Am J Transl Res 2025;17(6):4733-4743
www.ajtr.org /ISSN:1943-8141/AJTR0163643

Original Article

Exploring the landscape of autoimmune disorder-associated genes and their impact on immune microenvironment in breast cancer patients

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Received January 31, 2025; Accepted May 26, 2025; Epub June 15, 2025; Published June 30, 2025

Abstract: Objectives: Breast cancer (BC) remains a leading cause of cancer-related mortality among women worldwide. Emerging evidence suggests that autoimmune-associated genes may critically influence tumor progression and immune evasion. This study investigates the dysregulation of autoimmune-associated genes in BC and explores their potential roles in immune modulation and tumor progression. Methods: Two publicly available bulk RNA-sequencing datasets (GSE233242 and GSE227679) were analyzed to identify differentially expressed genes (DEGs) between BC and normal tissues. A curated set of autoimmune-related genes was compiled from multiple databases, including ClinVar, UniProt, OMIM, MedlinePlus, GWAS Catalog, and GeneCards. Enrichment analysis was conducted using KEGG pathways via Enrichr, and protein-protein interaction (PPI) networks were constructed using STRING and Cytoscape to identify hub genes. Results: Out of 3,676 autoimmune genes, 125 were found to be upregulated and 75 downregulated in BC tissues. Key enriched pathways included Cytokine-cytokine receptor interaction, Chemokine signaling, IL-17 signaling, and PI3K-Akt signaling. Ten hub genes were identified, with CXCR4, MMP9, CTLA4, CD80, and ICOS upregulated, and IL6, KIT, PPARG, SLC2A4, and CEBPA downregulated. CXCR4 and MMP9 overexpression was associated with increased metastasis, while downregulation of KIT and PPARG indicated impaired immune surveillance and poorer prognosis. Conclusions: This study reveals the pivotal role of autoimmune gene dysregulation in BC progression and immune microenvironment remodeling. Integrating autoimmune gene signatures with transcriptomic data provides novel insights into BC pathogenesis and highlights potential biomarkers and therapeutic targets for immune-based interventions.

Keywords: Autoimmune disorders, breast cancer, immune microenvironment, gene expression, immunotherapy, biomarkers

Introduction

Breast cancer (BC) is a malignancy characterized by the abnormal and uncontrolled proliferation of cells within breast tissue, commonly originating in the lobules or milk ducts. This pathological growth often leads to the invasion of surrounding tissues and may result in metastasis to distant sites within the body. BC is a heterogeneous disease that displays a significant level of variability in molecular profiles and phenotypic characteristics. Broadly utilized clinical classification identifies it based on estrogen receptor (ER), human epidermal growth factor receptor 2 (HER2), hormone receptors, and progesterone receptor (PR) [1].

According to the 2022 GLOBOCAN report, BC is the fourth leading cause of cancer-related deaths. Approximately 2.3 million new cases

https://doi.org/10.62347/EANH4082

and about 666,103 fatalities were reported globally. BC remains the highest diagnosed malignancy, it accounts for approximately 12% of all cancer diagnoses. Developed countries typically exhibit a higher incidence of this disease compared to underdeveloped countries. It has been predicted that by 2030, the number of new cases will reach 3.9 million worldwide, while deaths are expected to escalate to 766,000 [1]. In the United States, BC solely is projected to represent 29% of all emerging cancers in women [2]. Interestingly, recent studies have begun to explore potential links between BC and autoimmune disorders, as both involve dysfunctions in cellular regulation and the immune system. Autoimmunity is one of the leading causes of morbidity among women in the United States and ranks among the top ten causes of death [3].

Normally, antibodies are produced by the immune system against antigens that allow it to destroy adverse substances [4]. However, autoimmune diseases frequently lead to a compromised immune system, wherein immune cells are mistakenly targeted for destruction. This phenomenon arises when the immune system generates autoantibodies that are unable to distinguish between self and non-self, resulting in an erroneous attack on tissues of the body [5].

The immune system aims to eliminate abnormal cells and pathogens through immune surveillance. However, this mechanism becomes ineffective over time as tumors change the tumor immune microenvironment (TIME) into an immunosuppressive condition hence, escaping the immune defenses of the host [6]. BC is considered to be poorly immunogenic. The reason is a lack of expression of antigens on the surface of BC cells, which is vital for recognition by the immune system. Innate and adaptive immune systems influence BC progression. Although BC is associated with fewer infiltrating immune cells compared to other cancers, primarily T lymphocytes, infiltration is still more frequent. Innate immune cells are crucial in inhibiting the immune response during BC progression [7].

Notably, tumor formation can be influenced by cytotoxic adaptive and innate immune cells. However, cancer cells develop mechanisms that mimic immune tolerance that copy adjacent immune tolerance to escape tumor-ridding attacks, even as they progress from neoplastic tissue to clinically identifiable tumors. The fate of the tumor is decided by the balance between tolerogenic and effector immune response [8, 9]. Moreover, recent studies present that preserving regulatory and effector immune function balance is also essential for preventing autoimmunity [3].

Tumor-associated immune genes generally refer to genes that regulate immune responses within the tumor microenvironment, including immune checkpoint molecules (e.g., PD-1, CTLA-4), cytokines, and chemokines that modulate tumor progression and immune escape. In contrast, autoimmune genes are primarily implicated in the breakdown of self-tolerance and the development of immune reactivity against self-antigens. These genes are often involved in pathways such as T cell receptor signaling, Th17 differentiation, IL-17 signaling, and regulatory T cell dysfunction, which are central to autoimmune disorders like systemic lupus erythematosus and rheumatoid arthritis [10]. While some immune genes may overlap between cancer and autoimmunity, their roles and regulatory mechanisms differ substantially depending on the context. Therefore, this study focuses specifically on autoimmune-associated genes, those known to drive systemic immune dysregulation in the setting of breast cancer.

Therefore, this study utilized RNA-sequencing to detect the dysregulated autoimmune genes in BC. Two distinct bulk transcriptomics datasets from BC cohorts were analyzed to identify common molecular markers across the different BC groups. From these shared markers, genes associated with autoimmune responses were shortlisted. Subsequently, the top hub genes with a documented autoimmune profile were identified for further investigation. This study uniquely integrates curated autoimmune gene databases with transcriptomic breast cancer datasets to identify immune-related disruptions that overlap with known autoimmune regulatory pathways. By narrowing the analysis to genes implicated in systemic autoimmune responses and tracking their dysregulation in breast cancer progression, we aim to uncover a cross-disciplinary biomarker space that has not been thoroughly explored. Specifically, we highlight the contribution of autoim-

mune-specific signaling such as IL-17 and genes implicated in T cell regulation and self-tolerance.

Methodology

Retrieval of autoimmune-associated genes

A comprehensive list of autoimmune-associated genes was curated through literature review and integration of gene-disease information from multiple biomedical databases. Genes were extracted by querying autoimmune-related conditions (e.g., systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis) across the following resources: ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) [9]; UniProt (https://www.uniprot.org/) - a detailed repository of protein sequences and functional annotations [10]; OMIM (https://www.omim.org/) [11]; MedlinePlus Genetics (https://medlineplus.gov/genetics/gene/) [12]; GWAS Catalog (https://www.ebi.ac.uk/gwas/) [13]; and GeneCards (https://www.genecards.org/). Genes appearing in multiple autoimmune contexts were retained. Duplicate entries were removed to generate a non-redundant set of autoimmune-related genes for further analysis.

RNA-sequencing data retrieval and pre-processing

Two bulk RNA sequencing datasets of human BC tissue samples were retrieved from the National Center of Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) (https://www.ncbi.nlm.nih.gov/gds), a public database that contains high-throughput functional genomics and expression datasets. The datasets contained tumor and normal samples, having accession ID GSE233242 (t=43, n=43) and GSE227679 (t=17, n=17), respectively. While GSE227679 includes only 17 tumor and 17 normal samples, it was selected for its high-quality transcriptomic profiling and consistency with GSE233242. To mitigate the risk of statistical bias due to small sample size, we cross-validated findings by identifying consistently dysregulated genes across both independent datasets. Only overlapping DEGs were selected for downstream autoimmune gene mapping and pathway analysis to increase robustness.

Quality control was performed to minimize noise by trimming poor-quality reads, primers, and adapters. Quality assessment is the initial step of preprocessing in which quality reports are generated for each sample using the FastQC tool. After which filtered reads were obtained by trimming poor-quality reads this is done by removing adapter and primer content through the fastp tool (v0.20.0) [14]. Furthermore, FastQC (https://github.com/s-andrews/FastQC) was employed to verify removal of poor-quality reads and adapters.

Additionally, the HISAT2 tool (v2.1.0) was utilized for mapping filtered reads to the Homo sapiens (GRCh38) reference genome (15). Reads were aligned using default parameters, with the addition of -rna-strandness FR (reflecting the library preparation protocol) and dta (to enable downstream transcriptome assembly). These parameters were aligned with HISAT2 documentation recommendations for stranded RNA-seq alignment and accurate transcript reconstruction [15]. Subsequently, SAM (sequence alignment map) format files were made enclosing aligned reads. SAM files were converted to BAM (binary alignment map), a compressed and binary format of aligned reads, using Samtools (v1.16) before read quantification [16]. BamUtil (v1.0.15) was used for deduplication to remove duplicates from mapped reads. Finally, FeatureCounts was employed to quantify gene expression levels by counting the number of reads aligned to each gene, providing a robust measure of gene activity across different samples [17].

Differentially Expressed Genes (DEG) analysis

DEG analysis was conducted utilizing the Wlad test in the DESeq2 package [18]. In this method, gene expression variance is estimated and a negative binomial distribution is allocated to each gene. Moreover, quantified read counts were used for DEG analysis between BC vs. normal groups. Upregulated and downregulated genes were identified and the volcano plots were utilized to visualize the DEGs. The dysregulated genes obtained were sorted into upregulated and downregulated genes based on their $\log_2$FoldChange value, which was greater than 1 and less than -1, respectively, and p-value <0.05. After duplicated genes were removed, upregulated and downregulated genes were retrieved from BC datasets.

Filtration of autoimmune genes from BC dysregulated genes

Subsequently, the previously obtained autoimmune genes were compared with upregulated and downregulated genes. After the duplicated genes were removed, upregulated and downregulated common autoimmune genes in BC were shortlisted. These genes were utilized for further analysis.

Functional enrichment analysis

Enrichr webserver (https://maayanlab.cloud/Enrichr/), is an extensive resource that contains curated gene sets and is a searching tool that compiles biological knowledge [19]. The dysregulated autoimmune genes in BC were then utilized to predict the functional pathways through Kyoto Encyclopedia of Genes and Genomes (KEGG) database. Subsequently, a literature review was carried out to determine the KEGG pathways that were directly related to BC. Thereafter, genes involved in these pathways were shortlisted.

Dysregulated autoimmune hub genes identification

The shortlisted genes involved in pathways related to autoimmunity were then utilized on Search Tool for the Retrieval of Interacting Genes (STRING) (https://string-db.org/) database for protein-protein interaction (PPI). STRING assembles both physical and functional PPIs [20]. Moreover, Cytoscape, a software used to visualize and explore biological networks, was used to visualize the interactions [21-23]. The Cytohubba module in Cytoscape was used to identify the 5 upregulated and downregulated hub genes, using the degree method. Furthermore, a literature review was performed to identify the role of these hub genes in BC progression and growth.

Statistical analysis

Differential gene expression analysis between tumor and normal tissue samples in both GSE233242 and GSE227679 datasets was performed using the DESeq2 R package, which fits a negative binomial distribution to RNA-seq count data. Statistical significance was evaluated using the Wald test, and genes were considered differentially expressed if they met the criteria of $|\log_2\text{FoldChange}| > 1$ and adjusted p-value <0.05 (Benjamini-Hochberg correction). Pathway enrichment analysis of the filtered autoimmune-related genes was conducted using Enrichr, employing Fisher's exact test to identify significantly enriched KEGG pathways.

Results

Identification of dysregulated autoimmune genes in BC

After removing duplicate genes identified from the literature and various databases, a total of 3,676 unique autoimmune genes were compiled. Using the DESeq2 package, differential expression analysis was conducted on two datasets: GSE233242 and GSE227679. In GSE233242, 3,559 DEGs were identified, with 2,029 genes upregulated and 1,530 downregulated. Similarly, GSE227679 revealed 2,019 DEGs, including 1,026 upregulated and 993 downregulated genes (**Figure 1A**, **1B**). Common genes from both datasets were compiled, resulting in 795 upregulated and 660 downregulated genes for further analysis. Comparing these dysregulated genes with a curated list of autoimmune-related genes, 125 autoimmune genes were found to be upregulated and 75 downregulated in BC compared to healthy individuals.

To evaluate autoimmune gene variation across breast cancer molecular subtypes, expression trends were compared in Luminal A and Triple-negative subgroups. Genes such as CTLA4 and CXCR4 showed higher expression in TNBC compared to Luminal A, suggesting stronger immune checkpoint activation and potential evasion mechanisms in more aggressive tumor types. These findings indicate the importance of tumor subtype in modulating autoimmune-associated immune responses and highlight the need for subtype-specific immunotherapeutic strategies.

Pathway enrichment analysis of autoimmune genes involved in BC

Both up- and down-regulated shortlisted autoimmune genes were subjected to pathway enrichment analysis using Enrichr. The association of these pathways with our study was fur-

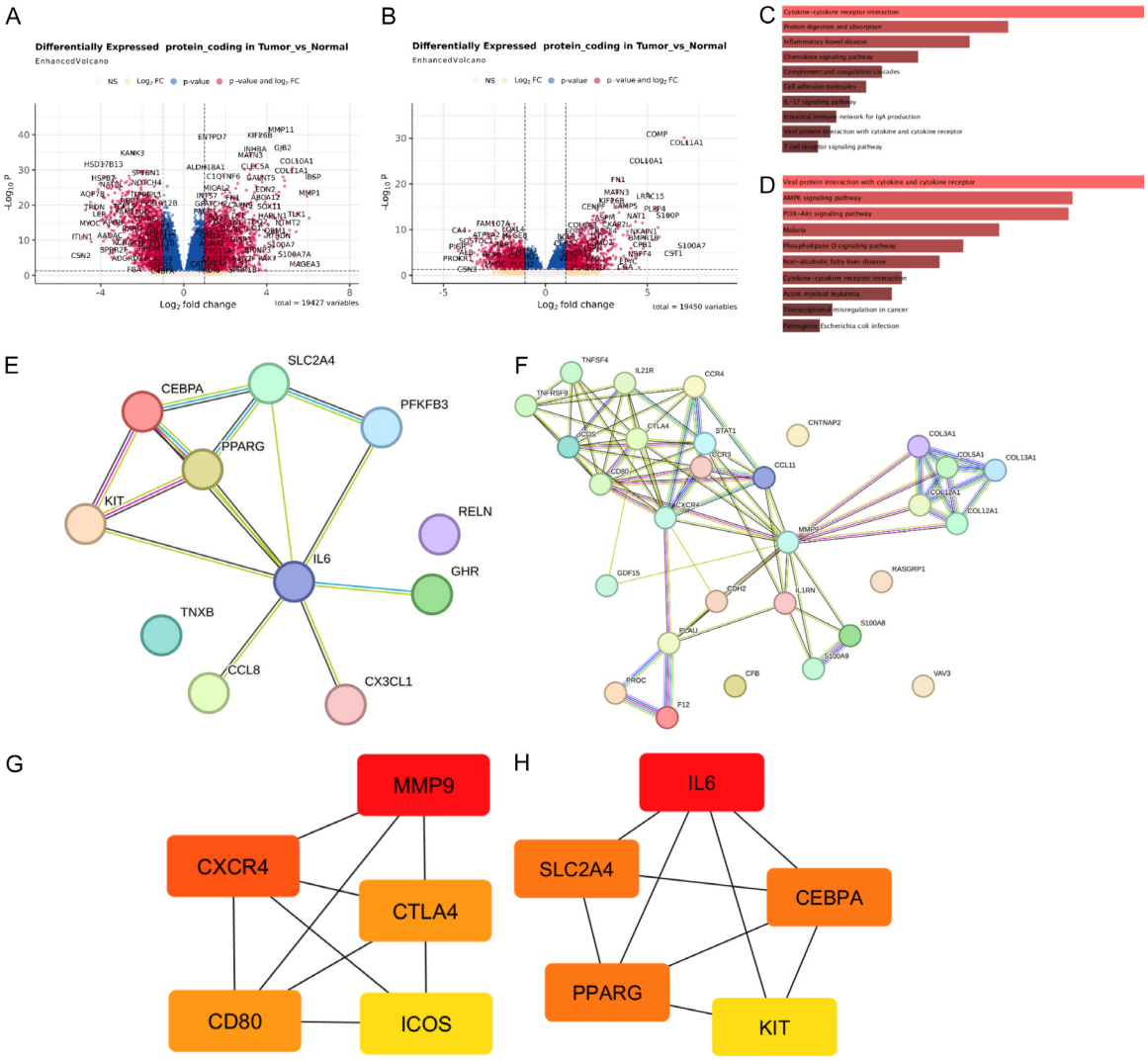

Figure 1. Volcano plots, functional enrichment analysis, STRING analysis, and hub gene identification (A, B) Volcano plot of Tumor vs. Normal GSE233242 and GSE227679 showing the significantly dysregulated genes, respectively (C, D) Top 10 upregulated KEGG pathways of the upregulated and downregulated genes in the datasets (E, F) Protein-protein interactions of the biological functional genes showing a network of proteins in upregulated and downregulated genes, respectively (G, H) Highly interacting upregulated hub genes involved in, upregulated and downregulated genes, respectively.

ther validated through an extensive literature review and shortlisted based on reported involvement in BC. The pathway enrichment of the upregulated genes exhibited significant pathways such as Cytokine-cytokine receptor interaction, Protein digestion and absorption, Chemokine signaling pathway, Complement and coagulation cascades, Cell adhesion molecules, IL-17 signaling pathway, Intestinal im mune network for IgA production, Viral protein interaction with cytokine and cytokine receptor, and T cell receptor signaling pathway as shown in **Figure 1C**. Meanwhile, the pathways of the downregulated genes were included the AMPK signaling pathway, PI3K-Akt signaling pathway, Cytokine-cytokine receptor interaction, and Transcriptional misregulation in cancer as shown in **Figure 1D**. Notably, the Cytokine-cytokine receptor interaction was common in both up and down-regulated genes, however, a total of 29 genes were identified to be upregulated and 11 genes were downregulated. The BC-related pathways and their respective genes are listed in **Table 1**.

The dysregulation of these key pathways plays a significant role in BC progression and metastasis. The Cytokine-Cytokine Receptor In-

Table 1. KEGG pathways related to autoimmunity in BC

Upregulated	
Pathway	Genes
Cytokine-cytokine receptor interaction	IL1RN, CCL11, GDF15, TNFRSF9, TNFSF4, IL21R, CXCR4, CCR4, CCR3
Protein digestion and absorption	COL3A1, COL13A1, COL5A1, COL11A1, COL12A1
Chemokine signaling pathway	VAV3, CCL11, STAT1, CXCR4, CCR4, CCR3
Complement and coagulation cascades	PROC, PLAU, F12, CFB
Cell adhesion molecules	CNTNAP2, CDH2, CD80, CTLA4, ICOS
IL-17 signaling pathway	CCL11, MMP9, S100A9, S100A8
Intestinal immune network for IgA production	CD80, CXCR4, ICOS
Viral protein interaction with cytokine and cytokine receptor	CD80, CXCR4, ICOS
T cell receptor signaling pathway	VAV3, CTLA4, ICOS, RASGRP1
Downregulated	
Pathway	Genes
AMPK signaling pathway	PFKFB3, PPARG, SLC2A4
PI3K-Akt signaling pathway	GHR, IL6, TNXB, RELN, KIT
Cytokine-cytokine receptor interaction	GHR, IL6, CCL8, CX3CL1
Transcriptional misregulation in cancer	CEBPA, IL6, PPARG

teraction pathway is central to immune responses and inflammation in the tumor microenvironment. Dysregulated genes, such as upregulated IL6 and CXCR4, contribute to chronic inflammation, promoting tumor growth and immune evasion. The Chemokine Signaling Pathway, particularly through CXCR4, is crucial in recruiting immune cells and facilitating metastasis to organs like bones and lungs.

The PI3K-Akt Signaling Pathway, a major regulator of cell survival and proliferation, is often altered in BC, leading to increased tumor growth. The IL-17 Signaling Pathway's involvement in chronic inflammation is highlighted by the upregulation of MMP9 and S100A9, which promote tumor growth through extracellular matrix remodeling and angiogenesis. Additionally, the Complement and Coagulation Cascades contribute to a pro-thrombotic state and chronic inflammation, aiding cancer progression. The Transcriptional Misregulation in Cancer pathway indicates that downregulation of genes like CEBPA and PPARG leads to uncontrolled cell growth. Finally, the upregulation of genes like CTLA4 and ICOS in T Cell Receptor Signaling Pathway reflects an active immune response, though immune checkpoints allow the tumor to evade surveillance. Genes from these pathways were then used for further analysis.

Identification of autoimmune hub genes involved in BC

Genes associated with autoimmunity pathways in BC compared to healthy individuals, as identified in the previous step, were then subjected to STRING analysis. This analysis evaluated PPIs for both up-regulated and down-regulated genes to determine their functional partners (**Figure 1E**, **1F**). Additionally, hub genes were identified using the STRING database output, highlighting key genes among both up-regulated and down-regulated autoimmune gene sets. For the up-regulated autoimmune genes, the five hub genes identified were MMP9, CXCR4, CTLA4, CD80, and ICOS (**Figure 1G**). These upregulated genes exhibited 16, 12, 10, 10, and 9 interactions, respectively. Whereas *IL6*, *SLC2A4*, *CEBPA*, *PPARG*, and *KIT* were identified as the 5 hub genes for the downregulated autoimmune group (**Figure 1H**), exhibiting 8, 4, 4, 4, and 3 interactions, respectively. These upregulated hub genes suggest enhanced immune activation and potential support for tumor growth, reflecting a more aggressive disease phenotype. Conversely, down-regulated hub genes indicate possible suppression of immune responses or disruptions in the tumor microenvironment.

To further validate the transcript-level findings, protein expression of key hub genes (CXCR4, MMP9, CTLA4, PPARG) was examined using the Human Protein Atlas (HPA) database. Immunohistochemistry results revealed consistent expression patterns with our transcriptomic data, highlighting increased protein levels of CXCR4 and MMP9 in tumor tissues compared to normal, and reduced PPARG and KIT expression. These findings support the potential clinical rel-

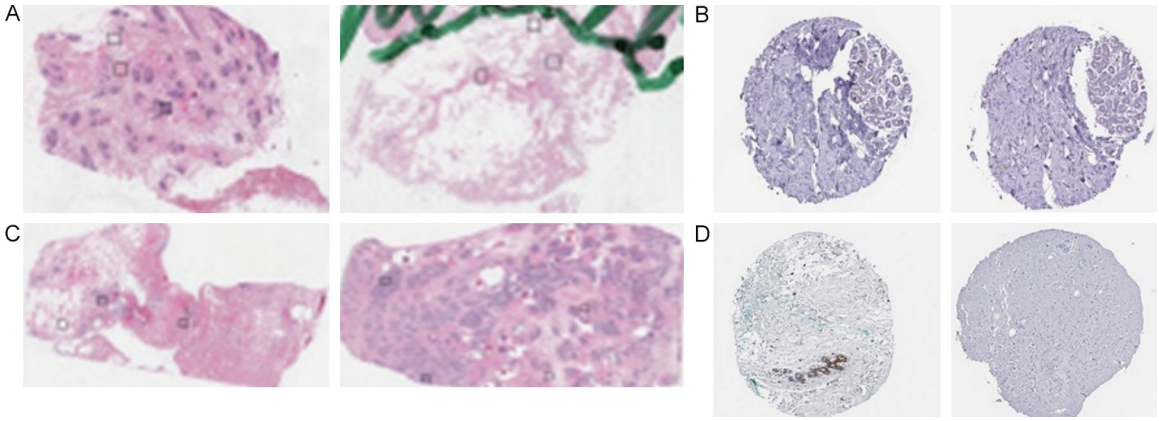

Figure 2. Immunohistochemical validation of hub gene expression in breast cancer tissues using HPA. A. CXCR4 expression in breast cancer tissues. Increased CXCR4 staining is observed in tumor tissue, consistent with transcriptomic upregulation. B. MMP9 expression in breast cancer tissue. Tumor tissue shows higher MMP9 levels, indicating active matrix remodeling. C. PPARG expression in breast cancer tissue. Lower PPARG expression in tumor samples supports its proposed tumor-suppressive role. D. KIT expression in breast cancer tissue. KIT is markedly reduced in tumor tissue, in agreement with downregulation observed in RNA-seq data.

evance of these genes in breast cancer progression (**Figure 2**).

Discussion

This study explores the association between autoimmune gene dysregulation and BC progression, focusing on key genes and pathways that contribute to poor prognosis and reduced survival. By analyzing gene expression data from BC tissues with an emphasis on autoimmune-related genes, the findings demonstrate the significant role of the immune system in modulating tumor behavior. The study corroborates and extends prior research on several biomarkers linked to immune-mediated breast cancer progression.

The identification of hub genes within the dysregulated autoimmune gene set refines our understanding of BC prognosis. Among the upregulated hub genes, CXCR4, CTLA4, CD80, and ICOS have been associated with poor survival outcomes in BC patients. CXCR4, a chemokine receptor, plays a pivotal role in facilitating the migration of cancer cells to distant organs, thereby promoting metastasis [24-34]. Elevated CXCR4 expression has been correlated with adverse outcomes, including lymph node involvement, distant metastasis, and reduced 5-year overall survival and disease-free survival rates. CXCR4 may serve as a stronger prognostic marker than its nuclear expression suggests [35-37].

CTLA4 is a well-known immune checkpoint regulator that modulates T-cell activity. The study reveals that elevated soluble CTLA-4 levels in the tumor microenvironment are associated with poor prognosis, likely due to the preferential accumulation of Tregs expressing high levels of CTLA-4, which negatively impacts BC outcomes [38-41]. ICOS, along with its ligand ICOSL, is also overexpressed in tumor-infiltrating Tregs, enhancing the immunosuppressive environment and further impeding effective antitumor immune responses [42].

MMP9, another upregulated hub gene, has long been implicated in BC progression. This study reinforces its role in facilitating metastatic spread through its effects on circulating tumor cells and the formation of new metastatic sites. High MMP9 expression has been consistently associated with an increased number of distant metastases and poor clinical outcomes [29-33].

Conversely, the study found that downregulated hub genes such as KIT, IL6, and PPARG were also linked to poor prognosis. KIT, a receptor tyrosine kinase essential for hematopoiesis and cell survival, has its downregulation associated with reduced immune cell infiltration and weakened anti-tumor immune responses, contributing to tumor progression [43, 44]. The loss of KIT correlates with significantly worse prognosis, reinforcing its potential as a crucial prognostic marker. Similarly, the downregula-

tion of IL6, a cytokine involved in inflammation and immune regulation, may diminish the anti-tumor immune response, exacerbating BC progression. PPARG downregulation is also associated with poorer prognosis, potentially through its effects on tumor-infiltrating cells within the tumor microenvironment [45, 46]. CEBPA, also found to be downregulated, is known for maintaining epithelial integrity and suppressing the epithelial-to-mesenchymal transition, supporting its function as a tumor suppressor.

Pathway enrichment analysis identified several critical immune-related pathways in BC. Among these, the IL-17 signaling pathway, commonly associated with Th17-mediated autoimmunity - was significantly upregulated, supporting its role in both tumorigenesis and autoimmune inflammatory responses. The IL-17 signaling pathway, particularly with genes like CCL11 and MMP9, was found to foster an inflammatory environment that supports tumor growth and metastasis in BC [27, 28].

Although several identified pathways such as cytokine-cytokine receptor interaction (CCRI) and chemokine signaling are broadly involved in immune regulation, our analysis specifically highlights autoimmune-relevant signals within these broader categories. The presence of both upregulated and downregulated genes within the CCRI pathway suggests a bidirectional regulatory mechanism that may reflect complex immune dynamics in the tumor microenvironment. Upregulated components such as CXCR4 and IL1RN may contribute to chronic inflammation, immune cell recruitment, and metastatic potential. Conversely, downregulated cytokines like IL6 and GHR may indicate immune exhaustion or suppression, underscoring the paradoxical roles of cytokine signaling in immune tolerance and evasion strategies in BC.

Immune checkpoint regulators such as CTLA4, ICOS, and IL6 are critical for peripheral immune tolerance and self-reactivity control. Their dysregulation in BC, mirroring autoimmune conditions like systemic lupus erythematosus and rheumatoid arthritis, suggests overlapping immunopathogenic mechanisms between autoimmunity and cancer. These observations were made possible by integrating curated autoimmune gene sets with breast cancer transcriptomic datasets, uniquely revealing immune disruptions relevant to both diseases.

CXCR4 and MMP9, both upregulated in breast cancer tissues, have been linked to tumor invasion and immune evasion. CXCR4 antagonists and MMP9 inhibitors have shown promise in early cancer studies. CTLA4 and ICOS, two immune checkpoint regulators, are actionable targets in immunotherapy; anti-CTLA4 antibodies like ipilimumab and ICOS-targeting agents are under active clinical investigation. Conversely, downregulated genes such as KIT and PPARG suggest disrupted immune surveillance. While KIT is targeted by tyrosine kinase inhibitors (e.g., imatinib), its low expression may limit efficacy in breast cancer. PPARG agonists (e.g., pioglitazone) exhibit anti-tumor effects and may offer benefit in selected patient subgroups. Overall, integrating autoimmune gene expression profiles with drug sensitivity resources provides a foundation for identifying patient-specific therapeutic vulnerabilities and guiding immunomodulatory strategies in breast cancer.

Implications for breast cancer pathogenesis and future research

The identification of autoimmune-associated genes such as CXCR4, CTLA4, and MMP9 in the context of breast cancer highlights the emerging concept that chronic immune dysregulation and loss of self-tolerance may serve as underlying drivers of tumor evolution. These findings bridge the gap between tumor immunology and autoimmunity, suggesting that breast cancer may exploit similar immune escape mechanisms observed in autoimmune conditions. For instance, CTLA4 upregulation not only contributes to tumor immune evasion but also reflects pathways known to suppress autoreactive T cells - indicating a shared regulatory axis. Additionally, the enrichment of IL-17 signaling, traditionally associated with Th17-driven autoimmune inflammation, implies a potential role in shaping the pro-tumorigenic microenvironment. These insights extend current models of breast cancer pathogenesis beyond traditional oncogenic signaling to include immune tolerance mechanisms, offering promising avenues for dual-purpose immunotherapies that target both cancer and autoimmune dysregulation. Future studies may explore patient stratification based on autoimmune gene expression profiles to predict prognosis or response to immunomodulatory treatment.

Conclusion

This study highlights the critical role of autoimmune gene dysregulation in BC progression. Through comprehensive analysis, key pathways such as Cytokine-cytokine receptor interaction and IL-17 signaling were found to be significantly enriched in dysregulated autoimmune genes, suggesting their contribution to chronic inflammation and immune evasion in the tumor microenvironment. The identification of hub genes like CXCR4 and MMP9 underscores their potential as prognostic markers and therapeutic targets, given their roles in promoting metastasis and immune suppression. Conversely, downregulated genes such as KIT and PPARG point to compromised immune responses and poorer prognosis. These findings suggest that targeting dysregulated autoimmune pathways and their key genes could offer novel therapeutic strategies in BC, ultimately improving patient outcomes by restoring immune balance and inhibiting tumor growth and metastasis.

Acknowledgements

The authors extend their appreciation to the ongoing Research Funding Program (ORF-2025-552) King Saud University, Riyadh, Saud Arabia.

Disclosure of conflict of interest

None

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