Comprehensive analysis of STAT family members as prognostic markers in human breast cancer

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Abstract

Breast cancer has the highest morbidity and mortality among cancers in women owing to its malignancy, and its incidence increases with age. However, the specific mechanisms underlying breast cancer recurrence and metastasis remain poorly understood. Numerous tumors have shown extensive dependence on janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling. However, the STAT family has not yet been studied systematically in breast cancer. In this study, we investigated the expression differences, prognostic values, molecular functions, and immune infiltration of STAT members in breast cancer. For these analyses, we used The Cancer Genome Atlas (TCGA), cBioPortal, Kaplan-Meier plotter, and the TIMER databases. Significant changes were observed in the STAT expression in breast cancer, and higher expression levels of STAT1/3/4/5A/5B/6 were associated with a longer overall survival in breast cancer. Moreover, significant differences in STAT3, STAT5A, and STAT6 expression were observed at different tumor stages. Members of the STAT family and the associated genes were found to be involved in the regulation of various biological functions, such as “defense response to virus”, “innate immune response”, and “protein binding” in breast cancer. The expression levels of the STAT family members were positively associated with the infiltration of B cells, CD4⁺ T cells, CD8⁺ T cells, macrophages, dendritic cells, and neutrophils in breast cancer. Our results indicate that the expression of the members of the STAT family may be correlated with breast cancer progression and prognosis. Therefore, the STAT family can be used as a prognostic biomarker for confirming disease prognosis and immune infiltration levels in breast cancer.

Keywords

Bioinformatics analysis; STAT family; Breast cancer; Tumor microenvironment; Prognosis

1. Introduction

Breast cancer is a common malignant tumor affecting women globally [1]. Recently, relevant reports have shown that the incidence of breast cancer continues to increase. Early screening, diagnosis, and treatment are of great significance in the prevention of breast cancer and improve the survival rate and prognosis of breast cancer [2]. In the clinical diagnosis of breast cancer, imaging and pathological examination are the methods primarily used; however, these techniques are expensive, and the value of pathological examination in predicting the prognosis of patients is limited. The recurrence and metastasis of breast cancer in the advanced stage often predict a poor prognosis [3].

The effectiveness of existing treatment methods for breast cancer (radiotherapy, chemotherapy, endocrine therapy, and immune therapy) are unsatisfactory owing to the development of treatment resistance [4]. Moreover, molecular targeted therapy is a type of therapy developed in recent years that has shown good therapeutic effect in various tumors [5]. Breast cancer treatment, including endocrine therapy, is associated with challenges such as a poor response and drug resistance [6, 7]. To further explore the specific mechanism underlying breast cancer progression, the development of new diagnostic and therapeutic targets for breast cancer will be helpful for clinical treatment.

STAT, which stands for signal transducer and activator of transcription, constitutes a unique family of proteins that bind to DNA [8, 9]. STAT is activated by phosphorylation and binds to promoter sequence of the target genes and promotes transcription [10]. The regulation of JAK/STAT signaling pathways has attracted increasing attention [12, 13]. JAK/STAT signaling pathways have been found to play important roles in tumor cell immunity and...
inflammation, which can be used to develop therapeutic targets for malignant tumors [14]. Seven members of the STAT family, namely STAT1/2/3/4/5A/5B/6, have been identified in mammals [15]. These were proposed as biomarkers for the treatment and prognosis of various tumors [16]. STAT1 acts as a potential prognostic marker for colorectal cancer [17]. STAT2 participates in the inhibition of interferon response in breast cancer [18], whereas the inhibition of STAT3 signaling can prevent prostate cancer progression [19]. Increasing STAT4 expression is correlated with better survival in gastric cancer [20]. In castration-resistant prostate cancer, STAT3 and STAT5A show potential as a therapeutic target [21], whereas STAT5B is associated with tumor invasion, metastasis, and chemotheraphy resistance in pancreatic cancer [22]. In thyroid cancer, STAT6 is associated with tumor prognosis and therapeutic efficacy with immune checkpoint inhibitors [23]. However, specific functions of the STAT family in breast cancer are yet to be analytically described.

To this end, we adopted various bioinformatics analysis methods based on datasets obtained from public databases to acquire a more comprehensive and detailed understanding of the STATs and their association with disease progression and prognosis in breast cancer. The Oncomine was used to estimate the expression of STAT family members [24]. Following this, we used the Kaplan-Meier (KM) curve to evaluate the prognostic value of the STAT family members. Additionally, to elucidate the involvement of STAT in immunomodulatory processes, we evaluated the relationship between the STATs and the tumor-associated immune cell invasion level. We further evaluated the relationship between STAT and drug reactivity to identify a new target for drug therapy in breast cancer. To our knowledge, this is the first study to provide a comprehensive and detailed evaluation of the STAT family members as targets for immune invasion, drug sensitivity, and breast cancer prognosis. The findings about STATs will provide a theoretical basis for discovering new diagnostic and therapeutic targets for patients with breast cancer.

2. Materials and Methods

2.1 Expression of STAT family members

Oncomine is a website that contains information about gene expression [24]. We used this tool to obtain the expression data of STAT family members in breast cancer. Subsequently, we selected RNA-seq data from the TCGA Breast invasive carcinoma (BRCA) project to perform the log2 transformation of RNA-seq data in the fragments per kilobase million format. We used the TCGA BRCA dataset by UALCAN to further analyze the expression of STAT family genes in different stages of breast cancer, molecular subtypes, and lymph node metastasis conditions. \( p < 0.05 \) was considered to represent a significant difference.

2.2 Relationship between STAT family genes and breast cancer prognosis

We used the KM Plotter to analyze the intrinsic association between STAT expression and prognosis [25]. We included data from all 2976 patients enrolled in the KM Plotter database. We categorized the cases into two groups based on the level of STAT expression in the samples, following which we prepared survival curves accordingly.

2.3 Protein-protein interaction (PPI) network analysis of the STAT family genes

The cBio Cancer Genomics Portal is a multidimensional database providing genomic information about cancers [26]. We used this database to analyze STAT family gene co-expression in the TCGA BRCA samples.

2.4 Gene ontology and pathway enrichment analysis

The Database for Annotation, Visualization and Integrated Discovery (DAVID) website contains annotated genome information for multiple species. Using this, we performed gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis for genes related to the STAT family.

2.5 Transcriptional network analysis

NetworkAnalyst (http://www.networkanalyst.ca) is an online gene expression analysis tool comprising differential gene screening, functional enrichment analysis, and gene network construction [27]. We attempted to explore the transcription factor targets of STAT family genes using the NetworkAnalyst tool with human transcription factor (TF) information and visualize the same using the Cytoscape software (version 3.9.0, USA).

2.6 Correlation between STAT family gene expression and methylation

MethSurv (https://biit.cs.ut.ee/methsurv/) contains DNA methylation data for various tumors [28]. We used this tool to analyze the methylation status of STATs.

2.7 TIMER database and drug response analysis

In our study, we examined the relationship between STAT expression and immune cell infiltration in breast cancer using data from the TIMER database [29]. Tumor purity refers to the ratio of tumor cells in tumor tissues. Genomics of Drug Sensitivity in Cancer (GDSC) data included in GSCALite were used to analyze the association between STAT expression and drug sensitivity [30].

3. Results

3.1 Expression of STAT family members

To confirm the mRNA expression of STAT family members, we used the Oncomine database for comparing the differences in STAT transcription levels between the tumor and normal tissues (Fig. 1). The expression levels of STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6 were assessed based on data from 463, 426, 452, 445, 415, 462, and 448 samples, respectively. The STAT1 levels in breast cancer tissues were 20, 15, and 21, whereas the inhibition of STAT3 signal-
**Figure 1.** Expression of STATs in data obtained from the Oncomine database. Significant differences were observed in gene expression between normal and tumor tissues, as represented by the numbers in the figure. Red and blue represent the upregulated and downregulated genes, respectively. Total unique analyses refer to the number of analyses showing STAT expression in various tumors retrieved from the Oncomine database, and significant unique analyses refers to the number of analyses with gene expression differences between tumor and normal tissues obtained according to the screening threshold. $p < 0.01$ and $|\log$ fold-change$| > 2$ were used as the threshold. Box color is determined by the gene rank percentile for the analyses. STAT, signal transducer and activator of transcription; CNS, central nervous system.
were significantly higher in 14 datasets, whereas the levels of STAT3, STAT5A, and STAT5B in breast cancer tissues were significantly lower in two, 13, and 7 datasets, respectively. Other members of the STAT family showed no significant differences in expression between breast cancer tumor tissues and normal tissues.

Consistent with the findings in Oncomine, STAT1 was expressed at higher levels in tumor tissues than in normal tissues in the TCGA BARC database, whereas STAT5A and STAT5B were expressed at lower levels in tumor tissues. Moreover, analysis of the TCGA BARC database showed that STAT4 and STAT6 were downregulated in breast cancer tissues, whereas the STAT2 and STAT3 expression levels showed no significant difference between breast cancer tissues and normal tissues (Fig. 2).

3.2 Relationship between STAT expression levels and disease prognosis

To further explore the prognostic value of STAT expression, we conducted group statistics based on the expression level of STAT and prepared the KM curve. We then calculated the correlation between STAT expression and overall survival (OS) (Fig. 3). Higher expression levels of STAT1/3/4/5A/5B/6 were associated with a longer OS in breast cancer ($p < 0.05$). Thus, some members of the STAT family may serve as breast cancer survival markers.

3.3 PPI and gene enrichment analysis of STAT family members

Based on data from cBioPortal, we constructed a network for STATs and the neighboring genes (Fig. 4A). We then performed enrichment analysis on the genes associated with
STAT expression to understand their biological functions.

STATs and the neighboring genes were found to primarily affect the “defense response to the virus,” “innate immune response,” and “protein binding” in breast cancer (Fig. 4B–D). The KEGG, measles, JAK-STAT signaling, Hepatitis B, and Epstein-Barr virus infection pathways were found to include more genes (Fig. 4E). Most of these signaling pathways are related to physiological immunity. Previously, survival analysis also revealed that high STAT expression was helpful for prolonging the survival of patients with breast cancer, which suggested that the activation of the expression of STATs is helpful for enhancing the body’s immune response and aids tumor treatment.

### 3.4 Transcriptional network analysis

After activation, STATs enter the nucleus and perform biological functions by regulating gene expression [16]. To explore the gene transcription regulatory network that STATs are involved in, transcription factor targets of STAT family genes were explored using the NetworkAnalyst tool with human TF information; this was visualized using the Cytoscape software (Fig. 5A). STAT family members may regulate tumor progression through the transcriptional regulation of the expression of related genes. Additionally, we determined the correlation of the expression of STATs with each other using the cBioPortal online tool. A heatmap was created based on the RNA-seq data of TCGA BRCA available in the website. The results indicated significant positive correlations among the STAT family members (Fig. 5B). The highest correlation was observed for STAT1 with STAT2 and STAT5A with STAT5B, suggesting that these genes may function synergistically in breast cancer.

### 3.5 STAT expression and the clinicopathological parameters

We analyzed the mRNA expression of STATs and their relationship with different pathological stages of tumors in cases of tumors from TCGA to explore the relationship between STAT expression and breast cancer progression (Fig. 6A–G). In addition to the differences in the expression levels of
STATs between tumor and normal tissues, significant differences were observed in the expression of STAT3, STAT5A, and STAT6 at different tumor stages ($p < 0.05$). The expression of these genes decreased as the tumor progressed. These findings suggest that the above three genes may deeply regulate disease progression in breast cancer tumors. Moreover, we analyzed the expression of STATs with different tumor subtypes for breast cancer (Fig. 7A–G). The expression levels of STATs were found to be correlated with the different molecular subtypes of breast cancer. Particularly, STAT3, STAT5A, STAT5B, and STAT6 showed significant differences in expression among the different molecular subtypes of breast cancer. Among the different subtypes of breast cancer, the expression of these genes was higher in luminal or triple-negative breast cancer and lower in human epidermal growth factor receptor 2 (HER2) positive breast cancer. This was mutually verified with the differential expression results of these genes in breast cancer progression. Tumor metastasis is an important reason for the poor prognosis of breast cancer. To explore the internal relationship between the expression of STATs and breast cancer metastasis, we explored the relationship between STATs and lymph node metastasis in breast cancer. 

**FIGURE 4.** Enrichment analysis of STATs and related genes. (A) Protein-protein interaction network of STAT genes and related genes. Red represents members of the STAT family, whereas blue represents genes associated with STAT members. (B) biological processes; (C) cellular components; (D) molecular functions; (E) KEGG. The color variation represents the $p$-value, whereas the dot size represents the number of enriched genes. JAK/STAT, janus kinase/signal transducer and activator of transcription, Th, T helper; ISGF3, interferons-induced genes factor 3; ADP, Adenosine diphosphate; DNA, deoxyribonucleic acid.
FIGURE 5. Transcriptional network and correlation between the expression of STAT genes. (A) Transcriptional network of STAT genes. Red represents STAT proteins, whereas blue represents genes regulated by STAT members. (B) Correlation between the expression of different STATs in breast cancer. Genes are represented by the abscissa and ordinate, whereas the correlation coefficients are represented by colors; red and blue represent positive and negative correlations, respectively. STAT, signal transducer and activator of transcription.
cancer using data from the UALCAN database. A close association was observed between STAT expression and lymph node metastasis in patients with breast cancer. A positive correlation was observed between the STAT1 expression levels and lymph node metastasis in breast cancer, whereas a negative correlation was observed with the expression levels of other STAT family members (Fig. 6A–G). Compared with normal tissues, breast cancer tissues with different lymph node metastases expressed significantly lower levels of STAT4, STAT5A, STAT5B, and STAT6, suggesting that these 4 STATs play a protective role in breast cancer. Thus, our findings indicate the correlation between the expression levels of STATs and tumor clinicopathological parameters.

### 3.6 DNA methylation analysis

The altered methylation levels in the DNA promoters of some tumor-associated genes can affect tumor survival [31]. A significant reduction was observed in the methylation level of...
FIGURE 7. Relationship between STAT family gene expression and breast cancer molecular subtypes. (A) Expression of STAT1; (B) Expression of STAT2; (C) Expression of STAT3; (D) Expression of STAT4; (E) Expression of STAT5A; (F) Expression of STAT5B; (G) Expression of STAT6. *, \( p < 0.05 \); **, \( p < 0.01 \); ***, \( p < 0.001 \). STAT, signal transducer and activator of transcription.

STATs in breast cancer, and changes in the CpG methylation sites were associated with prognosis. STAT5A had higher methylation levels than other STAT members (Fig. 9). Furthermore, an association was observed between the prognosis of breast cancer and specific CpG sites in STAT family members, including one site in STAT1, two sites in STAT2, five sites in STAT3, two sites in STAT4, three sites in STAT5A, seven sites in STAT5B, and three sites in STAT6 (\( p < 0.05 \); Table 1).

Additionally, the methylation of some CpG sites indicated a poor prognosis in breast cancer, including cg06378498 in STAT3, cg01004382 and cg01453441 in STAT4, cg16777510 in STAT5A, and cg25157914 of STAT6.

3.7 Correlation of STAT expression with immune infiltration and drug response

Tumor immune infiltration levels are known to be associated with patient prognosis [32]. In our study, we examined the relationship between STAT expression and breast cancer immune invasion using data from the TIMER database. The expression of STATs was positively associated with the infiltration of macrophages, neutrophils, and B, CD4+T, CD8+T, and dendritic cells in breast cancer (Fig. 10). These results indicate that STATs may exert a significant impact on tumor immunology. As shown previously, we found that STAT expression was related to tumor immunity, which often affects the therapeutic effect of drugs [33]. To investigate the availability of STAT as a therapeutic target, we evaluated the role of STAT expression in
Table 1. The significant prognostic values of CpG in the STAT family members.

<table>
<thead>
<tr>
<th>Name</th>
<th>CpG Name</th>
<th>HR</th>
<th>CI</th>
<th>p.value</th>
<th>UCSC RefGene Group</th>
<th>Relation to UCSC CpG Island</th>
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<td>STAT1</td>
<td>cg10311754</td>
<td>0.459</td>
<td>(0.309; 0.681)</td>
<td>0.000109056</td>
<td>Body</td>
<td>Open_Sea</td>
</tr>
<tr>
<td>STAT2</td>
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<td>(0.351; 0.816)</td>
<td>0.003659609</td>
<td>TSS200</td>
<td>Island</td>
</tr>
<tr>
<td></td>
<td>cg16637254</td>
<td>0.646</td>
<td>(0.418; 0.998)</td>
<td>0.048961245</td>
<td>5'UTR</td>
<td>N_Shore</td>
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<tr>
<td></td>
<td>cg04517036</td>
<td>0.615</td>
<td>(0.391; 0.968)</td>
<td>0.035739649</td>
<td>TSS200</td>
<td>Island</td>
</tr>
<tr>
<td></td>
<td>cg06378498</td>
<td>1.586</td>
<td>(1.067; 2.357)</td>
<td>0.022663127</td>
<td>5'UTR; 1stExon;</td>
<td>Island</td>
</tr>
<tr>
<td>STAT3</td>
<td>cg12873903</td>
<td>0.463</td>
<td>(0.268; 0.801)</td>
<td>0.005884431</td>
<td>TSS200</td>
<td>Open_Sea</td>
</tr>
<tr>
<td></td>
<td>cg19557623</td>
<td>0.593</td>
<td>(0.37; 0.952)</td>
<td>0.030373862</td>
<td>TSS200</td>
<td>Island</td>
</tr>
<tr>
<td></td>
<td>cg25857307</td>
<td>0.571</td>
<td>(0.339; 0.963)</td>
<td>0.035487140</td>
<td>5'UTR</td>
<td>N_Shelf</td>
</tr>
<tr>
<td></td>
<td>cg01004382</td>
<td>1.738</td>
<td>(1.163; 2.599)</td>
<td>0.007022564</td>
<td>TSS200</td>
<td>Open_Sea</td>
</tr>
<tr>
<td>STAT4</td>
<td>cg01453441</td>
<td>1.914</td>
<td>(1.115; 3.286)</td>
<td>0.018549660</td>
<td>1stExon; 5'UTR</td>
<td>Open_Sea</td>
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<td>(0.432; 0.965)</td>
<td>0.032916169</td>
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<td>N_Shore</td>
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<td>STAT5A</td>
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<td>(0.331; 0.746)</td>
<td>0.000732165</td>
<td>3'UTR</td>
<td>N_Shore</td>
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<tr>
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<td>0.001665652</td>
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<td>0.031622173</td>
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<td></td>
<td>cg24158452</td>
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<td>(0.335; 0.771)</td>
<td>0.001446775</td>
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<td>Island</td>
</tr>
<tr>
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<td>(0.444; 0.975)</td>
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<td>0.588</td>
<td>(0.359; 0.964)</td>
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STAT, signal transducer and activator of transcription; CI, confidence interval; HR, hazard ratio; UCSC, University of California Santa Cruz.

Drug sensitivity. Bubble colors and sizes indicated the Spearman correlation and drug targeting strength. A significant relation was found between STAT5A and STAT5B expression and drug sensitivity and small molecule resistance of 42 and 56 types of tumors (Fig. 11). These results suggest that STAT5A and STAT5B are potential biomarkers for drug screening.

4. Discussion

The expression of genes encoding members of the STAT family has been reported in several types of cancers. Previous studies have shown that STAT3 promotes gastric cancer cell proliferation and migration by downregulating programmed cell death 4 (PDCD4) [34]. Moreover, proteins of the STAT family are extensively involved in tumor immune infiltration. The regulation of immune cells through STAT can be used as a therapeutic target for cancer in various tumors. The nuclear factor-kappaB (NF-κB) downregulation was shown to regulate the immune and inflammatory processes in gastric cancer through STAT1 [35]. Mutations in the Interferon (IFN) gamma-JAK-STAT pathway in melanoma cause drug resistance to immune checkpoint inhibitors in tumors [36].

STAT members were also studied in breast cancer. The activation of the STAT signaling pathway is closely related to the regulation of the breast cancer microenvironment [37]. Phosphoryl-STAT1 expression may be useful for guiding breast cancer immunotherapy [38]. The specific role of STAT1 in breast cancer is yet to be determined. STAT1-deficient mice were shown to spontaneously develop estrogen receptor-α and progesterone receptor-positive breast cancer [39], and STAT1 expression increases the degree of malignancy in breast cancer [40]. In our study, patients with breast cancer with a high STAT1 expression showed longer survival. In addition, the expression of STAT in breast cancer has been shown to be associated with an improved prognosis in several studies, which is consistent with our findings [41]. STAT5A and STAT5B are the two isoforms of STAT5, and STAT5 is known to be associated with a good prognosis of breast tumors [42]. The results of our study supported this conclusion. This may be related to the involvement of STAT5 in the regulation of epithelial-mesenchymal transition in tumors [43].

However, the correlation of STAT expression with breast...
cancer progression has only been studied in a few systematic studies. Our study aimed to further explore the role of STATs in breast cancer progression, immune invasion, and drug resistance and to determine their diagnostic and therapeutic value. The mRNA expression levels of STAT members in breast cancer tissues were first found to be differential. Moreover, the correlation between the difference in expression levels and disease stage suggests that STAT3, STAT5A, and STAT6 were strongly associated with breast cancer progression.

In recent times, tumor-associated immune cells have been a topic of research globally because of their important role in tumor progression and treatment [44]. Tumor-associated immune cells play a complex role in tumor development, and different immune cells promote or inhibit tumor growth differently [45, 46]. The abundance of T cells and macrophages has been found to be correlated with prognosis in bladder cancer [47], whereas natural killer cells, neutrophils, and dendritic cells can be used as target cells for tumor prevention and treatment [48–50]. Further exploration of immune infiltration in tumors will help improve our understanding of tumor progression. Our findings suggest that STAT family members were associated with tumor immune response in breast cancer. The activation of STAT members can enhance tumor immune response, and a high STAT expression can prolong the prog-
FIGURE 9. DNA methylation of STATs in data from MethSurv. (A–G) Heat map of DNA methylation at the CpG sites in the STATs, as determined using the MethSurv database. The changes in red and blue represent the degree of methylation.

nosis of breast cancer, which provides a novel idea for the treatment of breast cancer. Breast cancer, especially triple-negative breast cancer, exhibits extensive tumor heterogeneity, and existing treatment methods are ineffective. Owing to its high immune response, immunotherapy is highly suitable for triple-negative breast cancer [51]. Currently, numerous treatments are used for breast cancer; however, metastatic breast cancer is still not treatable effectively owing to its advanced stage [52]. Current guidelines for hormone-receptor-positive advanced breast cancer recommend the use of endocrine therapy as first-line therapy [53]. However, drug resistance in tumors remains a major obstruction to effective cancer treatment; thus, it is of utmost importance to further explore the mechanism underlying drug resistance in tumors and develop new drugs. Drug sensitivity analysis revealed that the low expression of STAT5A and STAT5B corresponded to resistance to most drugs or small molecules in GDSC. Collectively, these results indicate that STATs are potential biomarkers for the prognosis and treatment of breast cancer.

Key genes of breast cancer have been identified [54, 55]. The changes in the expression of these genes are closely related to the biological process of tumor pathogenesis, progression, recurrence, and metastasis. We found that STATs play a vital biological role in several other solid tumors, but we are uncertain about its biological function in breast cancer. Therefore, in this study, we first used high-throughput sequencing
FIGURE 10. Correlation between STAT expression and immune cell infiltration in breast cancer.
**FIGURE 11. STATs and drug resistance in tumors.** Different colors represent the different correlation coefficients. Red and blue represent positive and negative correlations, respectively. STAT, signal transducer and activator of transcription; FDR, false discovery rate.
data from TCGA, Oncomine, and other databases to identify the differences in the expression of STAT members in breast cancer and their influence on survival.

5. Conclusion

In summary, our findings demonstrate that the expression of STAT genes was altered in breast cancer, and the changes in STAT gene expression were closely related to disease development, prognosis, and survival in breast cancer. The overexpression of STAT proteins increased the infiltration of tumor-associated immune cells, such as T cells, B cells, and macrophages, thus affecting the sensitivity of multiple treatment drugs. As the conclusions drawn in this study are based on the analysis of data obtained from public databases, further experimental studies are needed to obtain more detailed conclusions. Nevertheless, our study provides a promising target for the diagnosis and treatment of breast cancer.

AUTHOR CONTRIBUTIONS

LYG—responsible for the main concept. TA—wrote the first draft of the manuscript, is responsible for the tables design. All authors discussed the results and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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