PECAM-1 is a prognostic-related biomarker and correlated with immune infiltrates in breast cancer

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Research

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Abstract

Background: Breast invasive carcinoma (BRCA) is the primary cause of cancer-associated mortality worldwide. Platelet endothelial cell adhesion molecule 1 (PECAM-1) has been implicated in a number of important biological processes. However, the interrelation between PECAM-1 gene expression, tumor immunity, and prognosis of patients with BRCA is unclear. The current study is aimed to analyze the expression and clinical significance of PECAM-1 in breast cancer and the correlation between PECAM-1 and immune infiltrations.

Methods: The differential expressions of PECAM-1 in breast cancer tissues and normal tissues were evaluated via exploring TIMER, Oncomine and UALCAN databases; the relationship within expression level of PECAM-1 and outcome of breast patients was evaluated via Kaplan-Meier plotter and PrognoScan; the methylation of PECAM-1 were investigated through the MethSurv platform; the correlation between PECAM-1 and tumor immune cell infiltration was further investigated by TIMER and GEPIA databases; the correlation between PECAM-1 and gene makers of immune infiltration were checked using TIMER and GEPIA.

Results: There were significant differences in PECAM-1 expression levels between breast invasive carcinoma tissues and adjacent normal tissues. Low PECAM-1 expression was significantly related to poor overall survival, progression-free survival and distant metastasis free survival in patients with breast cancer. In DNA methylation level, PECAM-1 hypermethylation in three CpG sites (cg20830094, cg00427260 and cg00879592) showed poor survival in breast cancer. PECAM-1 expression exhibited significantly positive correlations with the levels of infiltrated B cell, CD4+T cells, CD8+ T cells, neutrophils, macrophages, and dendritic cells in breast cancer. Furthermore, PECAM-1 expression is positively correlated with multiple immune gene makers in breast cancer.

Conclusion: The expression of PECAM-1 can serves as a prognostic biomarker in breast invasive carcinoma and is correlated with immune infiltrates.

Introduction

Breast cancer is the most common malignancy in women and remain the second cancer-related death worldwide[1]. Treatments have progressed substantially over the past years based on systemic and multidisciplinary treatment, while the overall outcomes remain rather unsatisfactory[2], immunocytes infiltrated in tumors are most likely to be used as drug targets for improving survival. In recent years, 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[3]. Therefore, 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[4]. PECAM-1 is an adhesion molecule expressed

by vascular endothelial cells, platelets, monocytes, neutrophils, natural killer cell and naive T lymphocytes[5-8]. PECAM-1 has been implicated in a number of important biological processes, including vascular development[9], leukocyte emigration at sites of inflammation[10, 11], T cell activation[12, 13], platelet aggregation and homeostasis[14, 15], and the maintenance of vascular endothelial barrier function[16]. What's more, there is evidence that PECAM-1 play an important role in human tumor angiogenesis[17-19]. Previous studies have demonstrated that treatment with blocking antiPECAM-1 antibodies inhibits cytokine- and tumor-induced angiogenesis in various animal models[17, 18]. Whether PECAM-1 gene expression in breast invasive carcinoma tissues are 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, including ONCOMINE, UALCAN, PrognoScan and Kaplan-Meier Plotter, and we investigated the DNA methylation results and their prognostic values of PECAM-1 via the MethSurv platform in breast cancer. We then explored the potential relationships between PECAM-1 expression and immune infiltration levels using the TIMER and GEPIA databases. Our findings indicate that PECAM-1 influences the prognosis of patients with breast cancer, probably via its interaction with infiltrating immune cells.

Oncomine database analysis

The mRNA expression of PECAM-1 in various types of cancer were identified in the Oncomine database (<https://www.oncomine.org/resource/login.htm>)[20]. The threshold was a p-value of 0.001, a fold change of 1.5, a top 10% gene ranking, respectively.

UALCAN Database Analysis

UALCAN (<http://ualcan.path.uab.edu/>) is an online tool for analyzing cancer transcriptome data[21]. The "CPTAC analysis" module of UALCAN provides protein expression analysis option using data from Clinical Proteomic Tumor Analysis Consortium (CPTAC) Confirmatory/Discovery dataset[22]. The comparison of PECAM-1 protein expression between breast cancer tissues and normal tissue was examined in UALCAN.

Prognostic values of the DNA methylation of PECAM-1

We used the DNA methylation result of PECAM-1 and corresponding survival analysis were performed via the MethSurv platform, an web portal providing univariable and multivariable survival analysis based on DNA methylation biomarkers using [TCGA \(The Cancer Genome Atlas\)](https://biit.cs.ut.ee/methsurv/) data(<https://biit.cs.ut.ee/methsurv/>)[23]. We verified the DNA methylation results and prognostic values of PECAM-1 in breast cancer.

PrognoScan database analysis

The Prognoscan database (www.prognoscan.org/) was used to evaluate PECAM-1 expression and survival in various types of cancers[24]. The threshold was an adjusted Cox p-value of < 0.05.

Kaplan-Meier plotter database analysis

Kaplan-Meier Plotter (<https://kmplot.com/>) was applied to assess the prognostic value of PECAM-1. Grouped according to the median expression of PECAM-1 (high vs low expression), all patients were analyzed for overall survival (OS), progression-free survival (PFS) and distant metastasis free survival(DMFS), and Kaplan-Meier was used to draw a survival chart[25].

TIMER database analysis

TIMER is a comprehensive website for the automatic analysis and visualization of association between immune infiltrate levels and a series of variables (<https://cistrome.shinyapps.io/timer/>)[26]. We assessed the correlation of PECAM-1 expression with the abundance of six kinds of immune cells (CD4 + T cells, CD8 + T cells, B cells, neutrophils, dendritic cells and macrophages) in breast cancer by the TIMER algorithm. Then, we also explored the prognostic value of PECAM-1 in BRCA patients with different abundance of immune cells. In addition, we exploited the correlation module to estimate the correlation of PECAM-1 with the markers of T cells (general), CD8 + T cells, B-cells, CD8 + T cells, neutrophils, monocytes, tumor-associated macrophages (TAM), M1 cells, M2 cells, dendritic cells, NK cells, Th1 cells, Th2 cells, Treg cells in breast cancer.

Gene correlation analysis in GEPIA

Gene Expression Profiling Interactive Analysis (GEPIA) (<http://gepia.cancerpku.cn/index.html>) was used to find the significant correlation of PECAM-1 expression with a lymphocyte-specific immune recruitment (LYM) metagene signature[27]. Gene expression correlation analysis was performed on The Cancer Genome Atlas (TCGA) expression data. The LYM attractor metagene evaluated by Cheng WY et al which consists mainly of lymphocyte-specific genes with prominent presence of PTPRC (CD45), CD53, LCP2 (SLP-76), LAPTM5, DOCK2, IL10RA, CYBB, CD48, ITGB2 (LFA-1), and EVI2B[28]. The LYM attractor metagene hints about the underlying immune mechanism, which could be valuable towards generating hypotheses for potential immunotherapies. In addition, the LYM metagene was a part of the winning prognostic model in the Sage Bionetworks DREAM breast cancer prognosis challenge[29].

Results

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). Meanwhile, PECAM-1 expression was lower in cancer types, including bladder, lung, sarcoma, melanoma, ovarian, 1 date set of central nervous system, kidney, pancreatic cancer, 2 date sets of leukemia. Higher

expression was observed in some types including 3 date sets of brain and central nervous cancer, colorectal cancer, esophageal cancer, 6 date sets of kidney cancer and leukemia, liver cancer, lymphoma and 1date set of pancreatic cancer. The details of PECAM-1 expression in multiple cancers are summarized in Supplementary Table 1

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).

The prognostic evaluation of PECAM-1 in breast cancer

We investigated the prognostic value of PECAM-1 for breast cancer in different databases. In PrognoScan, six datasets (GSE12276, GSE12093, GSE11121, GSE2034, GSE7378, GSE2990) including different stages of breast cancer revealed that low PECAM-1 expression was associated with poor prognosis. And only one cohort (GSE9893) showed low PECAM-1 expression was associated with good prognosis (Figure 3).

The Kaplan-Meier plotter database was used to further evaluate the prognostic role of PECAM-1 in breast cancer. Similarly, we found that high PECAM-1 expression was associated with favorable prognosis in breast cancer patients (Figure 4a; OS HR [95%CI] =0.7[0.56-0.87], p=0.0011; Figure4f; RFS HR [95%CI] =0.74[0.66-0.82], p= 4.2E-08; Figure4K; RFS HR [95%CI] =0.8[0.66-0.97], p=0.022). 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 OS in basal-like subtypes patients(Figure 4b;HR [95%CI] =0.49[0.29-0.82], p= 0.0052),whereas PECAM-1 was not related to prognosis in HER-2 positive, luminal A and luminal B subtypes(Figure 4c-4e; HR [95%CI] =0.71[0.37-1.36], p= 0.3, HR [95%CI] =0.74[0.5-1.09], p=0.13 and HR [95%CI] =0.54[0.54-1.09],p=0.14 respectively).High mRNA expression of PECAM-1 was correlated with better RFS in basal-like type(Figure 4G; HR [95%CI] =0.64[0.49-0.82],p=4E-04), luminal A type(Figure 4 i; HR [95%CI] =0.75[0.63-0.89],p=0.001) and luminal B type(Figure 4 j; HR [95%CI] =0.77[0.62-0.95],p=0.016). For DMFS, no significant difference was found between the high expression of PECAM-1 in the four intrinsic subtype patients (Figure 4l-4o). Therefore, it is conceivable that high expression of PECAM-1 may be a protective factor in breast cancer patients.

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 ($p<0.05$).

The prognostic values of DNA methylation of PECAM-1 expression.

As shown in the Figure 5a, we could clearly observe the distribution of four PECAM-1 CpG sites (cg20830994, cg00427260, cg00879592 and cg02459519), moreover, we investigated the expression and the prognostic values of these DNA CpG sites in patients with breast cancer. Kaplan-Meier plots demonstrated that high levels of methylation of the three CpG sites (cg20830994, cg00427260 and cg00879592; Figure5b-d) were significantly correlated with poor survival, however, there is no significance at the cg02459519 site for prognosis in breast cancer patients (Figure5e).

Relationship analysis between PECAM-1 expression and immune.

The amount of tumor infiltrating lymphocytes is an important indicator to predict the prognosis of cancer patients and the response to immunotherapy. Previous the studies have shown that the lymphocyte-specific immune recruitment (LYM) metagene signature is related to tumor infiltration by lymphocytes and associated with a favorable prognosis for breast cancer. Hence, it would be promising to analyze the correlation between PECAM-1 mRNA expression and LYM metagene signature. We found that there was a significant correlation between the PECAM-1 expression and LYM metagene signature in breast cancer patients in GEPIA (Figure 6). 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 7a, PECAM-1 is a key factor immune infiltration in breast cancer (tumor purity; $r=-0.54$, $p=1.58e-76$), including subtypes (Basal: $r=-0.571$, $p=1.56e-12$; Her2: $r=-0.584$, $p=1.23e-06$; Luminal: $r=-0.561$, $p=1.34e-46$). Furthermore, PECAM-1 expression was also significantly correlated with the infiltration levels of B cells($r=0.116$, $P=2.69e-04$), CD8+ T cells($r=0.468$, $p=2.68e-54$),CD4+ T cells($r=0.432$, $p=5.7e-45$), macrophages($r=0.38$, $p=3.51e-35$), neutrophils($r=0.338$, $p=7.05e-27$)and dendritic cells($r=0.395$, $p=8.25e-37$).In the basal-like subtype,PECAM-1 expression were positively correlated with infiltrating levels of B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, dendritic cells(Figure7b). Similarly, in luminal subtypes, PECAM-1 expression levels were also positively correlated to the six immune infiltrating cells (Figure 7d). In Her2 subtype, there were positive correlations with infiltrating CD8+ T cells, CD4+ T cells, macrophages, neutrophils, dendritic cells (Figure 7c).

Correlations analysis between PECAM-1 expression and immune markers

To further investigate the potential relationship between PECAM-1 and infiltrating immune cells, we evaluated the correlations between PECAM-1 and makers of immune cells in TIMER(Table2) and GEPIA (Table S2). These markers were used to characterize immune cells, including B cells, CD8+ T cells, M1/M2 macrophages, tumor-associated macrophages, monocytes, NK, neutrophils, DCs and the different functional T cells such as Th1, Th2, Tfh, Th17, Tregs and exhausted T cells in breast cancer. In TIMER,

after adjustments for tumor purity, the PECAM-1 expression level was significantly associated with makers of most immune cells, except for Th17 in BRCA(Table2). We further analyzed the correlations of PECAM-1 expression and the makers in GEPIA. We found that the results are similar to those of the TIMER analysis (Table S2). Hence, these results confirm that PECAM-1 expression in BRCA correlates with immune cell infiltration and high expression of PECAM-1 suggests that it could induce immunoreactivity in the breast cancer microenvironment.

Discussion

Here, we systematically analyzed the expression levels of PECAM-1 and the prognostic role of PECAM-1 mRNA as well as PECAM-1 methylation in breast cancer. For the first time, we found low expression of PECAM-1 mRNA in breast cancer tissues, and prognostic data from PrognoScan and Kaplan-Meier plotter indicated that low levels of PECAM-1 and PECAM-1 hypermethylation could predict poor survival in breast cancer. Moreover, the low levels of PECAM-1 were significantly correlated with poor prognosis in subtypes with basal-like, lymph node negative, grade 1, TP53 status and systemically treatments. These results indicated that PECAM-1 may be used as a novel prognostic biomarker in breast cancer.

Study has reported that the oncogenic role of PECAM-1. DeLisser H 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[30]. And previous studies also have shown that PECAM-1 is associated with metastasis and progression of solid tumors, including gastric cancer, lung cancer, and glioma cancer[31, 32]. 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. In addition, 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. Recent research demonstrated that high expression of PECAM-1 was predicted to better prognosis in renal clear cell carcinoma, but unfortunately the specific mechanism has not been studied in details[33]. 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. Among them, infiltrating immune cells account for a large proportion.[34] Infiltrated of immune cells in the tumor microenvironment plays an important function in the occurrence and development of tumors[35, 36]. Immune cells in the TME can affect patient's survival[37, 38]. Studies have demonstrated that PECAM-1 expressed by various immune cells and play a role in immune response[8, 39–43]. The major finding from this study is that PECAM-1 expression correlates diverse immune infiltration levels in breast cancer. The results revealed the PECAM-1 expression has strong negative correlation with tumor purity in TMER database. Furthermore, the

PECAM-1 expression level was positively correlated with the LYM signature and the infiltration level of B cell, CD8 + T cell, CD4 + T cell, macrophage, neutrophil and debris cell. The relationship between PECAM-1 expression and immune cells maker genes suggested that specific interactions between PECAM-1 and immune cell subtypes. 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. Recent researches have indicated that infiltrating lymphocytes are predictive for response to neoadjuvant chemotherapy and high level of infiltrating lymphocytes are associated with longer survival for patients with TNBC and HER-2 positive breast cancer[44, 45].

We must acknowledge that there are several inevitable limitations in our analysis. First, our study is based on the bioinformatics analysis of multiple databases and lacks in-vitro and in-vivo experimental validation. Future mechanistic studies at the cellular and molecular levels could confirm the role of PECAM-1 in the growth and progression of breast cancer and the relationship with the infiltration of immune cells in TME. Second, we could not prove that PECAM-1 affects patient survival through immune infiltration. Future prospective studies to focus on PECAM-1 expression and immune infiltration in cancer populations could help provide definitive answers.

Conclusions

In breast cancer, either low PECAM-1 expression or PECAM-1 hypermethylation is associated with poor prognosis. Moreover, high PECAM-1 expression potentially contributes to the regulation of B cells CD8 + T cells, CD4 + T cells, macrophages, neutrophils and dendritic cells. Hence, PECAM-1 probably plays an important role in the infiltration of immune cells, and could serve as a promising prognostic biomarker for breast cancer patients.

Abbreviations

PECAM-1, Platelet endothelial cell adhesion molecule 1; BRCA, Breast invasive carcinoma; TCGA, The Cancer Genome Atlas; TIMER, tumor immune estimation resource; CPTAC, Clinical Proteomic Tumor Analysis Consortium; GEPIA, Gene Expression Profiling Interactive Analysis; TILs, tumor-infiltrating; OS, overall survival; PFS, progression free survival; RFS, relapse-free survival; DMFS, distant metastasis-free survival; TAM, tumor-associated-macrophage; TME, tumor microenvironment; LYM, lymphocyte-specific immune recruitment; HR, hazard ratio.

Declarations

Ethical Statement

Our study did not require an ethical board approval because it did not contain human or animal trials.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Authors' contributions

Xianglong Duan and Jun Bai are responsible for the whole article design, Qingfang Yue is responsible for the manuscript writing and bioinformatics analysis, Fei Cao and Fei Wang are responsible for the proofreading and partial statistics. All authors read and approved the final manuscript.

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Tables

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
Basal-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

Table 2. Correlations between PECAM1 and gene makers of immune cells in TIMER.

Cell type	Gene maker	None			Purity		
		Cor	p-value		Cor	p-value	
Cell (general)	CD3D	0.534	5.82E-82	***	0.329	1.73E-26	***
	CD3E	0.559	1.54E-91	***	0.36	1.05E-31	***
	CD2	0.528	6.16E-80	***	0.331	7.75E-27	***
CD8+T cell	CD8A	0.529	3.52E-80	***	0.338	6.53E-28	***
	CD8B	0.447	4.02E-55	***	0.245	5.24E-15	***
Cell	CD19	0.405	1.38E-44	***	0.199	2.4E-10	***
	CD79A	0.447	4.87E-55	***	0.228	3.53E-13	***
Dendritic cell	CD86	0.443	4.89E-54	***	0.294	2.78E-21	***
	CD115(CSF1R)	0.525	8.75E-79	***	0.379	2.92E-35	***
Macrophage	CCL2	0.426	9E-50	***	0.283	9.67E-20	***
	CD68	0.42	3.16E-48	***	0.282	1.18E-19	***
	IL-10	0.408	2.77E-45	***	0.264	2.59E-17	***
Macrophage	INOS(NOS2)	0.271	6.55E-20	***	0.295	2.11E-21	***
	IRF5	0.237	1.5E-15	***	0.137	1.43E-05	***
Macrophage	COX2(PTGS2)	0.397	8.31E-43	***	0.269	6.63E-18	***
	CD163	0.376	2.51E-38	***	0.245	4.51E-15	***
Macrophage	VSIG4	0.425	1.38E-49	***	0.305	8.40E-23	***
	MS4A4A	0.558	7.27E-91	***	0.424	1.18E-44	***
	CD66b	0.008	7.79E-01		0.037	2.44E-01	
Macrophage	CD11b	0.346	2.58E-32	***	0.209	2.82E-11	***
	CCR7	0.504	7.4E-72	***	0.305	6.71E-23	***
Natural killer cell	KIR2DL1	0.233	4.89E-15	***	0.116	2.34E-04	***
	KIR2DL3	0.234	3.76E-15	***	0.12	1.45E-04	***
	KIR2DL4	0.202	1.33E-11	***	0.061	5.64E-02	
Natural killer cell	KIR3DL1	0.31	6.35E-26	***	0.178	1.48E-08	***
	KIR3DL2	0.268	1.7E-19	***	0.108	6.55E-04	***
	KIR3DL3	0.128	2.1E-05	***	0.04	2.11E-01	
Macrophage	KIR2DS4	0.231	8.42E-15	***	0.111	4.67E-04	***
	HLA-DPB1	0.574	1.56E-97	***	0.399	3.41E-39	***
	HLA-DQB1	0.374	6.91E-38	***	0.205	6.63E-11	***
Macrophage	HLA-DRA	0.519	1.02E-76	***	0.343	7.33E-29	***
	HLA-DPA1	0.543	2.2E-85	***	0.38	1.46E-35	***
	BDCA-1	0.561	4.68E-92	***	0.394	1.37E-38	***
Macrophage	BDCA-4	0.561	4.94E-92	***	0.477	1.48E-57	***
	CD11c	0.446	9.11E-55	***	0.295	2.38E-21	***
	T-bet	0.53	9.02E-81	***	0.34	2.91E-28	***
Macrophage	STAT4	0.549	1.58E-87	***	0.364	1.80E-32	***
	STAT1	0.142	2.26E-06	***	0.036	2.54E-01	
	IFN-g	0.323	3.95E-28	***	0.143	5.83E-06	***
Macrophage	TNF-a	0.061	4.31E-02	*	-0.04	2.07E-01	
	GATA3	-0.087	4.04E-03	**	0.074	1.93E-02	
	STAT6	0.205	6.83E-12	***	0.174	3.42E-08	***
Macrophage	IL-13	0.126	2.81E-05	***	0.052	1.04E-01	
	BCL6	0.157	1.7E-07	***	0.128	5.16E-05	***
	IL-21	0.206	4.93E-12	***	0.09	4.65E-03	***
Macrophage	STAT3	0.085	4.83E-03	**	0.056	7.81E-02	
	IL17A	0.116	1.14E-04	***	0.003	9.27E-01	
	FOXP3	0.305	4.16E-25	***	0.121	1.31E-04	***
Macrophage	CCR8	0.271	5.32E-20	***	0.14	9.57E-06	***
	STAT5B	0.244	2.27E-16	***	0.216	6.45E-12	***
	TGFb	0.545	4.38E-86	***	0.43	5.62E-46	***
Macrophage	PD-1	0.412	3.25E-46	***	0.203	1.10E-10	***
	CTLA4	0.336	1.67E-30	***	0.134	2.14E-05	***
	LAG3	0.199	2.72E-11	***	0.054	9.07E-02	
Macrophage	TIM-3	0.437	1.99E-52	***	0.3	4.32E-22	***
	GZMB	0.35	4.78E-33	***	0.152	1.41E-06	***

Figures

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 data 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. *** $p < 0.001$

Figure 3

Survival curves comparing high and low expression of PECAM-1 in breast cancer in PrognoScan. (a) RFS(n=204) in breast cancer cohort GSE12276. (b, c) DMFS(n=136) in breast cancer cohort GSE12093. (d, e) DMFS(n=200) in breast cancer cohort GSE11121. (f) DMFS(n=286) in breast cancer cohort GSE2034. (g) DFS (n=54) in breast cancer cohort GSE7378. (h) DMFS(n=125) in breast cancer cohort GSE2990. (i) DFS (n=156) in breast cancer cohort GSE9893. OS, overall survival; DMFS, distant metastasis-free survival; DFS, disease-free survival; RFS, relapse-free survival.

Figure 4

Survival curves comparing high and low expression of PECAM-1 in breast cancer in Kaplan-Meier Plotter. (a-e) OS of PECAM-1 in the subtype of breast cancer patients. (f-j) RFS of PECAM-1 in the subtype of breast cancer patients; (k-o) DMFS of PECAM-1 in the subtype of breast cancer patients. OS, overall survival; RFS, relapse-free survival; DMFS, distant metastasis-free survival.

Figure 6

The average expression of the LYM metagene signature in breast cancer samples from TCGA is shown relative to PECAM-1 mRNA.

Figure 7

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.

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