Bioinformatic analysis of the role of solute carrier-glutamine transporters in breast cancer

Xin Zhao[1,2,3#], Liang Jin[1,2#], Yujie Liu[1,2], Zhenzhen Liu[3], Qiang Liu[1,2]

[1]Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China; [2]Breast Tumor Center, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China; [3]Department of Breast Disease, Henan Breast Cancer Center, The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, China

Contributions: (I) Conception and design: X Zhao, L Jin, Y Liu; (II) Administrative support: Z Liu, Q Liu; (III) Provision of study materials or patients: X Zhao, Y Liu; (IV) Collection and assembly of data: X Zhao, L Jin; (V) Data analysis and interpretation: X Zhao, L Jin; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Zhenzhen Liu. Department of Breast Disease, Henan Breast Cancer Center, The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou 450008, China. Email: zlyyliuzhenzhen0800@zzu.edu.cn; Qiang Liu. Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China; Breast Tumor Center, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, 107 Yanjiang West Road, Guangzhou, 510120, China. Email: liuq77@mail.sysu.edu.cn.

Background: Breast cancer (BC) is a highly heterogeneous disease. Solute carriers (SLCs) have been involved in the tumor progression of various cancer types. This study aimed to evaluate the role of these SLC-related glutamine transporters in the prognosis of BC patients by bioinformatics analysis.

Methods: This study examined the transcription and prognostic data for glutamine-related transporters in BC from Oncomine Database, which is currently the largest oncogene microarray database platform in the world. As well as Gene Expression Profiling Interactive Analysis (GEPIA), Kaplan-Meier (K-M), and cBioPortal online resources. The Tumor Immune Estimation Resource (TIMER) and GEPIA were also used to examine the relationship between SLCs and immune cell infiltration.

Results: The expression levels of *SLC1A5*, *SLC3A2*, *SLC7A5*, *SLC7A8*, and *SLC38A1* were higher in BC tissues than normal breast tissues, but the expression level of SLC6A14 was lower. The expression levels of *SLC7A5*, *SLC7A8*, *SLC6A14*, and *SLC38A2* were related to a later clinical tumor stage. In the K-M analyses, The K-M curves revealed that patients with high *SLC1A5* expression had a poor prognosis (OS HR =1.28, 95% CI: 1.06–1.54; P=0.01). The high expression of *SLC3A2* was significantly correlated with a poor prognosis (DMFS HR =1.19, 95% CI: 1.02–1.39; P=0.027). Increased *SLC7A5* mRNA levels and decreased *SLC7A8* mRNA levels were significantly associated with a poor prognosis in terms of OS, RFS, DMFS and PPS. The high expression of *SLC6A14* was significantly correlated with a poor prognosis (PPS HR =1.35, 95% CI: 1.07–1.7; P=0.011). The high expression of SLC38A1 was correlated with a better prognosis than low expression of *SLC38A1* (RFS HR =0.84, 95% CI: 0.76–0.93; P=0.00077; DMFS HR =0.78, 95% CI: 0.67–0.91; P=0.0013). The infiltration of immune cells and their marker genes were associated with *SLC1A5*, *SLC3A2*, *SLC7A5*, *SLC7A8*, *SLC6A14*, *SLC38A1*, and *SLC38A2* expression. *SLC7A5*, *SLC7A8*, *SLC38A1*, and *SLC38A2* have the potential to regulate polarization in tumor-associated macrophages.

Conclusions: *SLC7A5*, *SLC7A8*, *SLC38A1*, and *SLC38A2* may regulate the polarization of tumor-associated macrophages (TAMs). *SLC1A5*, *SLC3A2*, *SLC7A5*, and *SLC6A14* may be promising biomarkers for the BC diagnosis and may represent potential therapeutic targets for these patients.

Keywords: Solute carrier (SLC); breast cancer (BC); prognosis; bioinformatics; tumor-immune infiltration

Submitted May 07, 2022. Accepted for publication Jun 28, 2022.
doi: 10.21037/atm-22-2620
View this article at: https://dx.doi.org/10.21037/atm-22-2620

Introduction

Globally, breast cancer (BC) is the most common malignant tumor among women. Based on the latest global cancer burden data released by the International Agency for Research on Cancer of the World Health Organization, there will be 19.29 million new cases of cancer in the world in 2020, and 2.26 million new cases of BC worldwide; thus, BC will replace lung cancer as the world's most prevalent cancer (1). BC is a highly heterogeneous disease. With the development of precision medicine, the classification of metabolic subtypes in the BC microenvironment is gradually developing.

Glutamine is the most abundant free amino acid in the body and is involved in a series of pathways, such as energy generation, macromolecular synthesis, and signal transmission in tumor cells. Additionally, certain tumor growth is dependent on glutamine transport uptake, a phenomenon known as "glutamine addiction" (2). Based on the above characteristics, glutamine transporter may play a key target role in tumor progression. However, little is known about the role of glutamine transporter in the occurrence and development of breast cancer.

Recent studies have shown that amino acid transport and metabolic pathways are crucial in the proliferation and development of BC (3,4). Based on the exploration of human genomes, about 430 solute carriers (SLCs) have been identified and classified by several classification systems (5). Many SLCs have been shown to function physiologically to transport amino acids (6). Glutamine is the most abundant free amino acid in the body and is involved in a series of pathways, such as energy generation, macromolecular synthesis, and signal transmission by a specific carrier in tumor cells (7). The tumorigenesis and progression of the glutamine transporters involved in SLCs mainly include *SLC1A5*, *SLC3A2*, *SLC7A5*, *SLC7A8*, *SLC6A14*, *SLC38A1*, and *SLC38A2*. However, further bioinformatics analyses of BC remain to be performed. A study has shown that amino acid transporter-mediated metabolic reprogramming is essential for the aggressive characterization of BC (8). The importance of glutamine for the proliferation and growth of tumor cells, and the role of these glutamine transporters in the occurrence and development of a variety of cancers has been partially confirmed (9). Research has shown that the co-expression of 3 transporters (i.e., *SLC1A5*, *SLC7A5*, and *SLC3A2*) is related to the poor prognosis of patients, especially in high-proliferative estrogen receptor positive (ER^+)/luminal B subtype (10). Additionally, *SLC7A5* may become a neo-target spot chemotherapeutic in luminal subtype of BC (11). In low proliferative ER^+/luminal A subtype BC, the high expression of *SLC7A8* indicates a good prognosis (12). The high expression of *SLC6A14* promotes tumor cell proliferation in ER^+ BC (13). Additionally, inhibiting the expression of *SLC38A1* inhibits the growth of 4T1 cells (14). The increased expression of glutamine transporter SLC38A2 promotes a glutamine-dependent proliferative pathway and oxidative stress resistance, which suggests a poor prognosis for triple negative (TN) patients (15). However, no bioinformatics analyses have been published on the glutamine transporters of SLCs in BC.

In this study, we used various publicly available online databases to analyze the expression variations or copy numbers of thousands of genes published online. Additionally, the Gene Expression Profiling Interactive Analysis (GEPIA) online tool was used to examine the transcription and prognostic data of glutamine-related transporters of BC patients in the Oncomine databases and a gene expression profile interaction analysis was undertaken. The correlations between the SLCs and the infiltration of the immune cell markers were investigated using the Tumor Immune Estimation Resource (TIMER 2.0). We sought to understand the tumorigenesis and progression of the glutamine transporters involved in SLCs (i.e., *SLC1A5*, *SLC3A2*, *SLC7A5*, *SLC7A8*, *SLC6A14*, *SLC38A1*, and *SLC38A2*) to investigate their clinicopathological significance and predictive prognostic value for BC patients. We present the following article in accordance with the REMARK reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2620/rc).

Methods

Ethical statement

The study was conducted in accordance with the

Declaration of Helsinki (as revised in 2013).

Dataset Acquisition and Bioinformatics Analyses

All the RNA-seq transcriptome data and corresponding clinicopathologic information were obtained from publicly available datasets (Oncomine; GEPIA; Kaplan-Meier; cBioPortal). Additionally, the Gene Expression Profiling Interactive Analysis (GEPIA) online tool was used to examine the transcription and prognostic data of glutamine-related transporters of BC patients and a gene expression profile interaction analysis was undertaken. The correlations between the SLCs and the infiltration of the immune cell markers were investigated using the Tumor Immune Estimation Resource (TIMER 2.0).

Oncomine database

Oncomine (https://www.oncomine.org/resource/login.html) is currently the largest oncogene microarray database platform in the world. Oncomine possesses the most complete tumor gene mutation spectrum, gene expression, and relevant clinical data, and can be used to explore novel biomarkers or therapeutic targets for cancer. Oncomine microarray data sets were used to analyze the transcription levels of *SLC1A5*, *SLC3A2*, *SLC7A5*, *SLC7A8*, *SLC6A14*, *SLC38A1*, and *SLC38A2* in various types of cancer.

GEPIA online analysis

GEPIA is a web-based tool that provides fast and customizable functionality based on data from The Cancer Genome Atlas (TCGA) and the GenotypeTissue Expression (GTEx) (16). GEPIA has key interactive and customizable analytical functions, including differential expression, gene mapping, correlation, patient survival, similar gene detection, and dimension reduction analyses.

Survival analysis

Kaplan-Meier (K-M) plotter (http://kmplot.com/analysis) assesses correlations between genes (mRNAs, micro RNAs, and proteins) and survival outcomes in samples from 21 tumor types including, breast, ovarian, lung, and gastric cancer. Overall survival (OS), relapse-free survival (RFS), distant metastasis-free survival (DMFS), and post-progress survival (PPS) were used as prognostic indicators for BC patients based on the hazard ratios (HRs) with 95% confidence intervals (CIs) and log rank P values.

TCGA Data and cBioPortal

TCGA comprises both sequencing and pathological data for 30 different cancers (17). The breast invasive carcinoma (TCGA, PanCancer Atlas) data set, comprises data from 1084 cases and was selected for the further analysis of SLCs using cBioPortal (http://www.cbioportal.org/index.do). The genomic profiles included mutations, putative copy number alterations from the genomic identification of significant targets in cancer, mRNA expression Z scores (RNA-seq v.2 RSEM), and protein expression Z scores (reverse phase protein arrays). According to the cBioPortal's online instructions, a co-expression module was used to obtain the top 100 genes with the strongest correlations with SLC1A5. The top 100 genes with the strongest correlations with other SLCs were obtained in the same way. The web tool Venn (http://bioinformatics.psb.ugent.be/webtools/Venn/) was used to intersect these 700 genes for the subsequent analysis.

PPI network and functional enrichment analysis

The Search Tool for the Retrieval of Interacting Genes (STRING) database was used to retrieve known proteins and establish the protein-protein interaction network (PPI) (18). Functional Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using Database for Annotation, Visualization, and Integrated Discovery (DAVID) software (https://david.ncifcrf.gov) as described previously (19).

Infiltration of immune cells

TIMER is a web server for the comprehensive analysis of tumor infiltrating immune cells (20). The abundances of 6 immune infiltrates, including B cells, cluster of differentiation 4 positive ($CD4^+$) T cells, $CD8^+$ T cells, neutrophils, macrophages, and dendritic cells (DCs) were estimated by the TIMER2.0 algorithm. TIMER also allows the user to select any gene of interest and visualize the correlation between its expression and the level of immune infiltration of different cancer types (21).

Statistical analysis

The messenger ribonucleic acid (mRNA) expression levels

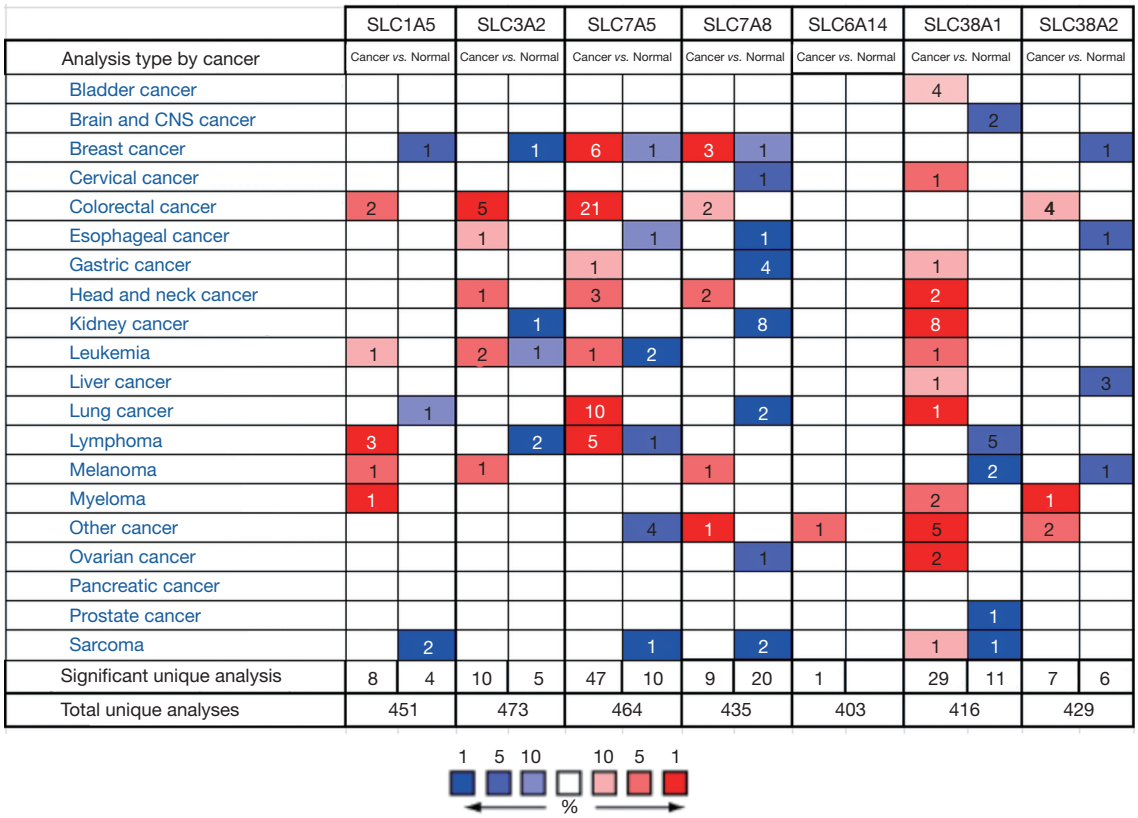


Figure 1 The transcription levels of SLCs in different types of cancers (Oncomine). SLCs, solute carriers.

of these SLCs in clinical cancer specimens were compared to those of normal controls, and the Student's *t* test was used to generate a P value. The cutoffs of the P value and fold change (FC) value were defined as 0.01 and 2, respectively. P<0.05 were defined as significant different.

Results

Transcriptional levels of SLCs in human BC

The main glutamine transporters involved in SLCs include *SLC1A5*, *SLC3A2*, *SLC7A5*, *SLC7A8*, *SLC6A14*, *SLC38A1*, and *SLC38A2*. These 7 glutamine transporter genes have been identified in mammalian cells. In summary, *SLC1A5*, *SLC3A2*, *SLC7A5*, *SLC38A1*, and *SLC38A2* are highly expressed in most tumors, while *SLC7A8* is lowly expressed in most tumors (see *Figure 1*).

The significant changes of SLC expression in transcription levels between different types of BC tissues and normal tissues showed that the mRNA expression level of *SLC1A5* was significantly downregulated in BC patients in the Finak Breast Statistics data set (22). In the Finak Breast Statistics data set, *SLC1A5* was more downregulated in invasive breast carcinoma tissues than normal tissue (FC: 7.248), as was SLC3A2 (FC: 8.545) (22). In TCGA breast data set, *SLC7A5* was overexpressed in invasive breast carcinoma (FC: 2.683) and invasive ductal breast carcinoma (FC: 3.443) (see *Table 1*). In the Curtis Breast Statistics (FC: 3.239) (23). In the Richardson Breast 2 Statistics data set, *SLC7A5* was more upregulated in ductal breast carcinoma tissue than normal tissue (FC: 3.620) (24). In the Finak Breast Statistics data set, *SLC7A8* was found to be highly expressed in invasive breast carcinoma (FC: 4.259) (22). SLC7A8 was found to be highly expressed in mixed lobular and ductal breast carcinoma (FC: 3.448) in TCGA, and mucinous breast carcinoma (FC: 2.323) in Curtis Breast data set versus normal samples (23). While in the Richardson Breast 2 Statistics data set, *SLC7A8* was found to be lowly expressed in ductal breast carcinoma (FC: 2.135) (24). The mRNA expression level of *SLC6A14* was significantly downregulated in BC patients in the Ma Breast 4 Statistics

Table 1 Significant changes of SLC expression in transcription levels between different types of BC tissues and normal breast tissues (Oncomine database)

Gene symbol	Types of BC tissues *vs.* normal breast tissues	Fold change	P value	*T*-test	Source and/or reference
SCL1A5	Invasive breast carcinoma	–7.248	2.97E-23	–23.570	Finak Breast Statistics (PMID: 18438415)
SLC3A2	Invasive breast carcinoma	–8.545	3.07E-32	–24.597	Finak Breast Statistics (PMID: 18438415)
SLC7A5	Medullary breast carcinoma	7.855	5.00E-16	13.504	Curtis Breast Statistics (PMID: 22522925)
	Invasive breast carcinoma	3.301	2.20E-7	6.984	Curtis Breast Statistics (PMID: 22522925)
	Invasive ductal breast carcinoma	3.239	5.80E-67	24.518	Curtis Breast Statistics (PMID: 22522925)
	Ductal breast carcinoma	3.620	1.45E-6	6.000	Richardson Breast 2 Statistics (PMID: 16473279)
	Invasive ductal breast carcinoma	3.443	1.65E-28	14.459	TCGA Breast Statistics
	Invasive breast carcinoma	2.683	3.06E-15	8.797	TCGA Breast Statistics
	Invasive breast carcinoma stroma	–4.573	5.17E-19	–13.846	Finak Breast Statistics (PMID: 18438415)
SLC7A8	Invasive breast carcinoma	4.259	1.07E-25	19.646	Finak Breast Statistics (PMID: 18438415)
	Mixed lobular and ductal breast carcinoma	3.448	1.55E-6	8.153	TCGA Breast
	Mucinous breast carcinoma	2.323	3.15E-14	10.145	Curtis Breast (PMID: 22522925)
	Ductal breast carcinoma	–2.135	6.72E-5	–4.450	Richardson Breast 2 Statistics (PMID: 16473279)
SLC6A14	Invasive ductal breast carcinoma epithelia	–55.571	6.94E-9	–10.383	Ma Breast 4 Statistics (PMCID: PMC2687710)
	Invasive ductal breast carcinoma stroma	–8.683	2.86E-6	–6.066	Ma Breast 4 Statistics (PMCID: PMC2687710)
	Ductal breast carcinoma in situ stroma	–6.807	2.83E-5	–4.924	Ma Breast 4 Statistics (PMCID: PMC2687710)
	Ductal breast carcinoma in situ epithelia	–21.600	2.37E-5	–6.107	Ma Breast 4 Statistics (PMCID: PMC2687710)
	Mixed lobular and ductal breast carcinoma	–6.465	2.39E-8	–8.280	TCGA Breast Statistics
	Invasive lobular breast carcinoma	–5.429	4.50E-13	–8.257	TCGA Breast Statistics
	Intraductal cribriform breast adenocarcinoma	–15.810	4.20E-5	–9.918	TCGA Breast Statistics
	Invasive breast carcinoma	–4.663	1.11E-11	–7.338	TCGA Breast Statistics
	Ductal breast carcinoma	–4.958	9.93E-5	–4.157	Richardson Breast 2 Statistics (PMID: 16473279)
SLC38A1	NA	NA	NA	NA	NA
SLC38A2	Invasive breast carcinoma stroma	–23.038	1.59E-28	–21.201	Finak Breast Statistics (PMID: 18438415)

NA, not available; TCGA, The Cancer Genome Atlas; SLCs, solute carriers; BC, breast cancer.

data set (25), TCGA Breast Statistics data set, and the Richardson Breast 2 Statistics data set (24). In the Ma Breast 4 Statistics data set, *SLC6A14* was more downregulated in the invasive ductal breast carcinoma epithelia (FC: 55.571), invasive ductal breast carcinoma stroma (FC: 8.683), ductal breast carcinoma in-situ stroma (FC: 6.807), ductal breast carcinoma *in situ* epithelia (FC: 21.600) tissues than the normal tissues. In TCGA Breast Statistics data set, *SLC6A14* was more lowly expressed in the mixed lobular and ductal breast carcinoma (FC: 6.465), invasive lobular breast carcinoma (FC: 5.429), and intraductal cribriform breast adenocarcinoma samples than the normal samples (FC: 15.810). In the Richardson Breast 2 Statistics data set, *SLC6A14* was significantly downregulated in patients with ductal breast carcinoma (FC: 4.958) (24). In the Finak's data set (22), *SLC38A2* was more lowly expressed in the ductal breast carcinoma samples (FC: 23.038) than the normal samples (see *Table 1*).

Expression of SLCs and their correlations with tumor stages in BC patients

The GEPIA data set (http://gepia.cancer-pku.cn/) was used to analyze the mRNA expression levels of *SLC1A5*, *SLC3A2*, *SLC7A5*, *SLC7A8*, *SLC6A14*, *SLC38A1*, and *SLC38A2* between BC tissues and normal tissues. The results showed that the expression levels of *SLC1A5*, *SLC3A2*, *SLC7A5*, *SLC7A8*, and *SLC38A1* were higher in the BC tissues than the normal tissues. Notably, the expression of *SLC7A5* and *SLC38A1* were more highly expressed in the BC tissues than the normal tissues. Compared to the normal tissues, *SLC6A14* and *SLC38A2* were lowly expressed in the BC tissues. Additionally, the expression level of *SLC6A14* was significantly lower in the BC tissues than the normal tissues (see *Figure 2*).

We also analyzed the expression of glutamine transporters (i.e., *SLC1A5*, *SLC3A2*, *SLC7A5*, *SLC7A8*, *SLC6A14*, *SLC38A1*, and *SLC38A2*) in different stages of BC. The results showed that the differential expression of the *SLC7A5*, *SLC7A8*, *SLC6A14*, and *SLC38A2* genes differed significantly based on the clinical stage of BC. There was no significant difference in relation to the *SLC1A5*, *SLC3A2* and *SLC38A1* genes (see *Figure 3*).

Association between the mRNA expression of SLC1A5, SLC3A2, SLC7A5, SLC7A8, SLC6A14, SLC38A1, and SLC38A2 and the prognosis of BC patients

To investigate the expression of *SLC1A5*, *SLC3A2*, *SLC7A5*, *SLC7A8*, *SLC6A14*, *SLC38A1*, and *SLC38A2* in relation to the prognosis of BC patients, we performed a prognosis analysis of *SLC1A5*, *SLC3A2*, *SLC7A5*, *SLC7A8*, *SLC6A14*, *SLC38A1*, and *SLC38A2* in BC patients using publicly available data sets (26). In the BC patients, the OS, RFS, DMFS, and PPS of the 2 groups with high expression and low expression levels of the target genes were used as prognostic indicators. The K-M curves revealed that patients with high *SLC1A5* expression had a poor prognosis (OS HR =1.28, 95% CI: 1.06–1.54; P=0.01). The high expression of *SLC3A2* was significantly correlated with a poor prognosis (DMFS HR =1.19, 95% CI: 1.02–1.39; P=0.027). Increased *SLC7A5* mRNA levels and decreased *SLC7A8* mRNA levels were significantly associated with a poor prognosis in terms of OS, RFS, DMFS and PPS. (*SLC7A5*: OS HR =1.64, 95% CI: 1.36–1.99; P=2.4e-07; RFS HR =1.58, 95% CI: 1.42–1.75; P<1e-16; DMFS HR =1.98, 95% CI: 1.69–2.32; P<1e-16; PPS HR =1.29, 95% CI: 1.02–1.62; P=0.032; *SLC7A8*: OS HR =0.77, 95% CI: 0.64–0.93; P = 0.0057; RFS HR =0.61, 95% CI: 0.55–0.67; P<1e-16; DMFS HR =0.67, 95% CI: 0.58–0.79; P=6e-07). The high expression of *SLC6A14* was significantly correlated with a poor prognosis (PPS HR =1.35, 95% CI: 1.07–1.7; P=0.011). The high expression of *SLC38A1* was correlated with a better prognosis than low expression of SLC38A1 (RFS HR =0.84, 95% CI: 0.76–0.93; P=0.00077; DMFS HR =0.78, 95% CI: 0.67–0.91; P=0.0013) (see *Figure 4*).

Network analysis of SLC co-expressed genes and identification of potential "Hub" genes with functions and pathways prediction

We used the cBioPortal online tool to analyze the genomic characteristics of the glutamine transporter-related genes (i.e., *SLC1A5*, *SLC3A2*, *SLC7A5*, *SLC7A8*, *SLC6A14*, *SLC38A1*, and *SLC38A2*) in invasive BC (cbioportal.org/) (27). About 8% of the patients with invasive breast carcinoma had the related SLC mutations (see *Figure 5A*). We then analyzed the correlations among related SLCs mRNA expression using the Pearson's correction in the cBioPortal online tool [mRNA Expression, RSEM (Batch normalized from Illumina HiSeq_RNASeqV2)].

We found positive correlations in the following related SLCs: *SLC3A2* with *SLC1A5* and *SLC7A5*; *SLC7A5* with *SLC3A2* and *SCL6A14*; *SLC7A8* with *SLC38A1*; *SLC6A14* with *SLC7A5*; *SLC38A1* with *SLC7A8* and *SLC38A2*; and *SLC38A2* with *SLC38A1*. Conversely, *SLC7A5* was found to be negatively correlated with *SLC7A8* (see *Figure 5B*). A Venn diagram was constructed of the top 100 frequently altered neighbor genes of each SLC, and a PPI analysis was conducted for those that were related to at least 2 or more SLCs at the same time (see *Figure 5C*). The functional annotation of the SLCs and the genes significantly associated with SLC alterations were predicted by analyzing GO and the KEGG in the DAVID database (https://david.ncifcrf.gov/summary.jsp). The GO analysis predicted the function of the target genes in relation to the following 3 aspects: biological process (BP), cellular component (CC), and molecular function (MF) (see *Figure 5D*). In relation to the BPs, the GO analysis indicated that the target genes were significantly enriched in the positive/negative regulation of transcription from RNA polymerase II promoter, cell division, and mitotic nuclear division. In relation to the CCs, the genes were significantly enriched in the nucleus and nucleoplasm. In relation to

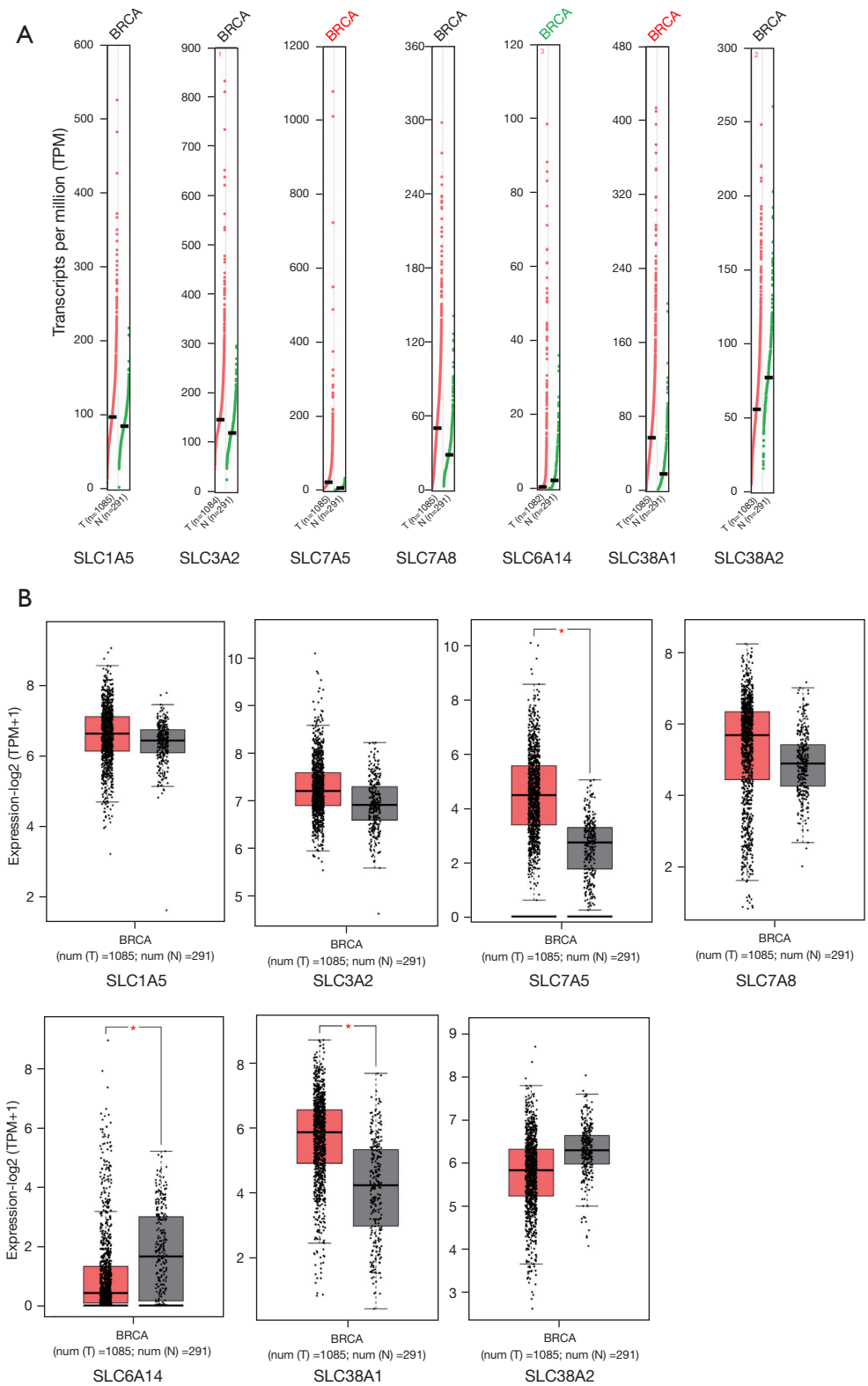


Figure 2 The expression of SLCs in BC [GEPIA; (A) scatter diagram; (B) box plot]. The "*" indicates a statistically significant difference between the two groups. SLCs, solute carriers; BC, breast cancer; BRCA, breast cancer.

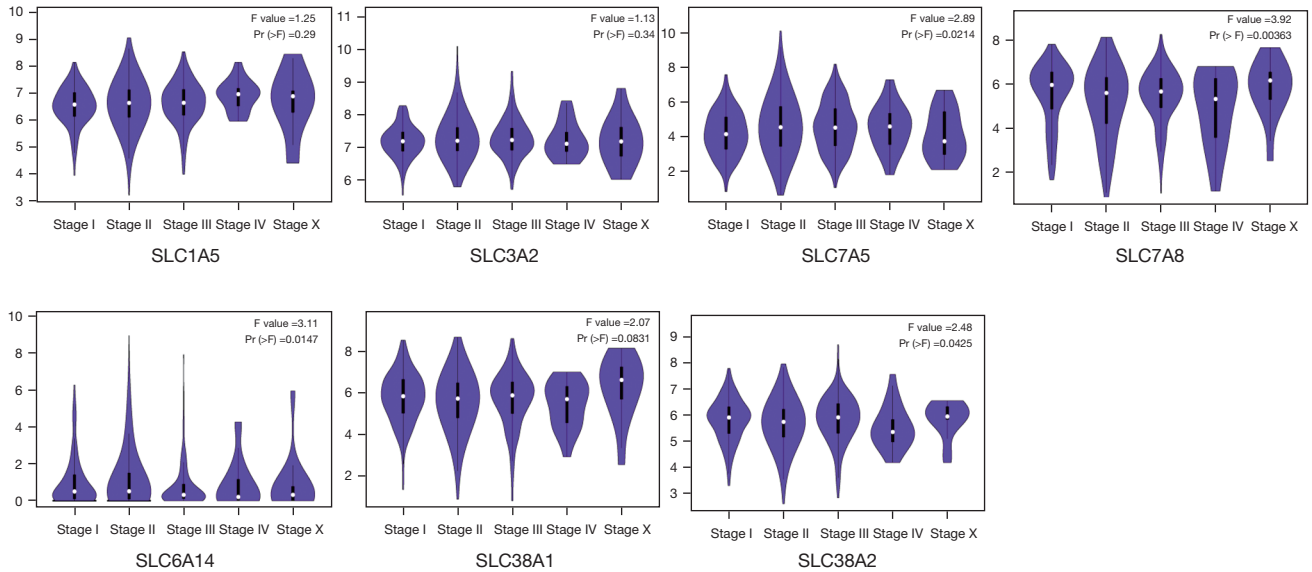


Figure 3 Correlation between SLCs expression and tumor stage in BC patients (GEPIA). SLCs, solute carriers; BC, breast cancer.

the MFs, the genes were significantly enriched in protein binding, deoxyribonucleic acid (DNA) binding, and metal-ion binding. The KEGG analysis defined the pathways related to the functions of the SLCs and their frequently altered neighbor genes, and the results showed that the cell-cycle pathway may significantly involve in the development of cancer (see *Figure 5E*).

Correlation of SLC expression with the infiltration of immune cells in BC and immune marker genes

Tumor-infiltrating lymphocytes are closely related to the chemotherapy reaction and survival prognosis of BC patients (28,29). To further explore the SLCs and immune cell infiltration in BC, we used the TIMER database to examine whether the expression of the related SLCs was correlated to the degree of immune cell infiltration in BC (see *Figure 6*). Among the seven SLC genes, we found that *SLC1A5* expression was correlated with the infiltration levels of $CD8^+$ T cells and macrophages, *SLC3A2* expression was correlated with the infiltration levels of neutrophils and DCs, *SLC7A5* expression was correlated with the infiltration levels of macrophages, neutrophils, and DCs, *SLC7A8* expression was correlated with the infiltration levels of B cells, macrophages, neutrophils, and DCs, *SLC6A14* expression was correlated with the infiltration levels of B cells, $CD8^+$ T cells, $CD4^+$ T cells, neutrophils, and DCs, *SLC38A1* expression was correlated with the infiltration levels of $CD8^+$ T cells and macrophages, and *SLC38A2* expression was correlated with the infiltration levels of $CD8^+$ T cells, $CD4^+$ T cells, macrophages, neutrophils, and DCs. These results strongly suggested that the expression of the related SLC genes is closely correlated with the degree of immune cell infiltration in BC, especially in macrophages, neutrophils, and DCs.

Macrophages, the most plastic cells in the hematopoietic system, commonly exist in various tissues of the body and play an important role in homeostasis, tissue repair, and disease (30). Tumor-associated macrophages (TAMs) are the key regulatory factors in the tumor microenvironment (31). I n the tumor microenvironment, under the influence of signals, such as chemokines, monocytes are actively recruited to the tumor site and differentiate into macrophages with specific phenotypes and functions. The expression of C-C motif chemokine ligand-2 (*CCL2*), interleukin (*IL*) 10, and *CD68* in TAMs, the interferon regulatory factor-5 of the M1 phenotype, and membrane-spanning 4-domains subfamily A4A (*MS4A4A*) and *CD163* of the M2 phenotype were significantly correlated with *SLC7A5* expression in BC. The expression of *CCL2* and *IL10* in TAMs, the interferon regulatory factor-5, nitric oxide synthase-2 (*NOS2*), and prostaglandin-endoperoxide synthase 2 (*PTGS2*) of the M1 phenotype, and *MS4A4A* and CD163 of the M2 phenotype were significantly correlated with *SLC7A8* expression in BC. The expression of *CCL2* in TAMs and interferon regulatory factor-5 of the

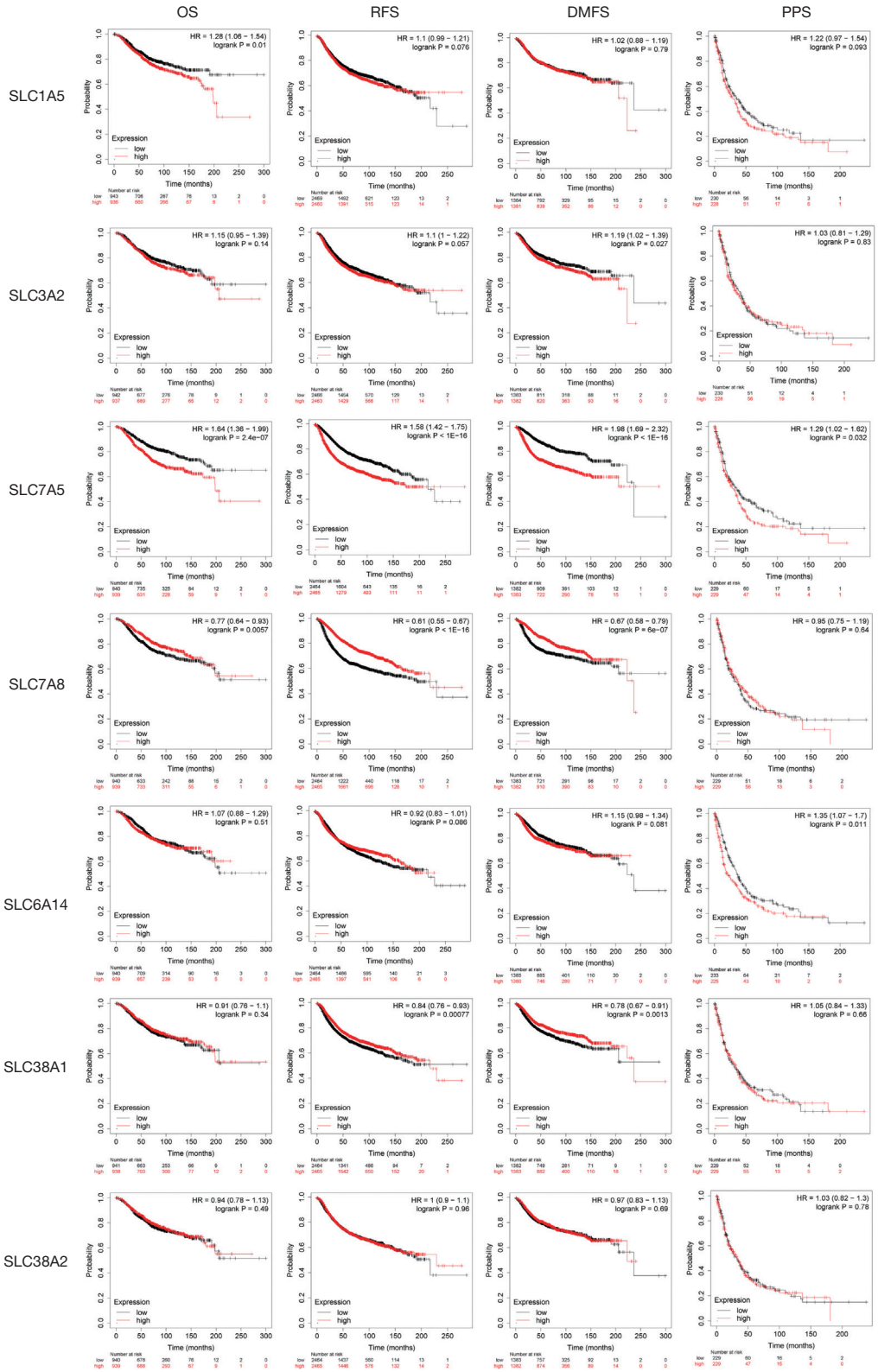


Figure 4 The prognostic value of the mRNA levels of SLCs in BC patients (K-M plots). SLCs, solute carriers; BC, breast cancer; OS, overall survival; RFS, relapse-free survival; DMFS, distant metastasis-free survival; PPS, post-progress survival.

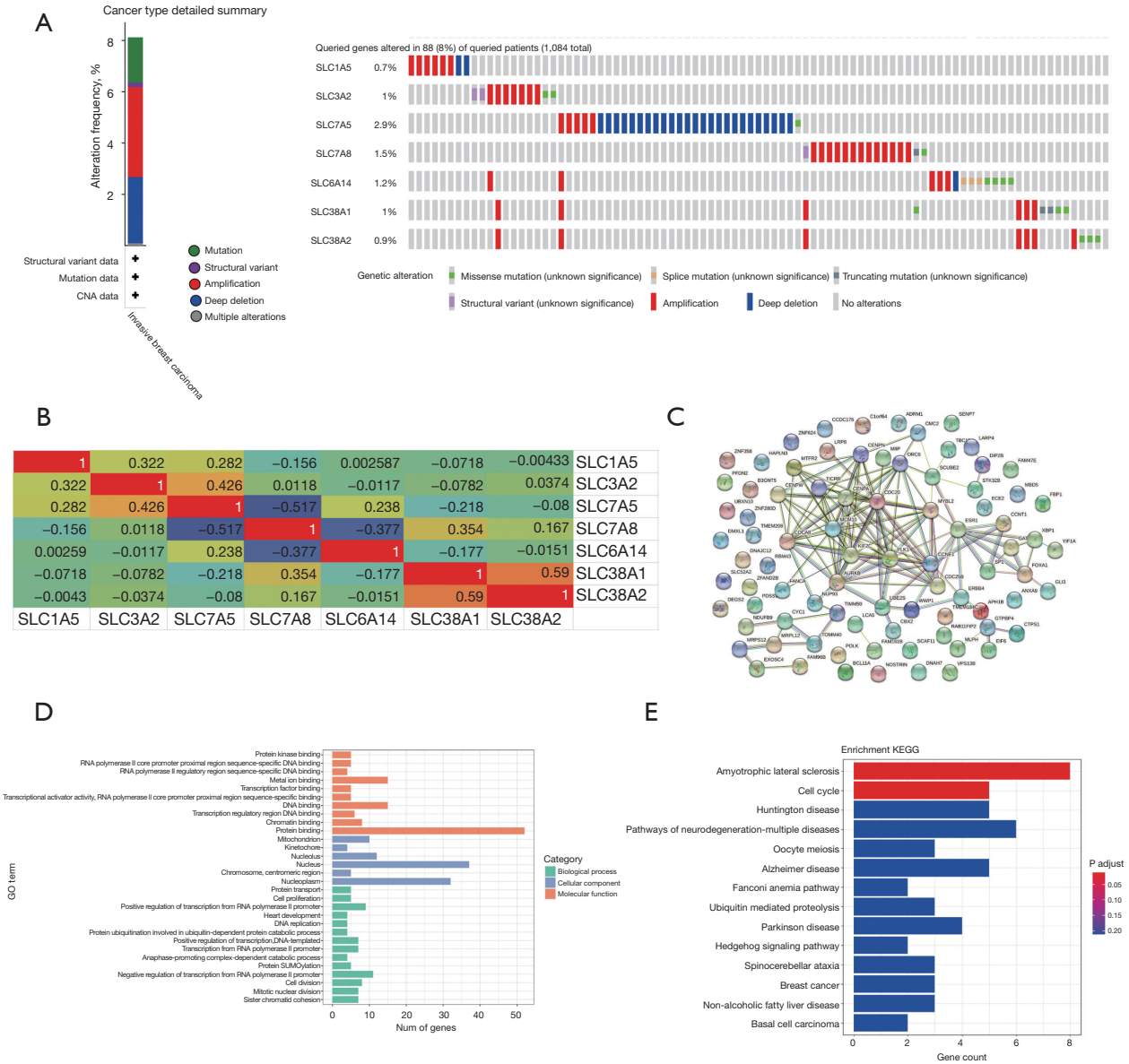


Figure 5 SLCs identified in the gene expression and mutation analysis of BC patients (cBioPortal). (A) SLC gene expression and mutation analysis of BC (cBioPortal). (B) Correlation between different SLCs in BC (cBioPortal). (C) Network analysis for SLCs and the 100 most frequently altered neighbor genes. (D) The functions of the SLCs and the genes significantly associated with the SLC alterations were predicted by an analysis of the GO by DAVID (https://david.ncifcrf.gov/summary.jsp). The GO enrichment analysis predicted the functional roles of the target host genes in relation to 3 aspects (i.e., BPs, CCs, and MFs). (E) The functions of SLCs and genes significantly associated with SLC alterations were predicted by the analysis of KEGG by DAVID tools (https://david.ncifcrf.gov/summary.jsp). SLCs, solute carriers; BC, breast cancer. BP, biological process; CC, cellular component; MF, molecular function; KEGG, Kyoto Encyclopedia of Genes and Genomes.

M1 phenotype were significantly correlated with *SLC38A1* expression in BC. The expression of *CD68* and *IL10* in TAMs, *NOS2* and *PTGS2* of the M1 phenotype, and *VSIG4*, *MS4A4A*, and *CD163* of the M2 phenotype were significantly correlated with *SLC38A2* expression in BC (see *Figure* 7). Thus, the glutamine transporter-related SLCs of *SLC1A5*, *SLC3A2*, *SLC7A5*, *SLC7A8*, *SLC6A14*, *SLC38A1*, and *SLC38A2* may affect the occurrence and development

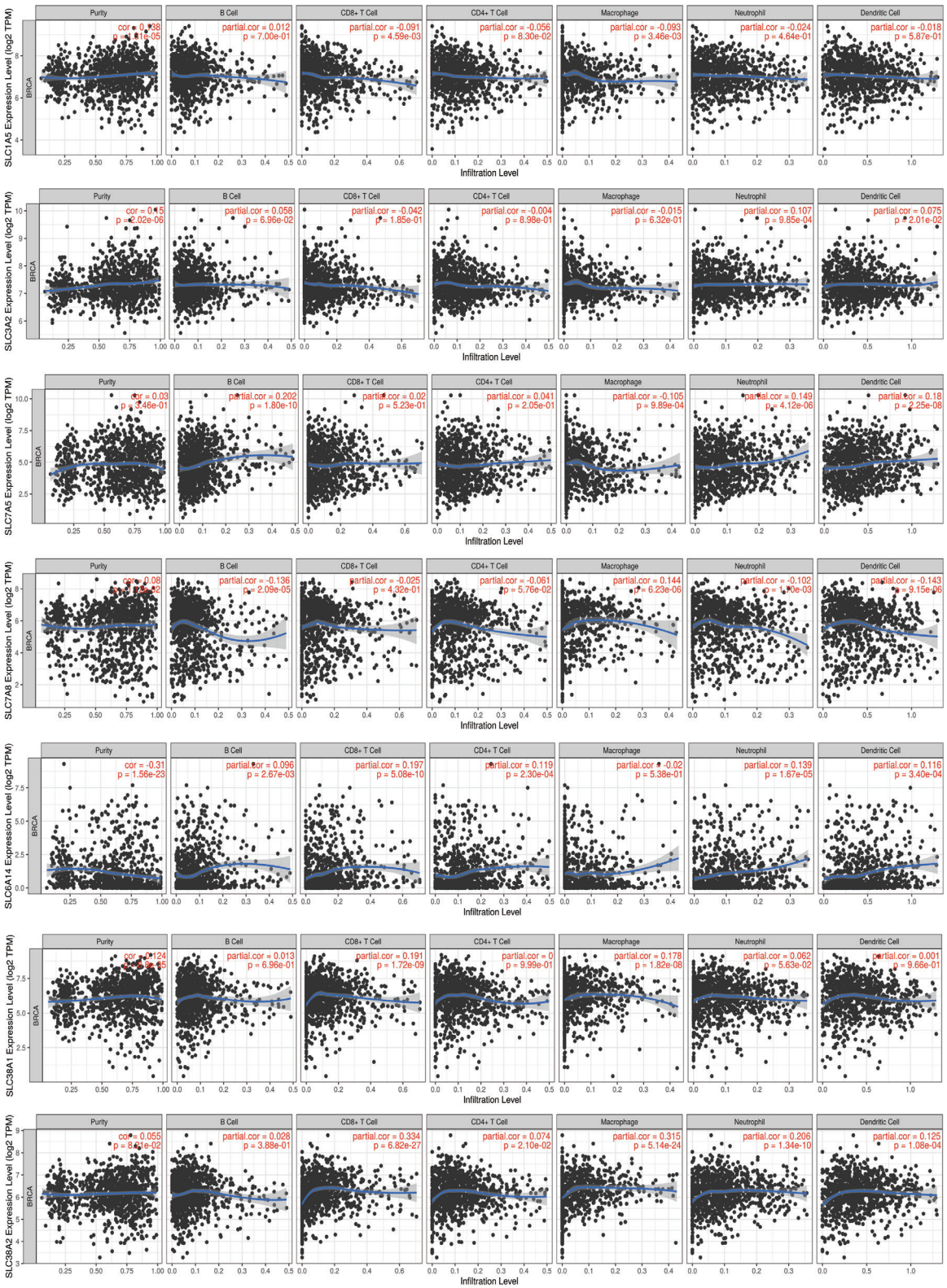
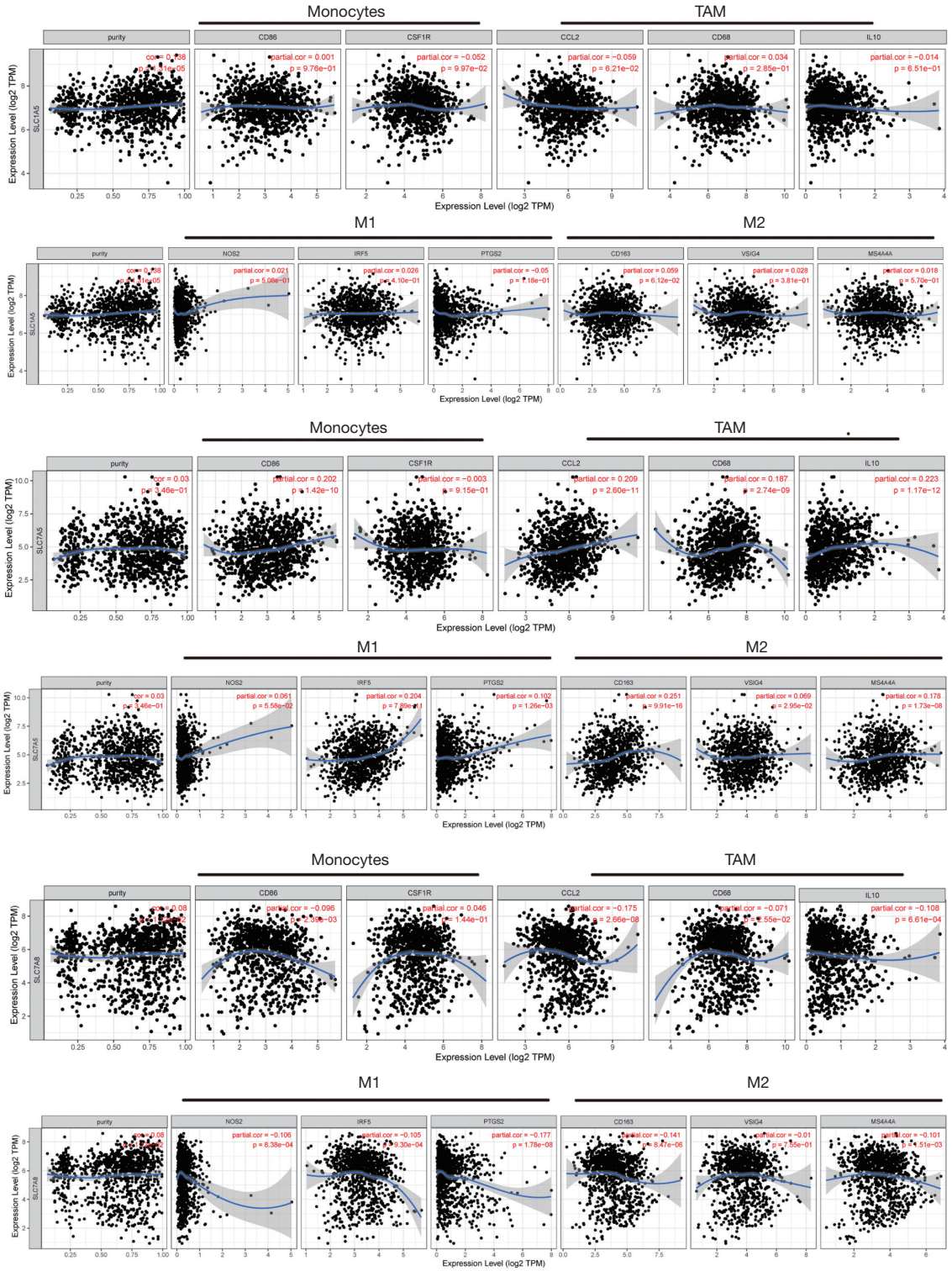


Figure 6 SLC expression is correlated with the infiltration of immune cells in BC; a correlation analysis of immune marker genes. SLC, solute carrier; BC, breast cancer.



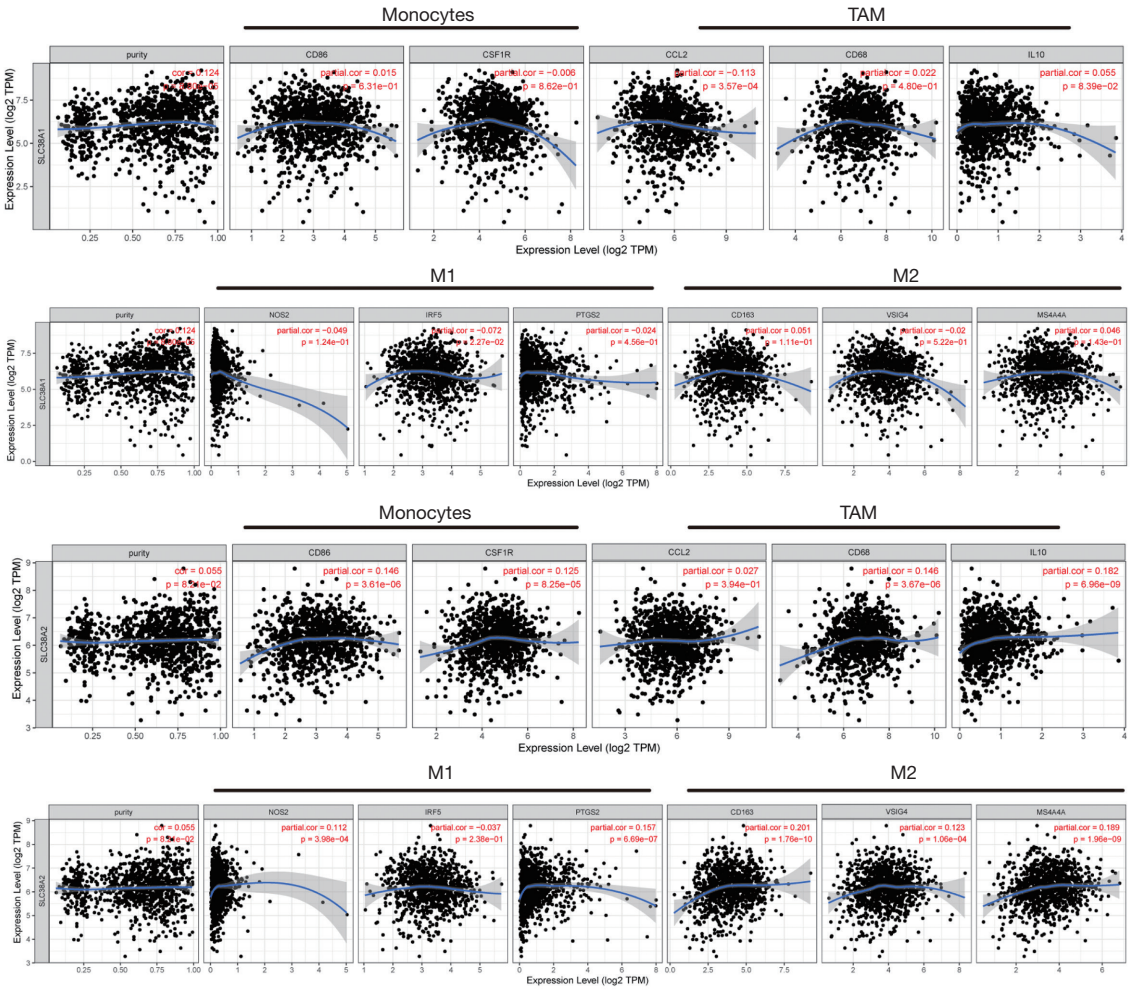


Figure 7 Scatterplots of correlations between SLC expression and the gene markers of monocytes, TAMs, M1 macrophages, and M2 macrophages in BC. Monocyte markers: CD86 and CSF1R. TAM markers: CCL2, CD68, and IL10. M1 macrophages markers: NOS2, IRF5, and PTGS2. M2 macrophages markers: CD163, VSIG4, and MS4A4A. SLC, solute carrier; TAMs, tumor-associated macrophages; BC, breast cancer; CCL2, C-C motif chemokine ligand-2; IL10, interleukin 10.

of BC by inducing and regulating the infiltration of immune cells with different phenotypes. Notably, *SLC7A5*, *SLC7A8*, *SLC38A1*, and *SLC38A2* have the potential to regulate the polarization of TAMs in the microenvironment.

Discussion

The SLC groups of membrane transport proteins, which comprise 65 families, control the influx of zinc, and are responsible for the transport of amino acids, participate in a range of physiological processes and may provide novel therapeutic targets for human malignances (9,32). In this study, we explored for the first time the mRNA expression and conducted K-M survival analyses of glutamine-associated transporters (i.e., *SLC1A5*, *SLC3A2*, *SLC7A5*, *SLC7A8*, *SLC6A14*, *SLC38A1*, and *SLC38A2*) in BC. We also analyzed the genomic characteristics and examined correlations between related SLCs and the infiltration of immune cells to examine how glutamine-associated transporters participate in the evolution and progression of BC. We found that glutamine transporters may have great potential as therapeutic targets for BC in the future.

SLC1A5, also called alanine-serine-cysteine transporter 2, is one of the most important and most studied transporters of glutamine in tumors (33). The treatment of two cells (i.e., luminal type and basal-like type) with a high

expression of *SLC1A5* with an inhibitor of *SLC1A5*-*GPNA* inhibited the growth of 1806 HCC cells and decreased the activity of rapamycin (*mTOR*) complex 1 (*mTORC1*). The inhibition of *SLC1A5* significantly increased the number of apoptotic HCCl806 cells but did not affect the cell viability of MCF7. Thus, BC cells with different molecular subtypes have different degrees of dependence on *SLC1A5* activity, and only the Basal-1ike type BC cell line requires *SLC1A5* to absorb glutamine for growth (34). The effective inhibition of *SLC1A5*-mediated glutamine uptake may be a therapeutic strategy for the treatment of type 2 diabetes mellitus (T2DM) BC patients (35). A proteomic analysis of BC metabolism identified serine hydroxymethyltransferase 2 (*SHMT2*) and *SLC1A5* as independent prognostic factors, and the high protein expression of *SLC1A5* was significantly found to be correlated with poor RFS (HR =1.31, 95% CI: 1.01–1.71; P≤0.05) (36). These findings are consistent with our analysis; that is, we found that the expression of *SLC1A5* is higher in BC tissues than normal tissues. The K-M curves revealed that high *SLC1A5* expression was correlated with poor OS.

SLC3A2, also known as CD98hc, is a transmembrane protein that, as a chaperone, dimerizes with amino acid transporters (such as *SLC7A5* and *SLC7A11*) to achieve functional expression in the plasma membrane (37,38). A large BC cohort study revealed a significant correlation between high *SLC3A2* protein expression and poor prognostic clinicopathological parameters, additionally, the high expression of *SLC3A2* has been shown to be significantly correlated with proliferation (39). We found that the expression of *SLC3A2* is significantly higher in BC tissues than normal tissues. The K-M curves revealed that patients with high *SLC3A2* expression had poor DMFS.

SLC7A5, also referred to as L-type amino acid transporter 1, is thought to regulate tumor metabolism and be related to tumor proliferation. Multiple studies have shown that the amino acid transporter *SLC7A5* is highly expressed in highly proliferating BC subtypes and indicates a poor prognosis for patients; thus, it is a key therapeutic target for ER^+ BC (11,40-42). Additionally, *SLC7A5* regulates the expression of *Myc* and constitutes a positive feedback loop mechanism that promotes essential amino acid transport and tumorigenesis (43,44). *SLC7A5* has also been shown to confer endocrine resistance (45). *SLC7A5* needs to be covalently bound to the *SLC3A2* heavy chain to achieve its functional expression in the plasma membrane (46). Further, the co-operative expression of *SLC1A5*, *SLC7A5*, and *SLC3A2* has been shown to be associated with poor prognostic characteristics and poor patient outcomes, particularly in the ER^+ high proliferation/luminal B subtype (10). In the present study, the expression level of *SLC7A5* in tumor tissues was higher than that in normal tissues, and the differential expression was significantly correlated with the clinical staging of BC. The high expression of *SLC7A5* was significantly associated with poor OS, RFS, DMFS, and PPS in all BC patients.

Previous research has shown that the amino acid transporter *SLC7A8* is overexpressed in the ER^+ BC. *SLC7A8* is a good prognostic marker of ER^+ low-proliferation invasive BC (12). In this data analysis, the expression of *SLC7A8* in tumor tissues was higher than that in normal tissues, but the difference was not statistically significant. The K-M curves revealed that the high expression of *SLC7A8* is prognostic and favorable in BC.

SLC6A14, also referred to as amino acid transporter $B^{0,+}$ ($ATB^{0,+}$), is an amino acid transporter with unique properties (47). Research has shown that *SLC6A14* is upregulated in ER^+ BC, and this has been confirmed in human BC tissues and human BC cell lines; thus, *SLC6A14* represents a novel effective drug target for the treatment of BC (13,48). In our study, the expression level of *SLC6A14* in tumor tissues was higher than that in normal tissues, and the differential expression was significantly correlated with the clinical stage. Further, the high expression of *SLC6A14* was significantly associated with poor PPS in BC.

The amino acid transporters *SNAT1* and *SNAT2* are encoded by *SLC38A1* and *SLC38A2*, both members of the *SLC38* gene family (49,50). The high expression of *SLC38A1* is closely related to tumor size, lymph node metastasis, disease stage, Ki-67, and ER negative (ER^-) expression. Thus, *SLC38A1* appears to be particularly important in the progression of BC. The specific short-hairpin RNA knockdown of *SLC38A1* can cause cell cycle arrest and the apoptosis of 4T1 cells by activating Serotonin N-acetyltransferase1 (*SNAT1*) pathway (14). Persistent hypermethylation and the downregulation of SLC38A1 are associated with trastuzumab resistance in human epidermal growth factor receptor 2-positive BC patients (51). Paclitaxel-induced endoplasmic reticulum stress promotes the ubiquitination associated with the ubiquitin ligase Ring finger protein 5 (*RNF5*) and promotes the degradation of *SLC1A5* and *SLC38A2*, which suggests that chemotherapeutic drugs have different effects on the expression of *SLC1A5* and *SLC38A2* in BC cells, and that the expression of *RNF5* and/or *SLC1A5/ 38A2* may be useful markers for patient stratification and prognosis (52).

However, no research appears to have been conducted on SLC38A2 in relation to the survival and prognosis of BC patients.

In the present study, the expression of *SLC38A1* in tumor tissues was higher than that in normal tissues, but this expression was not correlated with tumor stage in BC. Conversely, the low expression of *SLC38A1* was significantly associated with poor RFS and DMFS in BC. We also found that *SLC38A2* is highly expressed in normal tissues compared to tumor tissues, but the difference was not statistically significant. No valuable results were obtained from the survival analysis of BC in relation to *SLC38A2*. At present, the relevant research is still limited; thus, the biological function of *SLC38A1*, and *SLC38A2* in BC remains unclear in terms of disease prognosis, and further basic and clinical studies need to be conducted to clarify their value.

Alterations in the glutamine pathway in BC also play a role in the production of specific immune cell infiltrates. A bioinformatics analysis of the association between *SLC1A5* and the immune invasion of various cancers indicated that in liver cancer and low-grade glioma, the expression of *SLC1A5* is positively correlated with the number of tumor-infiltrating B cells, $CD4^+$ T cells, $CD8^+$ T cells, macrophages, neutrophils, and DCs (53). The regulation of the immune system by *SLC1A5* may be a potential mechanism by which *SLC1A5* can become a new target for the treatment of a variety of cancers (54). Enhanced glutamine uptake has been shown to affect immune cell infiltration in BC, and the expression of SLCs, including *SLC1A5*, *SLC7A5* and *SLC3A2*, have been shown to be significantly associated with programmed cell death-1/programmed cell death ligand 1 (*PD-1*$^+$*/PD-L1*), forkhead lineage-transcription factor (*FOXP3*$^+$), *CD68*$^+$, and *CD20*$^+$ infiltrates, and associated with an unfavorable prognosis in BC (55).

SLC7A5-mediated leucine influx contributes to pro-inflammatory cytokine production via mTORC1-induced glycolytic reprograming in activated human monocytes/macrophages (56). Multi-omics and a clinical data analysis of 13 BC cell lines and 2898 BC patients in a public database showed that the *SLC7A5* to *SLC7A8* ratio was significantly correlated with the essential amino acid (EAA) level and EAA-metabolic activity in BC (57). Further, these patients had a shorter OS time, higher *PD-L1* expression, and higher T regulatory cell infiltration, which indicates that a high level EAA metabolism is related to a poor prognosis and immune suppression in BC (57).

The human airway cell Calu-3 expresses a variety of amino acid transporters, including *SLC3A2* and *SLC6A14*, and when inhibitors are used, they can inhibit the production of nitric oxide by activated mouse macrophages (58). A study has shown that the high expression of *SLC38A1* in hepatocellular carcinoma is associated with an unfavorable prognosis and immune infiltration defects, and the high expression of *SLC38A1* is inversely proportional to $CD8^+$ T cells and directly proportional to macrophages M0, neutrophils, *PD-1/PD-L1*, and cytotoxic T lymphocyte-associated protein 4 (59). Both *SLC22A5/OCTN2* and *SLC38A2/SNAT2* are induced at the gene and protein levels during the differentiation of human monocytes into macrophages (60). We found that *SLC1A5* expression was correlated with the infiltration levels of *CD8*$^+$ *T* cells and macrophages, *SLC3A2* expression was correlated with the infiltration levels of neutrophils and DCs, *SLC7A5* expression was correlated with the infiltration levels of macrophages, neutrophils, and DCs, *SLC7A8* expression was correlated with the infiltration levels of B cells, macrophages, neutrophils, and DCs, *SLC6A14* expression was correlated with the infiltration levels of B cells, $CD8^+$ T cells, $CD4^+$ T cells, neutrophils, and DCs, SLC38A1 expression was correlated with the infiltration levels of $CD8^+$ T cells and macrophages, and *SLC38A2* expression was correlated with the infiltration levels of $CD8^+$ T cells, $CD4^+$ T cells, macrophages, neutrophils, and DCs.

Macrophages are the largest proportion of immune cells in the tumor microenvironment, so it is not difficult to understand that most SLCs are related to macrophage infiltration. We also assessed the expression of SLCs and the macrophage markers in the TIMER database. Our results suggested that *SLC7A5*, *SLC7A8*, *SLC38A1*, and *SLC38A2* may regulate macrophage polarization in the BC microenvironment. However, some biological functions and mechanisms have not yet been examined. Thus, further research and verification of their relationship will have profound clinical significance in the exploration of novel targets for the treatment of BC.

In this study, we used bioinformatics methods to systematically analyze the expression of glutamine transporter SLCs in BC and their prognostic value. Our findings provide a basis for an in-depth understanding of the heterogeneity and complexity of BC. The high expression of *SLC1A5*, *SLC3A2*, and *SLC7A5* was associated with a poor prognosis and immune cell infiltration. Our results suggest that the increased expression of *SLC1A5*, *SLC3A2*, *SLC7A5*, and *SLC6A14* in BC tissues may play an

important role in the development of BC cancer. Notably, *SLC7A8* and *SLC38A1* were lowly expressed in BC tissues and were associated with a poor prognosis. Additionally, the correlation between the SLCs and immune cell infiltration suggests that the interaction between glutamine transporters and immune cell infiltration plays a very important role in the occurrence and development of tumors. We believe that SLCs may become promising biomarkers in the diagnosis and prognosis of BC and may provide new directions and strategies for its treatment. The specific functional mechanism of SLCs is worth further exploration.

Acknowledgments

Funding: This work was funded by Natural Science Foundation of China grants (82061148016, 81630074, 81872141, 81702630, 81672622); Guangzhou Science and Technology Plan Key Projects (201804020076); Natural Science Foundation of Guangdong (2019A1515010146); and Joint Construction Project of Medical Science and Technology of Henan Province (LHGJ20190635).

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2620/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2620/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.
2. Wise DR, Thompson CB. Glutamine addiction: a new therapeutic target in cancer. Trends Biochem Sci 2010;35:427-33.
3. El Ansari R, McIntyre A, Craze ML, et al. Altered glutamine metabolism in breast cancer; subtype dependencies and alternative adaptations. Histopathology 2018;72:183-90.
4. Abulkhair O, El Saghir NS. BReast CAncer gene (BRCA): snapshot of the Middle East. Chin Clin Oncol 2021;10:51.
5. Perland E, Fredriksson R. Classification Systems of Secondary Active Transporters. Trends Pharmacol Sci 2017;38:305-15.
6. Schweikhard ES, Ziegler CM. Amino acid secondary transporters: toward a common transport mechanism. Curr Top Membr 2012;70:1-28.
7. Bröer S, Palacín M. The role of amino acid transporters in inherited and acquired diseases. Biochem J 2011;436:193-211.
8. Bacci M, Lorito N, Ippolito L, et al. Reprogramming of Amino Acid Transporters to Support Aspartate and Glutamate Dependency Sustains Endocrine Resistance in Breast Cancer. Cell Rep 2019;28:104-118.e8.
9. Lin L, Yee SW, Kim RB, et al. SLC transporters as therapeutic targets: emerging opportunities. Nat Rev Drug Discov 2015;14:543-60.
10. El-Ansari R, Craze ML, Alfarsi L, et al. The combined expression of solute carriers is associated with a poor prognosis in highly proliferative ER+ breast cancer. Breast Cancer Res Treat 2019;175:27-38.
11. Sato M, Harada-Shoji N, Toyohara T, et al. L-type amino acid transporter 1 is associated with chemoresistance in breast cancer via the promotion of amino acid metabolism. Sci Rep 2021;11:589.
12. El Ansari R, Alfarsi L, Craze ML, et al. The solute carrier SLC7A8 is a marker of favourable prognosis in ER-positive low proliferative invasive breast cancer. Breast Cancer Res Treat 2020;181:1-12.
13. Karunakaran S, Ramachandran S, Coothankandaswamy V, et al. SLC6A14 (ATB0,+) protein, a highly concentrative and broad specific amino acid transporter, is a novel and effective drug target for treatment of estrogen receptor-positive breast cancer. J Biol Chem 2011;286:31830-8.

14. Wang K, Cao F, Fang W, et al. Activation of SNAT1/SLC38A1 in human breast cancer: correlation with p-Akt overexpression. BMC Cancer 2013;13:343.
15. Morotti M, Zois CE, El-Ansari R, et al. Increased expression of glutamine transporter SNAT2/SLC38A2 promotes glutamine dependence and oxidative stress resistance, and is associated with worse prognosis in triple-negative breast cancer. Br J Cancer 2021;124:494-505.
16. Tang Z, Li C, Kang B, et al. GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses. Nucleic Acids Res 2017;45:W98-W102.
17. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature 2012;490:61-70.
18. Szklarczyk D, Franceschini A, Kuhn M, et al. The STRING database in 2011: functional interaction networks of proteins, globally integrated and scored. Nucleic Acids Res 2011;39:D561-8.
19. Huang da W, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc 2009;4:44-57.
20. Li T, Fan J, Wang B, et al. TIMER: A Web Server for Comprehensive Analysis of Tumor-Infiltrating Immune Cells. Cancer Res 2017;77:e108-10.
21. Li B, Severson E, Pignon JC, et al. Comprehensive analyses of tumor immunity: implications for cancer immunotherapy. Genome Biol 2016;17:174.
22. Finak G, Bertos N, Pepin F, et al. Stromal gene expression predicts clinical outcome in breast cancer. Nat Med 2008;14:518-27.
23. Curtis C, Shah SP, Chin SF, et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature 2012;486:346-52.
24. Richardson AL, Wang ZC, De Nicolo A, et al. X chromosomal abnormalities in basal-like human breast cancer. Cancer Cell 2006;9:121-32.
25. Ma XJ, Dahiya S, Richardson E, et al. Gene expression profiling of the tumor microenvironment during breast cancer progression. Breast Cancer Res 2009;11:R7.
26. Lánczky A, Győrffy B. Web-Based Survival Analysis Tool Tailored for Medical Research (KMplot): Development and Implementation. J Med Internet Res 2021;23:e27633.
27. Cerami E, Gao J, Dogrusoz U, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov 2012;2:401-4.
28. Stanton SE, Disis ML. Clinical significance of tumor-infiltrating lymphocytes in breast cancer. J Immunother Cancer 2016;4:59.
29. Metzger-Filho O, Tutt A, de Azambuja E, et al. Dissecting the heterogeneity of triple-negative breast cancer. J Clin Oncol 2012;30:1879-87.
30. Wynn TA, Chawla A, Pollard JW. Macrophage biology in development, homeostasis and disease. Nature 2013;496:445-55.
31. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. Nat Med 2013;19:1423-37.
32. Bai X, Moraes TF, Reithmeier RAF. Structural biology of solute carrier (SLC) membrane transport proteins. Mol Membr Biol 2017;34:1-32.
33. Bhutia YD, Babu E, Ramachandran S, et al. Amino Acid transporters in cancer and their relevance to "glutamine addiction": novel targets for the design of a new class of anticancer drugs. Cancer Res 2015;75:1782-8.
34. van Geldermalsen M, Wang Q, Nagarajah R, et al. ASCT2/SLC1A5 controls glutamine uptake and tumour growth in triple-negative basal-like breast cancer. Oncogene 2016;35:3201-8.
35. Silva C, Andrade N, Rodrigues I, et al. The pro-proliferative effect of interferon-gamma in breast cancer cell lines is dependent on stimulation of ASCT2-mediated glutamine cellular uptake. Life Sci 2021;286:120054.
36. Bernhardt S, Bayerlová M, Vetter M, et al. Proteomic profiling of breast cancer metabolism identifies SHMT2 and ASCT2 as prognostic factors. Breast Cancer Res 2017;19:112.
37. Fotiadis D, Kanai Y, Palacín M. The SLC3 and SLC7 families of amino acid transporters. Mol Aspects Med 2013;34:139-58.
38. Kanai Y, Segawa H, Miyamoto Ki, et al. Expression cloning and characterization of a transporter for large neutral amino acids activated by the heavy chain of 4F2 antigen (CD98). J Biol Chem 1998;273:23629-32.
39. El Ansari R, Craze ML, Diez-Rodriguez M, et al. The multifunctional solute carrier 3A2 (SLC3A2) confers a poor prognosis in the highly proliferative breast cancer subtypes. Br J Cancer 2018;118:1115-22.
40. Bodoor K, Almomani R, Alqudah M, et al. LAT1 (SLC7A5) Overexpression in Negative Her2 Group of Breast Cancer: A Potential Therapy Target. Asian Pac J Cancer Prev 2020;21:1453-8.
41. El Ansari R, Craze ML, Miligy I, et al. The amino acid transporter SLC7A5 confers a poor prognosis in the highly proliferative breast cancer subtypes and is a key therapeutic target in luminal B tumours. Breast Cancer

Res 2018;20:21.
42. Törnroos R, Tina E, Göthlin Eremo A. SLC7A5 is linked to increased expression of genes related to proliferation and hypoxia in estrogen-receptor-positive breast cancer. Oncol Rep 2022;47:17.
43. Yue M, Jiang J, Gao P, et al. Oncogenic MYC Activates a Feedforward Regulatory Loop Promoting Essential Amino Acid Metabolism and Tumorigenesis. Cell Rep 2017;21:3819-32.
44. Sinclair LV, Rolf J, Emslie E, et al. Control of amino-acid transport by antigen receptors coordinates the metabolic reprogramming essential for T cell differentiation. Nat Immunol 2013;14:500-8.
45. Shindo H, Harada-Shoji N, Ebata A, et al. Targeting Amino Acid Metabolic Reprogramming via L-Type Amino Acid Transporter 1 (LAT1) for Endocrine-Resistant Breast Cancer. Cancers (Basel) 2021;13:4375.
46. Yanagida O, Kanai Y, Chairoungdua A, et al. Human L-type amino acid transporter 1 (LAT1): characterization of function and expression in tumor cell lines. Biochim Biophys Acta 2001;1514:291-302.
47. Ganapathy ME, Ganapathy V. Amino Acid Transporter ATB0,+ as a delivery system for drugs and prodrugs. Curr Drug Targets Immune Endocr Metabol Disord 2005;5:357-64.
48. Babu E, Bhutia YD, Ramachandran S, et al. Deletion of the amino acid transporter Slc6a14 suppresses tumour growth in spontaneous mouse models of breast cancer. Biochem J 2015;469:17-23.
49. Hatanaka T, Huang W, Martindale RG, et al. Differential influence of cAMP on the expression of the three subtypes (ATA1, ATA2, and ATA3) of the amino acid transport system A. FEBS Lett 2001;505:317-20.
50. Mackenzie B, Erickson JD. Sodium-coupled neutral amino acid (System N/A) transporters of the SLC38 gene family. Pflugers Arch 2004;447:784-95.
51. Palomeras S, Diaz-Lagares Á, Viñas G, et al. Epigenetic silencing of TGFBI confers resistance to trastuzumab in human breast cancer. Breast Cancer Res 2019;21:79.
52. Jeon YJ, Khelifa S, Ratnikov B, et al. Regulation of glutamine carrier proteins by RNF5 determines breast cancer response to ER stress-inducing chemotherapies. Cancer Cell 2015;27:354-69.
53. Zhao J, Yang Z, Tu M, et al. Correlation Between Prognostic Biomarker SLC1A5 and Immune Infiltrates in Various Types of Cancers Including Hepatocellular Carcinoma. Front Oncol 2021;11:608641.
54. Masle-Farquhar E, Bröer A, Yabas M, et al. ASCT2 (SLC1A5)-Deficient Mice Have Normal B-Cell Development, Proliferation, and Antibody Production. Front Immunol 2017;8:549.
55. Ansari RE, Craze ML, Althobiti M, et al. Enhanced glutamine uptake influences composition of immune cell infiltrates in breast cancer. Br J Cancer 2020;122:94-101.
56. Yoon BR, Oh YJ, Kang SW, et al. Role of SLC7A5 in Metabolic Reprogramming of Human Monocyte/Macrophage Immune Responses. Front Immunol 2018;9:53.
57. Zhao Y, Pu C, Liu Z. Essential amino acids deprivation is a potential strategy for breast cancer treatment. Breast 2022;62:152-61.
58. Rotoli BM, Bussolati O, Sala R, et al. The transport of cationic amino acids in human airway cells: expression of system y+L activity and transepithelial delivery of NOS inhibitors. FASEB J 2005;19:810-2.
59. Liu Y, Yang Y, Jiang L, et al. High Expression Levels of SLC38A1 Are Correlated with Poor Prognosis and Defective Immune Infiltration in Hepatocellular Carcinoma. J Oncol 2021;2021:5680968.
60. Ingoglia F, Visigalli R, Rotoli BM, et al. Human macrophage differentiation induces OCTN2-mediated L-carnitine transport through stimulation of mTOR-STAT3 axis. J Leukoc Biol 2017;101:665-74.

Cite this article as: Zhao X, Jin L, Liu Y, Liu Z, Liu Q. Bioinformatic analysis of the role of solute carrier-glutamine transporters in breast cancer. Ann Transl Med 2022;10(14):777. doi: 10.21037/atm-22-2620

