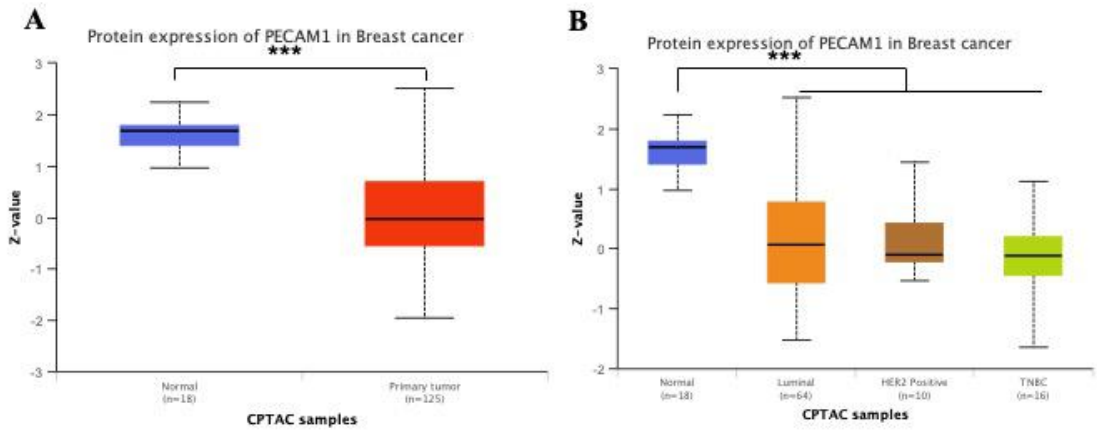

Figure 2. (A) PECAM-1 protein expression comparison between normal and tumor tissues obtained from the UALCAN web tool (Wilcoxon test). (B) PECAM-1 protein expression comparison between normal and subtypes of breast cancer tissues. ***P < 0.001

3.2 The prognostic evaluation of PECAM-1 in breast cancer

The Kaplan-Meier plotter database was used to further evaluate the prognostic role of PECAM-1 in breast cancer. Similarly, we found that PECAM-1 expression was associated with favorable prognosis in breast cancer patients (Figure 3A,3F,3K). In addition, the prognostic value of PECAM-1 was explored in breast cancer with intrinsic subtypes including the basal-like, HER-2 positive, luminal A and luminal B subtypes. High mRNA expression of PECAM-1 was significantly associated with favorable overall survival (OS) in basal-like subtypes patients (Figure 3B), whereas PECAM-1 was not related to prognosis in HER-2 positive, luminal A and luminal B subtypes (Figure 3C-3E). High mRNA expression of PECAM-1 was correlated with better relapse-free survival(RFS) in basal-like type (Figure 3G), luminal A type (Figure 3 I) and luminal B type (Figure 3J). For distant metastasis free survival (DMFS), no significant difference was found between the high expression of PECAM-1 in the four intrinsic subtype patients (Figure 3L-3O). Therefore, it is conceivable that high expression of PECAM-1 may be a protective factor in breast cancer patients.

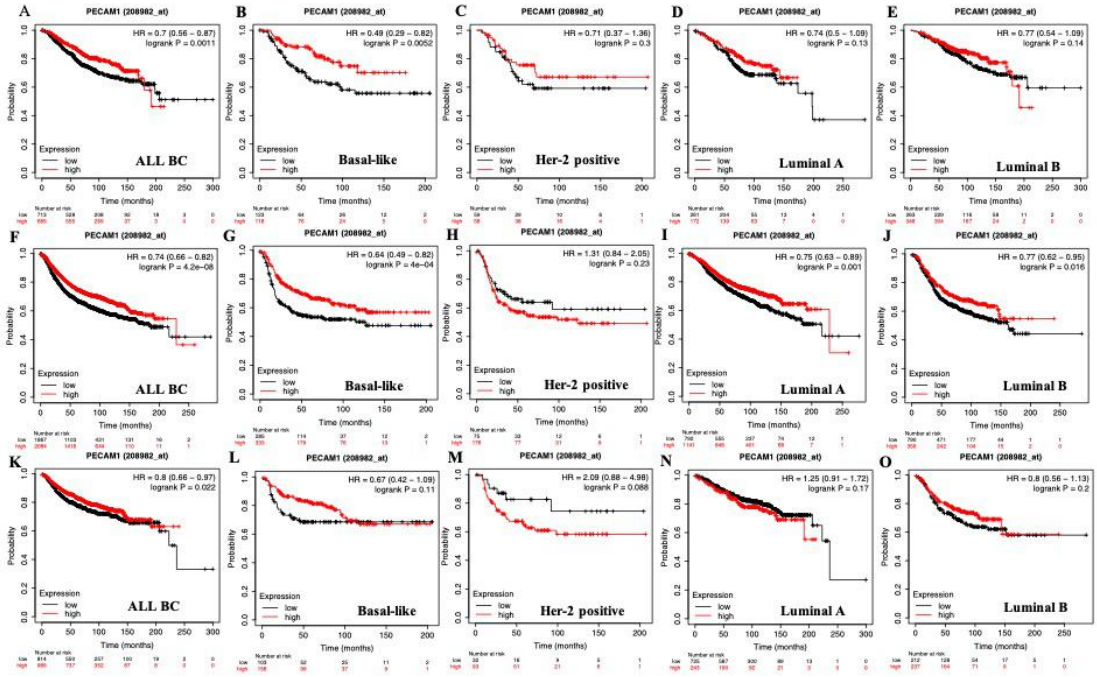

Figure 3. Kaplan-Meier survival curves comparing high and low expression of PECAM-1 in breast cancer in Kaplan-Meier Plotter. (A-E) OS of PECAM-1in the subtype of breast cancer patients. (F-J) RFS of PECAM1in the subtype of breast cancer patients; (K-O) DMFS of PECAM1 in the subtype of breast cancer patients. OS, overall survival; RFS, relapse-free survival; DMFS, distant metastasis-free survival.

3.3 Correlation analysis between clinical characteristics and PECAM-1 expression in breast cancer.

The Kaplan-Meier plotter was used to study the relationship between PECAM-1 expression and clinical characteristics in breast cancer patients. As shown in Table 1, low PECAM-1 mRNA expression was related to poor OS in basal-like subtype(p=0.0052), lymph node negative (p=0.0072) and grade 1 patients(p=0.0047). Low expression of PECAM-1 was related to poor OS in patients with mutated TP53 status(p=0.02) and wild type TP53 status(p=0.047). In addition, low

PECAM-1 mRNA expression was related to worse OS in patients who receive systemically treatment or not ($p<0.05$).

Table1 Correlations between PECAM-1 expression and clinical prognosis in breast cancer with respect to clinicopathological factors.

Clinicopathological characteristics	Overall survival		
	N	Hazard ratio	*P*-value
ER-status			
ER positive	548	0.75(0.52-1.08)	0.12
ER negative	251	0.75(0.43-1.33)	0.32
PR-status			
PR positive	83	0.33(0.09-1.23)	0.082
PR negative	89	2.47(0.88-6.94)	0.076
HER2 status			
HER2 positive	129	0.58(0.24-1.42)	0.23
HER2 negative	130	0.6(0.25-1.44)	0.25
Intrinsic subtype			
Basal-like	241	0.49(0.29-0.82)	**0.0052**
Luminal A	611	0.77(0.54-1.09)	0.14
Luminal B	433	0.74(0.5-1.09)	0.13
HER2+	117	0.711(0.37-1.36)	0.3
Lymph node status			
Lymph node positive	313	0.67(0.45-0.99)	0.041
Lymph node negative	594	0.6(0.41-0.87)	**0.0072**
Grade			
1	161	0.29(0.12-0.72)	**0.0047**
2	387	0.75(0.49-1.15)	0.19
3	503	0.7(0.49-1)	0.05
TP53 status			
Mutated	111	0.42(0.19-0.89)	**0.02**
Wild type	187	0.52(0.26-1)	**0.047**
Pietenpol subtype			
Basal-like 1	58	2.48（0.54-11.38）	0.23
Basel-like 2	38	2.49（0.72-8.64）	0.14
Immunomodulatory	100	0.43（0.16-1.16）	0.087
Mesenchymal	73	1.76（0.61-5.15）	0.29
Mesenchymal stem-like	19	-	-
Luminal androgen receptor	83	0.46(0.21-1.03)	0.052
Systemically untreated patients			
Include	382	0.52(0.33-0.82)	**0.0043**
Exclude	473	0.65(0.44-0.95)	**0.026**

3.4 Relationship analysis between PECAM-1 expression and immune

Next, we analyzed the correlation between PECAM-1 expression levels and six types of immune infiltrating cells in TMER. The results indicated that PECAM-1 expression had a significant negative correlation with tumor purity in breast cancer. As shown in Figure 4, PECAM-1 is a key factor immune infiltration in breast cancer. PECAM-1 expression was significantly correlated with the infiltration levels of B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils and dendritic cells. In the basal-like subtype, PECAM-1 expression was positively correlated with infiltrating levels of B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, dendritic cells. Similarly, in luminal subtypes, PECAM-1 expression levels were also positively correlated to the six immune infiltrating cells. In Her2 subtype, there were positive correlations with infiltrating CD8+ T cells, CD4+ T cells, macrophages, neutrophils, dendritic cells.

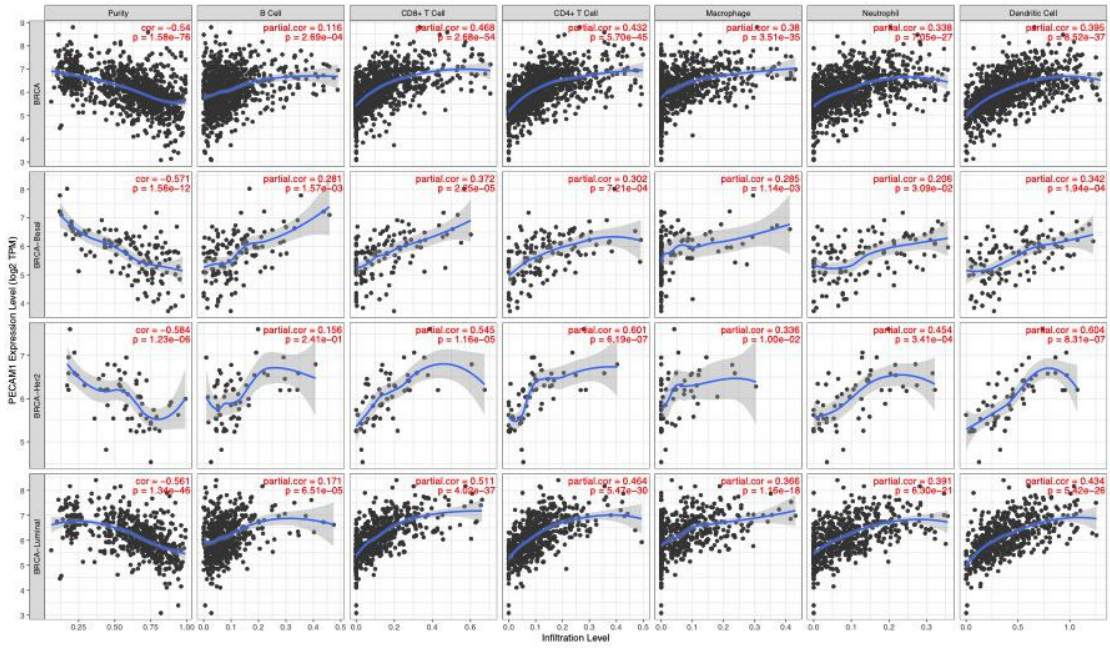

Figure 4. Correlation of PECAM-1 expression with immune infiltration level in the TIMER database. (A)PECAM-1 expression was significantly negatively related to tumor purity and significantly positively correlated with infiltrating levels of B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells in BRCA. (B) PECAM-1 expression was significantly negatively related to tumor purity and was significant positively correlated with infiltrating levels of B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells in BRCA-Basal. (C)PECAM-1 expression was significantly negatively related to tumor purity and was significantly positively correlated with infiltrating levels of CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells in BRCA-Her2. (D) PECAM-1 expression was significantly negatively related to tumor purity and was significantly positively correlated with infiltrating levels of B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells in BRCA Luminal.

Discussion

Study has reported that the oncogenic role of PECAM-1. DeLisser H et al. have reported that anti-PECAM-1 antibody can inhibit the late-stage metastatic progression of tumors, and the antimetastatic activity is mediated specifically by its binding to PECAM-1 expressed on vascular endothelial cells[5]. And previous studies also have shown that PECAM-1 is associated with metastasis and progression of solid tumors. It is noteworthy that the above studies are based on the fact that PECAM-1 is an endothelial cell marker which plays an important role in neovascularization in the tumor microenvironment, and that neovascularization is only one of the characteristics of tumor progression. This may serve as one of the molecular mechanisms by which PECAM-1 mediates such complex biological responses. The main reason for this inconsistency was attributed to the fact that our study analyzed the expression of PECAM-1 at the overall level. Additionally, the differences between our study using a cancer patient cohort and previous studies using animal models will require more comprehensive and precise studies in the future to explain tumor development. As indicated by this report and our findings, it is worth noting that PECAM-1 may be a tumor suppressor in different contexts.

The tumor microenvironment (TME) contains various cells. Immune cells in the TME can affect patient's survival. Our results revealed the PECAM-1 expression has strong negative correlation with tumor purity in TMER database. Taken together, these results suggest PECAM-1 mRNA levels could reflect lymphocyte infiltrations and PECAM-1 plays an important role in the regulation and recruitment of immune infiltrating cells in breast cancer, which may ultimately affect patient survival.

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References

[1] Topalian, S.L., Drake, C.G., Pardoll, D.M.,: Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell 2015, 27:450-461.

[2] Gumina, R.J., Kirschbaum, N.E., Rao, P.N., vanTuinen, P., Newman, P.J.,: The human PECAM1 gene maps to 17q23. Genomics 1996, 34:229-232.

[3] Berman ME, Xie Y, Muller WA: Roles of platelet/endothelial cell adhesion molecule-1 (PECAM-1, CD31) in natural killer cell transendothelial migration and beta 2 integrin activation. J Immunol 1996, 156:1515-1524.

[4] Baldwin HS, Shen HM, Yan HC, DeLisser HM, Chung A, Mickanin C, Trask T, Kirschbaum NE, Newman PJ, Albelda SM, et al.: Platelet endothelial cell adhesion molecule-1 (PECAM-1/CD31): alternatively spliced, functionally distinct isoforms expressed during mammalian cardiovascular development. Development 1994, 120:2539-2553.

[5] DeLisser H, Liu Y, Desprez PY, et al. Vascular endothelial platelet endothelial cell adhesion molecule 1 (PECAM-1) regulates advanced metastatic progression. Proc Natl Acad Sci U S A, 2010, 107(43): 18616-18621.