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Bioinformatics analysis of the clinical significance of HLA class II in breast cancer

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Abstract

Human leukocyte antigen (HLA) class II plays critical roles in antigen presentation and the initiation of immune responses. However, the correlation between the HLA class II gene expression level and the survival of patients with breast cancer is still under investigation. We analyzed microarray and RNA-Seq data of breast cancer from the cancer genome atlas (TCGA), genotype-tissue expression (GTEx) and Oncomine databases by using bioinformatics tools. The expression of the *HLA-DQA1, HLA-DQA2,* and *HLA-DQB2* genes was significantly upregulated in breast cancer. Higher expression levels of HLA class II genes in breast cancer, especially *HLA-DOB* and *HLA-DQB2*, were significantly associated with better overall survival. Furthermore, the expression of HLA class II genes was more closely associated with survival in breast cancer than in other cancer types. *CD48* coexpressed with both *HLA-DOB* and *HLA-DQB2* was also positively associated with the overall survival of breast cancer patients. The results indicated that HLA class II and *CD48* may enhance antitumor immunity, and their expression patterns may serve as potential prognostic biomarkers and therapeutic targets in breast cancer.

Abbreviations: CRC = colorectal cancer, DAVID = database for annotation, visualization and integrated discovery, GEPIA2 = gene expression profiling interactive analysis 2, GO = gene ontology, GTEx = genotype-tissue expression, HLA = human leukocyte antigen, HR = hazard ratio, OS = overall survival, STRING = search tool for the retrieval of interacting genes, TCGA = the cancer genome atlas.

Keywords: bioinformatics, breast cancer, *CD48*, HLA class II, oncoimmunology

1. Introduction

Breast cancer is the malignant tumor with the highest incidence among women, and the incidence has been on the rise.[1] Breast cancer is a systemic disease, and distant metastasis can occur at an early stage, so the mortality rate is also high. There are many therapies for breast cancer, including surgery, radiotherapy, chemotherapy, endocrine therapy, targeted therapy and immunotherapy.[2] Immunotherapy is a novel and promising therapy for breast cancer.[3]

Traditional concept of immune response was that endogenous antigen was combined with human leukocyte antigen (HLA) class I and presented to CD8 + T cells, while exogenous antigen was combined with HLA class II and presented to CD4 + T cells, and then the immune response was activated with the participation of costimulatory molecules. Tumor-associated antigens belonged to endogenous antigen, which was combined with HLA class I and presented to CD8 + T cells. Only HLA class I, not class II, were involved in anti-tumor immune response. However, the current research on immune response reveals that tumor cells can express HLA class II, which combine with their tumor-associated antigens and present them to CD4 + T cells to activate anti-tumor immune response, so HLA class II also play an important role in anti-tumor immune response.[4]

HLA class II is encoded by multiple gene loci, among which *HLA-DR*, *HLA-DP*, *HLA-DQ*, and encode classical HLA class II, forming heterodimer molecules and expressing on the surface of antigen presenting cells, while *HLA-DO* and *HLA-DM* encode non-classical HLA class II, which play a role in the binding process between intracellular antigens and HLA class II. Current research reveals that more solid tumor cells express HLA class II, which is closely related to the prognosis of tumor.[5,6] However, the results are not completely consistent in different tumors, and the application of HLA class II in tumor immunotherapy is still under study.

In order to clarify the role and clinical value of HLA class II in breast cancer, this study systematically analyzed the correlation between the expression level of HLA class II genes in breast cancer tissues and clinical results based on the public microarray and RNA-Seq database. The results are expected to provide important information for immunotherapy of breast cancer.

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The datasets generated during and/or analyzed during the current study are publicly available.

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2. Materials and Methods

2.1. Gene expression analysis

The expression levels of HLA class II genes in normal breast tissue and breast cancer tissue were analyzed by gene expression profiling interactive analysis 2 (GEPIA2) (http://gepia2.cancer-pku.cn),[7] which was established using microarray and RNA-Seq data from the cancer genome atlas (TCGA)[8] and genotype-tissue expression (GTEx) databases.[9] A total of 1085 breast cancer samples and 291 normal breast tissue samples were included in the TCGA and GTEx datasets.

2.2. Survival analysis

Kaplan–Meier survival curves were plotted to explore the correlation between gene expression and clinical outcome in patients with breast cancer by the Kaplan–Meier Plotter (http://kmplot.com/analysis/). The overall survival (OS) rate and hazard ratio (HR) estimation were also generated by GEPIA2. The patient samples were split into two groups (low vs. high expression) in GEPIA2 and Kaplan–Meier Plotter analysis.

2.3. OncoLnc tool

Cox coefficients of HLA class II genes and their coexpressed genes were generated to explore the association between gene expression and survival rates in breast cancer via OncoLnc (http://www.oncolnc.org).[10]

2.4. Coexpression gene analysis

Genes coexpressed with HLA class II were analyzed by the Oncomine[11] and the TCGA databases via cBioportal (http://www.cbioportal.org/).[12] Five breast cancer datasets were selected, including invasive breast carcinoma (TCGA, Pancancer Atlas) composed of 1084 breast carcinoma samples,[13] Loi Breast 3 composed of 77 primary breast carcinoma samples,[14] Ginestier Breast composed of 55 primary breast carcinoma samples,[15] Sorlie Breast 2 composed of 160 primary breast carcinoma samples[16] and Pollack Breast 2 composed of 41 primary breast carcinoma samples.[17] Genes coexpressed with both *HLA-DOB* and *HLA-DQB2* in breast cancer tissues were analyzed. The coexpressed genes were visualized in a Venn diagram (http://bioinformatics.psb.ugent.be/webtools/Venn/).

2.5. Gene ontology enrichment analysis

Gene ontology (GO) enrichment analysis was performed to determine the genes that coexpressed with both *HLA-DOB* and *HLA-DQB2* using the database for annotation, visualization and integrated discovery (DAVID; http://david.abcc.ncifcrf.gov/).[18] The categories of biological process, cellular component and molecular function were selected, and all options were set as defaults.

2.6. Statistical analysis

The HR and *P* value in survival analysis were generated by GEPIA2. The Cox coefficient and *P* value in Cox regression analysis were generated by OncoLnc. The GO enrichment analysis was conducted by DAVID. A *P* value < .05 or .01 was considered statistically significant.

2.7. Ethics statement

All datasets in the present study were downloaded from public databases. These public databases allowed researchers to download and analyze public datasets for scientific purposes and thus ethics approval was waived.

3. Results

3.1. Expression of some HLA class II genes increased in breast cancer tissue

The expression levels of 13 HLA class II genes in breast cancer from the TCGA were compared with normal breast tissue from the TCGA and GTEx datasets using GEPIA2. The expression of the *HLA-DQA1, HLA-DQA2,* and *HLA-DQB2* genes was significantly upregulated in breast cancer. There were no significant differences in the expression of *HLA-DRA, HLA-DRB1, HLA-DRB5, HLA-DPA1, HLA-DPB1, HLA-DQB1, HLA-DOA, HLA-DOB, HLA-DMA,* and *HLA-DMB* in breast cancer compared to normal breast tissues (Fig. 1).

3.2. Most high HLA class II mRNA expression levels were associated with good prognosis in patients with breast cancer

The survival analysis of the expression levels of 13 HLA class II genes in breast cancer was performed by the Kaplan–Meier Plotter. The OS between high and low expression levels of 13 HLA class II genes were displayed as a survival plot (Fig. 2), and the relative risk of patients with high versus low HLA class II gene expression levels was indicated by HR (Table 1). An HR < 1.0 indicated that patients with high expression of HLA class II genes had better OS.

3.3. Most HLA class II gene expression levels were correlated with survival in breast cancer

The mRNA expression levels of HLA class II genes were determined via OncoLnc, and the Cox regression results and the *P* value ranks for the 13 HLA class II genes in breast cancer are listed in Table 2. The expression of HLA class II genes in breast cancer was correlated with survival except for *HLA-DQA1, HLA-DQA2,* and *HLA-DMB*. Among the 13 HLA class II genes, the *P* value ranks of the *HLA-DOB* and *HLA-DQB2* genes had the highest *P* value rank and were more closely correlated with survival in breast cancer.

3.4. CD48 coexpressed with both HLA-DOB and HLA-DQB2 in breast cancer

We further analyzed the genes coexpressed with HLA class II to investigate the biological changes related to aberrant expression of HLA class II in breast cancer. We selected five datasets composed of breast cancer samples to analyze the genes coexpressed with HLA class II genes via Oncomine and TCGA for public microarray data of breast cancer. In the analysis of genes coexpressed with *HLA-DOB*, 15 genes were identified from the top 100 genes in each of the TCGA, Loi Breast 3 and Ginestier Breast datasets of breast cancer by their coexpression scores. Similarly, 13 genes were identified in the TCGA, Sorlie Breast 2 and Pollack Breast 2 datasets of breast cancer in the analysis of genes coexpressed with *HLA-DQB2* (Fig. 3). *CD48* was the only gene coexpressed with both *HLA-DOB* and *HLA-DQB2* (Table 3).

3.5. GO enrichment analysis revealed the association of CD48 coexpressed with both HLA-DOB and HLA-DQB2 with antigen binding, regulation of adaptive immune response and allergic reactions in breast cancer

To identify the mechanisms underlying the expression of HLA class II genes and *CD48*, GO enrichment analysis was conducted via DAVID. Six biological processes, 10 cellular constituents, and 3 molecular function terms were significantly enriched (Table 4). Biological functions related to the regulation

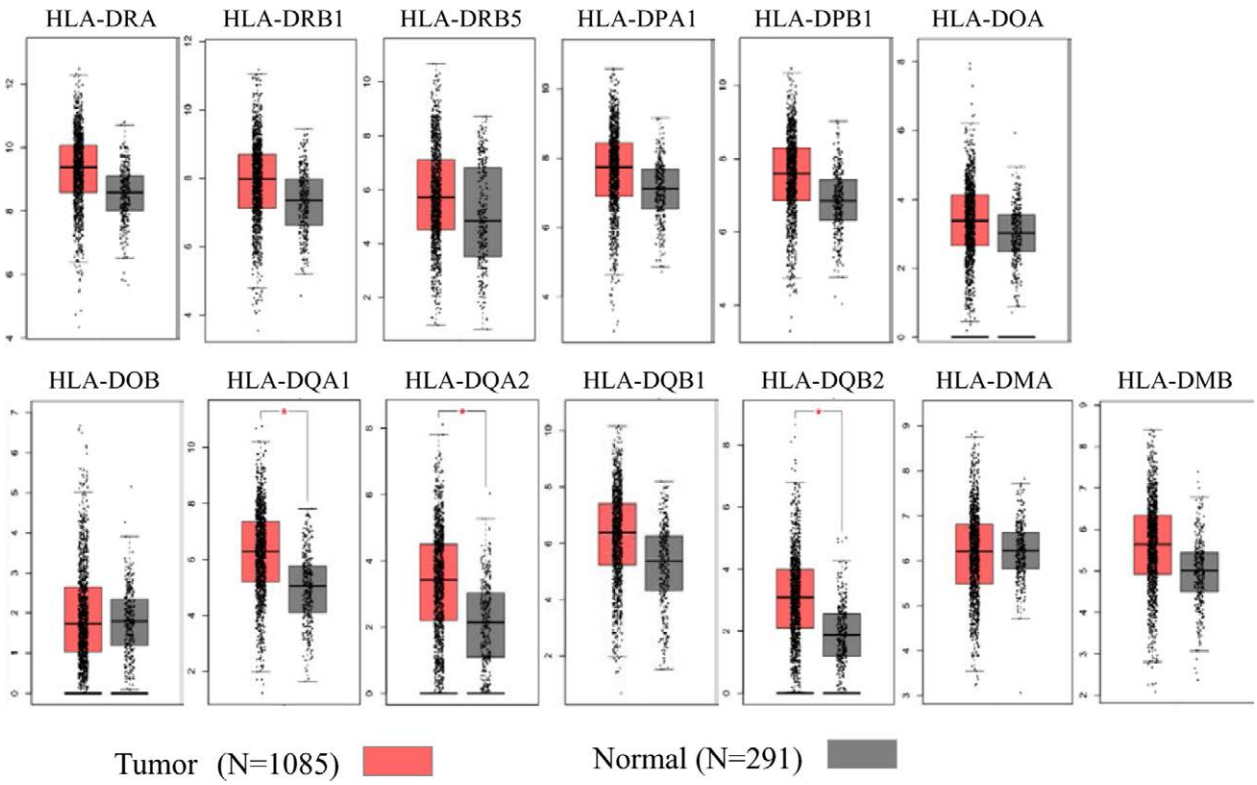

Figure 1. Expression levels of human leukocyte antigen (HLA) class II genes in breast cancer samples from the cancer genome atlas (TCGA) (N = 1085) were compared with those in samples of normal breast tissue from TCGA and the genotype-tissue expression (GTEx) (N = 291). The above results were obtained via gene expression profiling interactive analysis 2 (GEPIA2). The expression levels are shown on a $\log_2$ (TPM + 1) scale. *Indicates $P < .01$ between tumor and normal tissues.

of adaptive immune response, mast cell activation, T cell activation, defense response and antigen binding were the most enriched. *HLA-DOB, HLA-DQB2,* and *CD48* were entered into the search tool for the retrieval of interacting genes[19] for interaction network visualization. In the network, *CD74* was a molecule closely related to the HLA class, but *CD48* was indirectly related to HLA class II through *CD74* as a bridge (Fig. 4). The functional enrichment analysis results suggested that *CD48* may indirectly promote the antitumor immune response via HLA class II.

3.6. Expression of the CD48 positively associated with clinical outcome in patients with breast cancer

The expression of the *CD48* was significantly upregulated in breast cancer compared to normal breast tissue using GEPIA2 (Fig. 5A). High mRNA expression levels of the *CD48* in patients with breast cancer predicted a favorable prognosis by the Kaplan–Meier Plotter (Fig. 5B). The correlation between the gene expression of *CD48* in breast cancer and survival generated from Cox regression analysis via OncoLnc indicated that higher gene expression reduced the risk of death (Table 5).

4. Discussion

Almost all cancers express HLA class II, but the expression levels and their functions vary with cancer type. HLA class II affects the specific antitumor immune response and the prognosis of diseases.[4] This study demonstrated that the mRNA expression of the *HLA-DQA1, HLA-DQA2,* and *HLA-DQB2* genes was significantly upregulated in breast cancer. The mRNA expression of 11 genes out of 13 genes was positively correlated with the prognosis of breast cancer except *HLA-DQB1* and *HLA-DQA1*. Positive HLA class II expression in tumor cells was associated with better disease-free survival in patients who had lymph node metastasis in triple-negative breast cancer.[20] In skin melanoma, almost all HLA class II gene expression are upregulated, except *HLA-DPB2*, *HLA-DQA2*, *HLA-DQB1,* and *HLA-DOB*, and all the gene expression levels are positively correlated with long survival.[21] In addition, *CD48* coexpressed with both *HLA-DOB* and *HLA-DQB2* in breast cancer was associated with antigen binding, adaptive immune response and the inflammatory response. The mRNA expression of *CD48* increased significantly in breast cancer and was positively associated with OS in patients with breast cancer.

Previous studies have found that expression of the HLA class II pathway in triple-negative breast cancer tumor cells is associated with a good prognosis and infiltrating lymphocytes.[22] The correlation between HLA class II and prognosis has also been reported in other cancers: large B-cell lymphoma,[23] colorectal cancer (CRC),[24] and ovarian cancer.[25] These studies suggest that HLA class II plays a crucial role in tumor suppression. However, it was an inconsistency in the present study: the expression in breast cancer was upregulated but not correlated with OS. The reasons may be as follows: First, HLA class II is encoded by several different gene regions, and each coding product plays different roles in the process of antigen presentation. Even though some gene regions are upregulated, HLA class II antigen-processing machinery is defective, which leads to the dysfunction of stimulating antitumor immune response and cannot improve the prognosis of breast cancer.[4] Second, because the prognosis of breast cancer is affected by many factors, such as tumor size, stage, grade, histopathologic type, molecular type, etc., even though some HLA class II genes are upregulated and enhance the antitumor immune response, they are also affected by other adverse factors, which ultimately fail to improve the prognosis. Third, breast cancer is a highly heterogeneous malignant tumor,

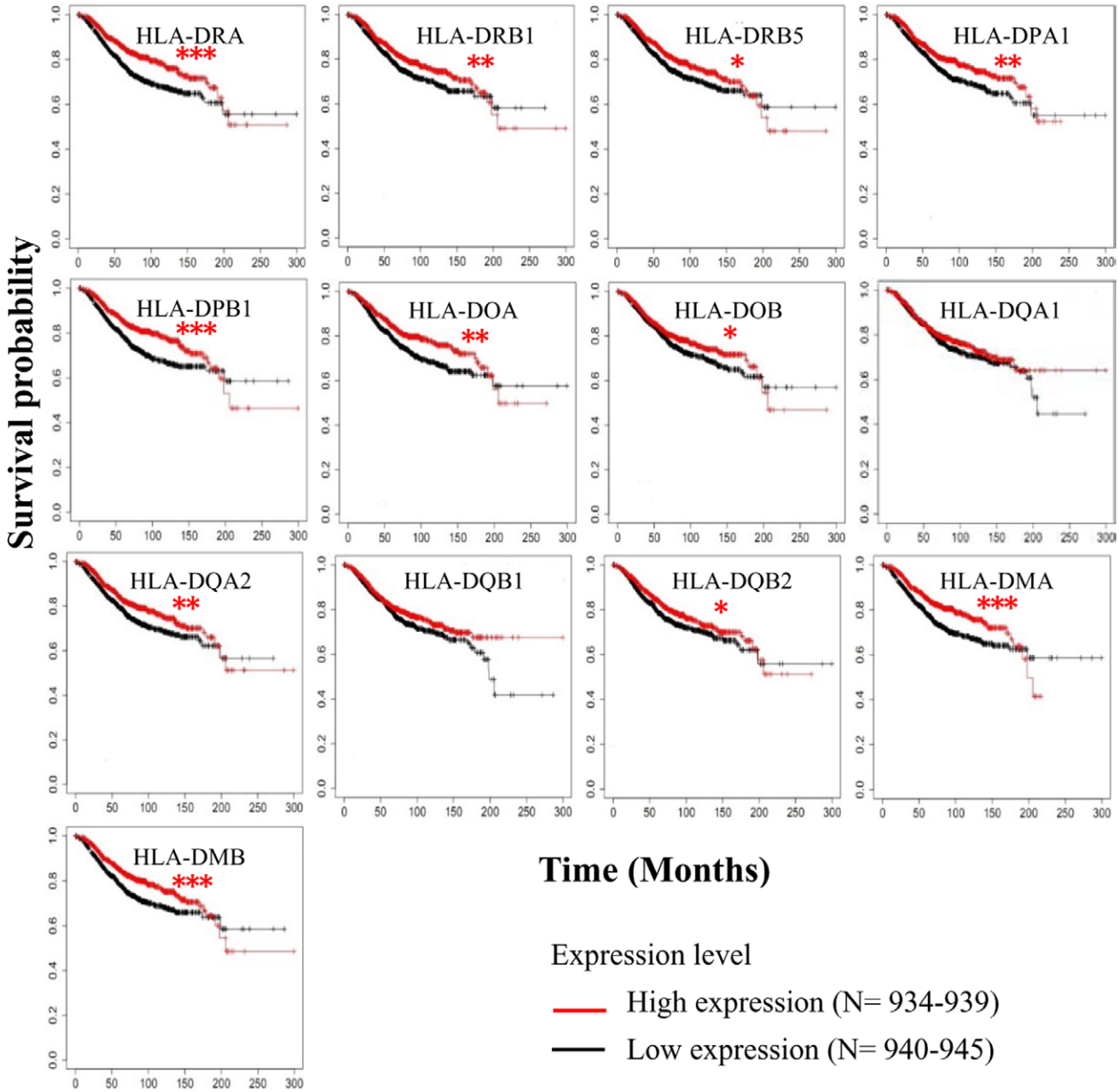

Figure 2. Effect of expression levels of HLA class II genes on overall survival of breast cancer. Survival analysis between the high and low expression groups of HLA class II genes in patients with breast cancer was performed using the Kaplan–Meier Plotter. Patients in the high expression group showed better overall survival. *Indicates a *P* value < .05, **indicates a *P* value < .01, ***indicates a *P* value < .001.

and an insufficient sample size or samples from different populations can easily lead to discrepant results. The sample size of GEPIA2 is different from that of the Kaplan–Meier Plotter, and the databases used by these two tools are not exactly the same. It is worth paying attention to which genes were not upregulated significantly in breast cancer but had a significant positive correlation with the prognosis of breast cancer because these genes can provide potential therapeutic targets, such as *HLA-DOB*. Upregulation of these genes can enhance the antitumor immune response and improve the prognosis of breast cancer. Genes whose expression is upregulated and positively correlated with prognosis have both potential therapeutic significance and prognostic value, such as *HLA-DQB2*. Therefore, the two types of HLA class II genes are of great significance in breast cancer.

According to the log-rank test, high expression of *HLA-DRA*, *HLA-DOB*, *HLA-DQB1*, *HLA-DQB2,* and *HLA-DMA* had a significant protective effect on the overall survival of patients with breast cancer, especially *HLA-DQB2*, which reduced the risk of death of patients with breast cancer by 41%. Cox regression analysis indicated that HLA class II was an independent protective factor for breast cancer except *HLA-DQA1* and *HLA-DQA2*. The mRNA expression levels of *HLA-DOB* and *HLA-DQB2* in breast cancer were relatively low, but their correlation ranked very high with breast cancer survival. Among the 15 common malignant tumors in the TCGA, they were the third most correlated with the OS of patients with breast cancer. *HLA-DOB* is inferior to skin cutaneous melanoma and ovarian serous cystadenocarcinoma, and *HLA-DQB2* is inferior to skin cutaneous melanoma and sarcoma in correlation rank. Moreover, the two genes had the largest absolute Cox coefficients, which indicated a great effect on the OS of breast cancer. To date, no other relevant research has been reported.

The CD48 is a glycosyl-phosphatidyl-inositol-anchored protein that belongs to the *CD2* subfamily, is expressed on the outer surface of all hematopoietic cell membranes in humans, has the strongest affinity for *CD244* and mainly mediates the immune

Table 1

Survival analysis and HR estimation of the expression of HLA class II genes in breast cancer via gene expression profiling interactive analysis 2 (GEPIA2).

Gene	HR	*p* value	Log rank *p* value
HLA-DRA	0.67	.018	.017
HLA-DRB1	0.73	.055	.053
HLA-DRB5	0.75	.075	.073
HLA-DPA1	0.78	.13	.13
HLA-DPB1	0.75	.085	.083
HLA-DOA	0.87	.41	.41
HLA-DOB	0.70	.033	.032
HLA-DQA1	0.79	.15	.15
HLA-DQA2	0.83	.26	.25
HLA-DQB1	0.66	.011	.01
HLA-DQB2	0.59	.0018	.0016
HLA-DMA	0.70	.03	.029
HLA-DMB	0.84	.30	.30

GEPIA2 = gene expression profiling interactive analysis 2, HLA = human leukocyte antigen, HR = hazard ratio.

Table 2

Correlation of HLA class II gene expression with survival in breast cancer generated from Cox regression analysis via OncoLnc.

Gene	Cox coefficient	*p* value	FDR corrected	Rank	Median expression	Mean expression
HLA-DRA	−0.191	.029	0.313	1525	11992.61	15710.87
HLA-DRB1	−0.174	.045	0.359	2067	3996.03	5483.97
HLA-DRB5	−0.197	.025	0.297	1374	972.55	1914.29
HLA-DPA1	−0.183	.038	0.342	1834	5003.01	6437.27
HLA-DPB1	−0.218	.015	0.257	948	3166.61	4039.74
HLA-DOA	−0.096	.029	0.662	7200	502.77	686.02
HLA-DOB	−0.273	.022	0.159	222	43.64	98.61
HLA-DQA1	−0.159	.071	0.419	2813	1498.35	2416.63
HLA-DQA2	−0.162	.065	0.406	2650	311.62	520.16
HLA-DQB1	−0.182	.038	0.342	1835	1658.76	2543.25
HLA-DQB2	−0.23	.085	0.229	613	111.52	215.15
HLA-DMA	−0.179	.042	0.353	1961	1094.54	1401.77
HLA-DMB	−0.131	.014	0.509	4445	880.54	1146.03

The Cox coefficient and *P* value were generated from multivariate Cox regressions. The FDR correction and the rank were calculated per cancer analysis per data type. A negative Cox coefficient indicated that the gene is a protective factor.
FDR = false discovery rate, HLA = human leukocyte antigen.

response and inflammatory reaction through antigen binding and receptor activation.[26,27] Inflammation is closely related to cancer and drives tumor initiation, growth, progression, and metastasis.[28] The present study found that *CD48* was the only gene coexpressed with both *HLA-DOB* and *HLA-DQB2*, and its expression in breast cancer was significantly higher than that in normal breast tissue and significantly correlated with better prognosis in breast cancer. *CD48* was an independent protective factor in OS via Cox regression analysis in breast cancer. At present, no similar findings on the relationship between *CD48* and breast cancer have been reported. However, the results are not always consistent in different cancers. High *CD48* expression can reverse acute myeloid leukemia immune evasion and activate NK cell function in vivo.[29] *CD48* can reduce the proliferation, migration, and invasion ability of CRC cells and significantly suppress CRC tumor growth in vivo.[30] However, *CD48* is an independent risk factor for poor outcome in glioma.[31]

CD48 may play a critical role in inflammation, allergic reactions and antitumor immune responses by promoting the interaction between activated lymphocytes and regulating the activation of T cells. This was consistent with our findings from GO enrichment analysis. This study demonstrated that the *CD48* molecule had no direct connection with HLA class II but was bridged to these genes through *CD74* by search tool for the retrieval of interacting genes. It may be that interferon-γ can regulate the expression of both *CD48* and *CD74*.[32,33]

The limitation of this study is that these results are derived from the analysis of several public databases, but there are differences in sample size, molecular subtypes, ethnicities and so on among the different databases. Different analysis tools can also lead to discrepancies in the results. Therefore, it is necessary to collect more clinical samples for further study to verify the value of HLA class II in the diagnosis, treatment and prognosis of breast cancer.

In summary, the expression levels of most HLA class II genes in breast cancer were positively correlated with the prognosis of breast cancer, which indicated that these HLA class II were involved in tumor antigen presentation and the antitumor immune response. The high expression level of *CD48* coexpressed with both *HLA-DOB* and *HLA-DQB2* and was also correlated with better prognosis of breast cancer. Therefore, HLA class II and *CD48* are potential prognostic markers and therapeutic targets of breast cancer. However, the underlying regulatory mechanisms of HLA class II and *CD48* in the antitumor immune response are still unclear and need further study.

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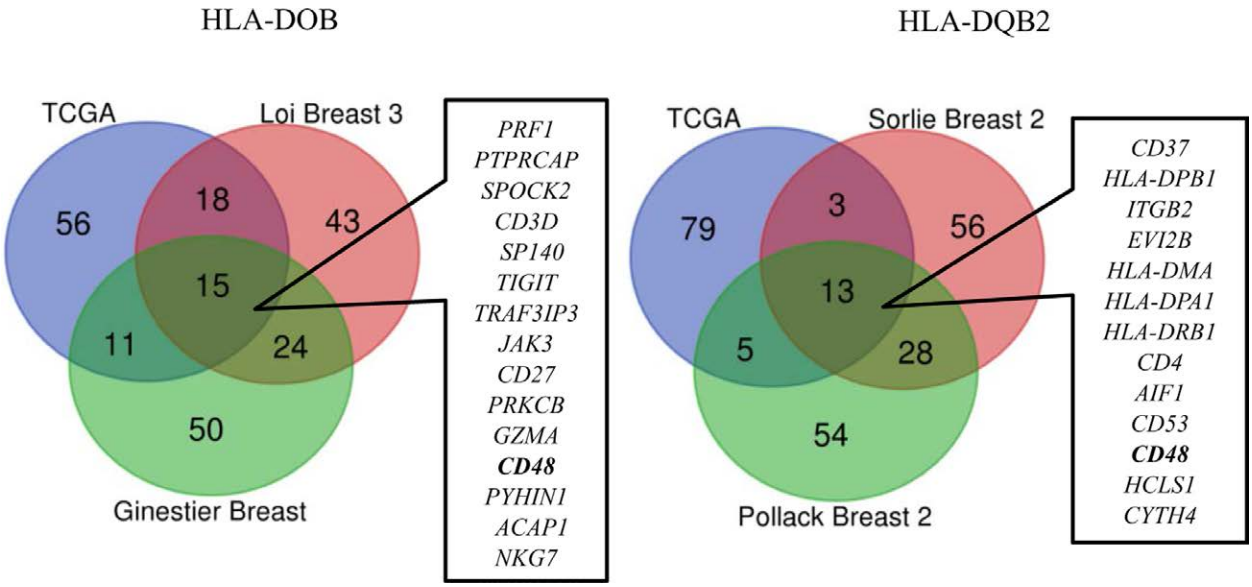

Figure 3. Venn diagram analysis of coexpressed genes in breast cancer. The left panel shows 15 genes coexpressed with *HLA-DOB* in breast cancer from the TCGA, Loi Breast 3 and Ginestier Breast datasets of breast cancer. The right panel shows 13 genes coexpressed with *HLA-DQB2* in breast cancer from the TCGA, Sorlie Breast 2 and Pollack Breast 2 datasets of breast cancer. TCGA = the cancer genome atlas.

Table 3

Genes coexpressed with *HLA-DOB* and/or *HLA-DQB2* in five datasets of breast cancer.

HLA class II	Gene
Coexpressed with ***HLA-DOB***	*PRF1, PTPRCAP, SPOCK2, CD3D, SP140, TIGIT, TRAF3IP3, JAK3, CD27, PRKCB, GZMA,* ***CD48****, PYHIN1, ACAP1, NKG7*
Coexpressed with ***HLA-DQB2***	*CD37, HLA-DPB1, ITGB2, EVI2B, HLA-DMA, HLA-DPA1, HLA-DRB1, CD4, AIF1, CD53,* ***CD48****, HCLS1, CYTH4*
Coexpressed with both **HLA-DOB** and **HLA-DQB2**	***CD48***

HLA = human leukocyte antigen.

Table 4

GO enrichment analysis of *CD48* via DAVID.

Gene	GO term and function	Fold enrichment	FDR	*p* value
CD48	**GOTERM_BP**		1.0	1.0
	GO:0002819, regulation of adaptive immune response	137.6		
	GO:0006952, defense response	250.6		
	GO:0042110, T cell activation	357.3		
	GO:0007165, signal transduction	14.5		
	GO:0045576, mast cell activation	2099.0		
	GO:0050900, leukocyte migration	137.6		
	GOTERM_CC			
	GO:0005886, plasma membrane	4.4		
	GO:0005887, integral component of plasma membrane	12.9		
	GO:0009897, external side of plasma membrane	85.6		
	GO:0016020, membrane	8.3		
	GO:0016021, integral component of membrane	3.5		
	GO:0031225, anchored component of membrane	161.3		
	GO:0043234, protein complex	44.2		
	GO:0045121, membrane raft	88.5		
	GO:0046658, anchored component of plasma membrane	650.9		
	GO:0070062, extracellular exosome	6.5		
	GOTERM_MF			
	GO:0003823, antigen binding	163.9		
	GO:0004872, receptor activity	77.8		
	GO:0005515, protein binding	1.9		

BP = biological process, CC = cellular component, DAVID = database for annotation, visualization and integrated discovery, FDR = false discovery rate, GO = gene ontology, MF = molecular function.

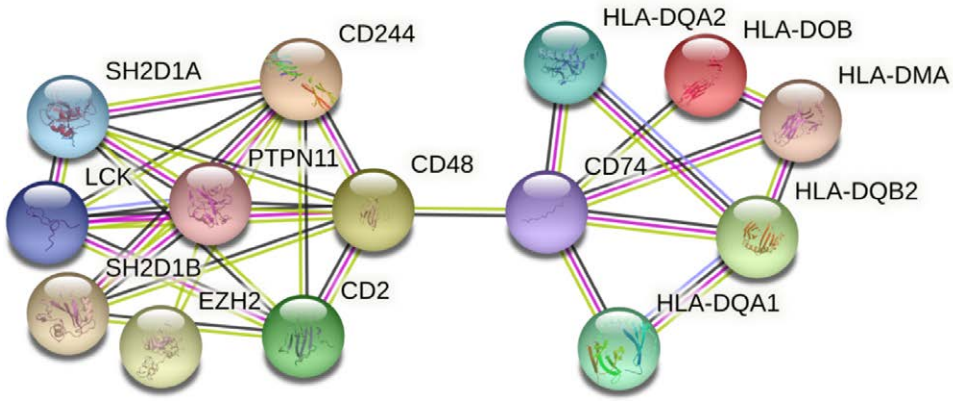

Figure 4. The interaction network of genes coexpressed with HLA class II was generated by STRING. *CD48* was indirectly related to HLA class II through *CD74* as a bridge. STRING = search tool for the retrieval of interacting genes.

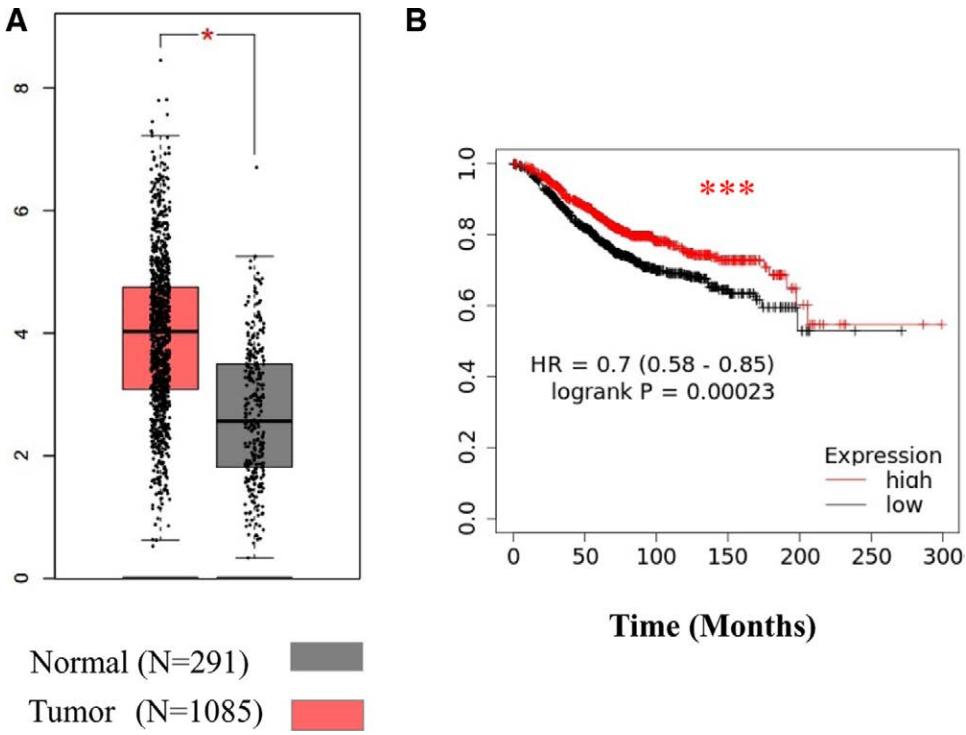

Figure 5. The effect of the *CD48* expression on overall survival (OS) in breast cancer. (A) The expression of the *CD48* in breast cancer was compared with that in normal breast tissue by GEPIA2. The expression levels are shown on a $\log_2$ (TPM + 1) scale. (B) Survival analysis of *CD48* in breast cancer was performed by the Kaplan–Meier Plotter. Patients in the high *CD48* expression group showed better OS. *Indicates a $P < .05$ between tumor and normal tissues, ***indicates a P value < .001. GEPIA2 = gene expression profiling interactive analysis 2.

Table 5

Correlation of *CD48* with survival in breast cancer generated by Cox regression analysis via OncoLnc.

Gene	Cox coefficient	*p* value	FDR corrected	Rank	Median expression	Mean expression
CD48	–0.194	0.026	0.30	1416	219.94	353.16

FDR = false discovery rate.

Author contributions

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