Association Between Depression and Breast Cancer: TNF/TNFRSF1β and LEP/LEPR Axis

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Abstract

Depression contributes to enhanced initiation, development and metastasis of breast cancer. Despite epidemiological studies and experimental data suggest that depression and breast cancer may share a common biological mechanism, the results from these studies remain inconsistent. Here, we fully focus on the underlying biological mechanism behind the adverse effects of depression against breast cancer patients, and highlight the practical therapeutic intervention and improving quality of life. Publicly available datasets deposited in the Gene Expression Omnibus (GEO) were downloaded. Gene ontology and Kyoto Encyclopedia of Genes and Genomes pathway analyses of the differentially expressed genes (DEGs), which were extracted by using R tools, were performed. The protein-protein interaction network of the target DEGs was constructed using Cytoscape software and the hub genes were identified. In our study, we found that genes encoding proinflammatory cytokine, such as IL-1β and TNF, had significantly increased expression in depression. Following chronically stimulated by TNFα and IL-1β (usually for 14-18 days), inflammatory cancer-associated fibroblasts (CAFs) had elevated expression of inflammatory genes. Furthermore, the TNF/TNFRSF1β and LEP/LEPR regulatory axes were proven to be hub pathways of the crosstalk between depression and breast cancer. Our findings demonstrate that inflammatory factors are messengers linking depression and breast cancer, and provided further guidance in clinical medication.

1 Introduction

In 2020, with an estimated 2.3 million new cases of breast cancer (BC) diagnosed in women, breast cancer has officially replaced lung cancer as the most common cancer worldwide [1]. The CONCORD study revealed that the estimated five-year survival of BC patients ranges from 40–80% in many countries [2]. After a long period of treatment, breast cancer survivors are prone to suffer from psychiatric symptoms such as anxiety or depression [3]. Depressive symptoms are common during survivorship in breast cancer patients, and the incidence rate is up to 32.2% [4, 5]. Notably, depressive symptoms increase the risk of development and recurrence of BC [6]. Intervention for depression in breast cancer patients have a better prognosis [7]. These findings emphasize the importance of targeting interventions toward cancer survivors with depressive disorders. One explanation for the relationship between BC and depression may be the attendance of shared susceptibility genes and biological pathways that act as hubs linking these diseases. A recent Mendelian randomization study has of patients with depression with breast cancer risk has been performed; it demonstrated that aberrant genes disposition to depression increases risk for breast cancer overall and especially ER (-) breast cancer by 10–15% [8]. However, to date, the potential common biological mechanisms and molecular regulators of these common mechanisms are still ambiguous. Understanding the biological mechanisms by which depression confers risk will enable disruption of these processes.

The pathophysiology of depression likely involves many factors: autonomic stress response system, neuroendocrine regulation, inflammation, and so on [9, 10]. However, substantial evidence implies that inflammation is a possible underlying mechanism [11, 12]. Inflammation-related depression is present in

a subgroup of patients with depression, and inflammation-related depressive symptoms are part of an established depressive phenotype [13]. Increases in inflammatory cytokines [14], CRP [15], proinflammatory monocytes [16], and effective responses to anti-inflammatory treatment have been demonstrated by a previous study of BC patients with depression [17]. Accordingly, as the main producers of such inflammatory cytokines, CD14+ monocytes might be a promising bridge in the network between breast cancer and depression. Accumulating preclinical experiments and clinical studies indicate that psychosocial stress may incurs persistent inflammation within and around the tumor mass and fosters survival progression and aggressiveness of in situ cancer [18, 19]. As such, continuous chronic inflammation has become recognized as an important common biological mechanism for breast cancer and depression comorbidity.

The tumor microenvironment (TME) involves in the onset and development of BC [20, 21]. Previous studies have reported that cancer-associated fibroblasts (CAFs) are the primary regulators within the TME of breast cancer [22]. Inflammation, in the context of a chronic inflammatory disease, has substantial effects on the components of the TME and particularly on the plasticity of CAFs [23]. Thus, we focused on the TME. Findings have revealed that sustained stimulation by chronic inflammation leads to the transition of mesenchymal stem cells (MSCs) into inflammatory CAFs [24, 25]. These inflammatory CAFs can secrete tumor-promoting inflammatory cytokines, recruit immune cells, and interact with tumor cells to promote breast cancer progression [26]. Considering this evidence, we hypothesized that depression-derived inflammation in breast cancer may affect the TME, contributing to reprogramming of CAFs with downstream effects on inflammatory control. However, the genetic regulators of this common mechanism have not been explored.

Herein, we reanalyzed three gene expression profiling datasets, including datasets of peripheral blood mononuclear cells from depression patients, inflammatory CAFs, and tumor cells from breast cancer patients. Through further bioinformatics data mining, we generated evidence that inflammatory factors are messengers linking depression and breast cancer and provided further guidance in clinical medication, targeting of inflammation to treat breast cancer patients suffering from depression. In addition, we revealed the network between breast cancer and inflammatory CAFs and identified the hub genes of this network as common genetic regulators in both depression and breast cancer.

2 Materials And Methods

2.1 Data

Microarray data GSE147582, GSE147583, and GSE147584, conducted by GPL28312 platform, were downloaded from the Gene Expression Omnibus (GEO) (https://www.ncbi.nlm.nih.gov/geo/). They include data from 197 depression patients and 95 healthy patients. In these datasets, the expression of 32 genes of an inflammation-associated gene signature in CD14 + monocytes of depression patients were detected [27]. The microarray dataset GSE161762, established on the GPL16791 platform, includes 3 samples of inflammatory CAFs which were chronically induced by TNFα and IL-1β (usually for 14-18

days) and 3 untreated control samples [24]. The GSE10797 dataset describes the gene expression profile of 5 samples of normal mammary epithelial cells and 28 samples of breast carcinoma cells and was established on the GPL571 platform [28]. The list of depression-associated genes was retrieved from PubMed Gene (https://www.ncbi.nlm.nih.gov/gene/) based on the search terms “depressive disorder”, “dysthymic disorder”, “mood disorders”, and “affective disorders”. Figure 1 shows the bioinformatics data mining process.

2.2 Differentially expressed genes (DEGs)

In microarray datasets GSE147582, GSE147583, and GSE147584, we calculated the fold change (FC) by dividing the ΔCT scores of patients with depression by the mean ΔCT score of healthy controls, and the relative gene expression was expressed as an FC value [29]. One-sample t test was employed when we performed the comparisons for gene expression and corrected the false discovery rate (FDR) using the Benjamini–Hochberg method. Next, we used GraphPad Prism (version 8.0.1) to perform statistics to describe our data. Data is reported as the mean ± SEM. $P<0.05$ is regarded as statistically significant.

In the GSE161762 dataset, to obtain the DEG list, we investigated those genes with $|\log2(FC)|>2$ and $P<0.05$ using the R (4.1.0) package limma.

In the GSE10797 dataset, we investigated DEGs with $FC>1.5$ and $P<0.05$ using the R (4.1.0) package limma.

Functional enrichment analysis

ClusterProfiler package of R was used for Gene ontology (GO) enrichment. Cellular component (CC), biological process (BP) and molecular function (MF) categories with $P <0.01$ and q-value <0.01 were identified. To further uncover the underlying signaling pathways involved, Database for Annotation, Visualization and Integrated Discovery (DAVID) was used to perform Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. P 0.05 is statistically significant.

2.3 Ligand-receptor interactions identification

The ligands of inflammatory CAFs and their receptors on breast cancer cells were identified based on “cytokine-cytokine receptor interaction” pathway in the KEGG database and the Search Tool for the Retrieval of Interacting Genes (STRING) database. The crosstalk network was visualized by Cytoscape software. Following the construction of the interaction network containing the possible ligands and receptors, maximal clique centrality (MCC) algorithm was selected to identify hub genes.

3 Result

3.1 The differential expression of inflammation-associated genes within depression

Comparison of gene expression revealed that the expression of genes associated with inflammation was significantly higher in the group of BC patient with depression than in healthy controls. Fourteen up-regulated genes reached statistical significance after FDR correction, and four were significantly down-regulated. Among the up-regulated genes, genes encoding proinflammatory cytokine, such as IL-1β and TNF, had significantly increased expression (Figure 2).

3.2 Long-term TNFα and IL-1β stimulation of CAFs

In addition to our above findings, we attempted to determine how inflammatory cytokines affect CAFs, a fundamental component of the TME in breast cancer. We explored the GSE161762 dataset, which includes samples treated continuously with TNFα and IL-1β and untreated samples. The heatmaps and volcano plot demonstrated that the gene expression levels were strongly altered in CAFs that were persistently exposed to TNFα and IL-1β stimulation compared to those in control cells administered vehicle treatment (Figure 3). Gene expression analysis found 776 up-regulated genes and 751 down-regulated genes. To understand the function of these DEGs, GO enrichment analysis was conducted by applying the DESeq2 package of R tools. In terms of MF terms, the DEGs were highly enriched in “signaling receptor activator activity”, “receptor ligand activity”, and “cytokine activity”. In terms of the BP terms, the DEGs were primarily associated with “extracellular matrix organization” and “extracellular structure organization”; as these processes are fundamental to tumor stroma formation, the results are reasonable. In terms of CC terms, the DEGs were mostly enriched in “collagen-containing extracellular matrix”, “external side of plasma membrane”, and “synaptic membrane” (Figure 4A, B, C).

The terms “cytokine-cytokine receptor interaction”, “pathway in cancer”, and “PI3K-AKT signaling pathway” were enriched in the KEGG enrichment analysis. (Figure 4D).

3.3 Crosstalk between breast cancer cells and CAFs

Because cytokines secreted by inflammatory CAFs may affect breast tumor cells, we analyzed their crosstalk. In GSE1797, differential gene analysis identified 1009 up-regulated genes and 194 down-regulated genes. The DEGs were primarily enriched in “gland development” and “response to oxidative stress” in the BP category in GO analysis. The KEGG enrichment analysis identified the terms “PI3K-AKT signaling pathway”, pathway in cancer”, “MAPK signaling pathway”, and “Ras signaling pathway” as enriched. All these terms are related to the inflammatory process (Figure 5).

Given our results of pathway enrichment analyses, we decided to construct a network of cytokine-cytokine receptor interactions. Among the DEGs, 23 genes in inflammatory CAFs were determined to encode ligands, and 7 genes in breast tumor cells were determined to encode receptors. The integrated interaction network of crosstalk between inflammatory CAFs and breast cancer cells is constructed (Figure 6). The top 10 hub genes (GHR, CX3CR1, LEPR, IL13RA1, IFNGR1, CSF2, IL12A, IL6, IL7, and IL24) in the crosstalk network were determined based on the MCC algorithm, and these genes might be of great importance.

A total of 1140 depression-associated genes retrieved from the PubMed Gene, and this list was compared with the hub genes. The hub genes also found in the list of depression-associated genes were TNFRSF1β and LEPR.

4 Discussion

Breast cancer is the most prevalent type of malignant tumor and the leading cause of tumor-related morality in women. However, with the improvement of detection methods and various treatments, the mortality rate has declined. A systematic review based on seventy-two studies showed that the global prevalence of major depressive disorder (MDD) among individuals with breast cancer was 32.2% [5]. It has been reported that major depression remarkably affects the prognosis of breast cancer. Due to the inconsistent criteria used and the fact that depression has long been neglected, existing studies may not fully represent the scope of problems caused by depression in cancer populations. For example, studies on the possible contribution of chronic stress to breast cancer progression have mainly focused on epidemiology and have focused little on molecular biology [30]. In addition, it is difficult to unravel potential causal relationships between depression and breast cancer. Therefore, it is crucial to comprehensively and accurately explore possible pathways and mechanisms and the molecular regulators of common mechanisms linking depressive symptoms with poorer overall survival for breast cancer survivors.

In our study, we explored the GSE147582, GSE147583, and GSE147584 datasets to identify key inflammatory genes in depression patients for further analysis. The results from our present study demonstrated that most inflammation-related genes were overexpressed in depression patients, which is consistent with previous studies. Proinflammatory cytokines such as IL-1β and TNF-α show overall upregulation in depression, which suggests that immune activation is present. Indeed, the relationship between these proinflammatory cytokines and depression among patients with breast cancer has been confirmed by many researchers [31, 32]. IL-1β and TNF-α are generated by monocytes, and can induce MSCs to differentiate into inflammatory CAFs that promote the metastasis of breast tumor cells [33]. Thus, we explored the GSE161762 dataset to uncover the role of inflammatory CAFs that links tumor progression with depression-induced inflammation. With continuous stimulation with IL-1β and TNF-α, inflammatory CAFs showed drastic transcriptome changes. Based on GO term analysis, we discovered that many genes contribute to components of the TME. The KEGG enrichment analysis for the DEGs involved pathway in “cytokine-cytokine receptor interactor”, “pathway in cancer”, and “PI3K-AKT signaling pathway”. This result is consistent with formal reports that long-term stress is associated with the development of cancer. Thus, our preliminary results suggest that depression-derived inflammatory cytokines affect the TME, contributing to the reprogramming of CAFs, and that IL-1β and TNF-α could be a crucial part in the toxic effects of depression. Circulating level of IL-1β and TNF-α may be a reliable indicator and have important treatment implications for breast cancer patients suffering from depression.

In the TME, tumor cells and stromal cells communicate through a series of cytokines to reshape the microenvironment and promote the growth and metastasis of tumor cells [34]. Cytokines mainly

encompass interleukins, interferons, tumor necrosis factor, colony-stimulating factors, chemokines and growth factors. In our study, most of the DEGs were found to be enriched in the term “cytokine-cytokine receptor interaction”. Therefore, understanding the role of cytokines in the modulation of the interaction between inflammatory CAFs and tumor cells will be interesting.

Then, we compared the gene expression between breast cancer cells and normal breast epithelium and identified candidate receptors in the KEGG pathway term “cytokine-cytokine receptor interaction”. Similarly, we identified candidate ligands related to the term “cytokine-cytokine receptor interaction” among inflammatory CAFs. There were 21 up-regulated and 2 down-regulated ligands secreted by inflammatory CAFs, and 7 receptors for these ligands were expressed in tumor cells. A crosstalk network of the ligand, receptor, and interacting protein relationships was constructed using STRING and visualized using Cytoscape.

To reveal potential common molecular regulators, we identified the hub genes of the crosstalk network. Among these hub genes, TNFRSF1β and LEPR were found to be expressed in both breast tumors and depression. The TNF/TNFRSF1β regulatory axes participates in the activation of NF-κB signaling pathway, which is a common occurrence in cancer and will influence the treatment outcomes of breast cancer [35]. TNFRSF1β is a known factor involved in the pathogenesis of depression and is overexpressed in depression [36]. Radiation-treated breast cancer patients who exhibited moderate-to-severe depression exhibited overexpression of gene transcripts regulated by NF-κB [37]. It has been suggested that the TNFRSF-NF-κB axes may related to the development of BC. Regarding the leptin-leptin receptor (LEP/LEPR) pathway, a recent study confirmed that higher leptin was associated with MDD in both patients with remission and those with existing disease [38]. Furthermore, leptin has a proliferative effect in breast cancer cells [39]. Renna and his colleague found that obese breast cancer survivors with a significantly higher leptin level [40]. In the context of depression, high circulating LEP levels may activate downstream signaling pathways by bind to the overexpressed LEPR to promote breast carcinogenesis. In mouse model research, periodic cycles of a fasting-mimicking diet, with leptin-lowering effects, can promote breast tumor regression and reverse acquired drug resistance [41]. Hence, the two core genes LEPR and TNFRSF1β may increase risk among breast cancer survivors with depression. In addition, there is a potential cancer-preventive effect of targeting the TNF/TNFRSF1β regulatory axes and LEP/LEPR pathway.

In the era of precision medicine, susceptibility gene testing is considered an effective way to predict the prognosis of disease and evaluate treatment outcomes. The results of such tests related to LEPR and TNFRSF1β may remind healthcare providers to be more proactive in addressing depressive symptoms; for example, they could administer frequent questionnaires or suggest drug intervention. Depressive symptoms are a common problem in breast cancer patients. Therefore, a more detailed understanding of these symptoms, combined with a comprehensive understanding of biomarkers of inflammation, might aid doctors identify high-risk patients with poor prognosis and help the development of potential therapeutic targets. However, the limitations of our study need to be acknowledged. The molecular

mechanisms of inflammation-related depressive symptom-induced breast tumor progression require further investigation and more experimental validation.

5 Conclusion

In conclusion, we carried out an integrated bioinformatics analysis to explore the relationship between inflammation-related depressive symptoms and breast cancer. Our results showed that elevated inflammatory cytokines were associated with depressive symptoms. Long-term chronic inflammatory stimulation promotes the secretion of cytokines from inflammation-related CAFs in the TME, which act on breast tumor cells. Targeting LEPR and TNFRSF1β could be a promising intervention to interrupt depression-driven systemic perturbations. Disruption of the mechanisms shared between breast cancer and depression-producing inflammation will improve the outcomes of breast cancer patients.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jiaying Lin and Guangman Cui. The first draft of the manuscript was written by Jiaying Lin and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

TCGA and GEO belong to public databases. The patients involved in the database have obtained ethical approval. Users can download relevant data for free for research and publish relevant articles. Our study is based on open source data, so there are no ethical issues and other conflicts of interest.

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Figures

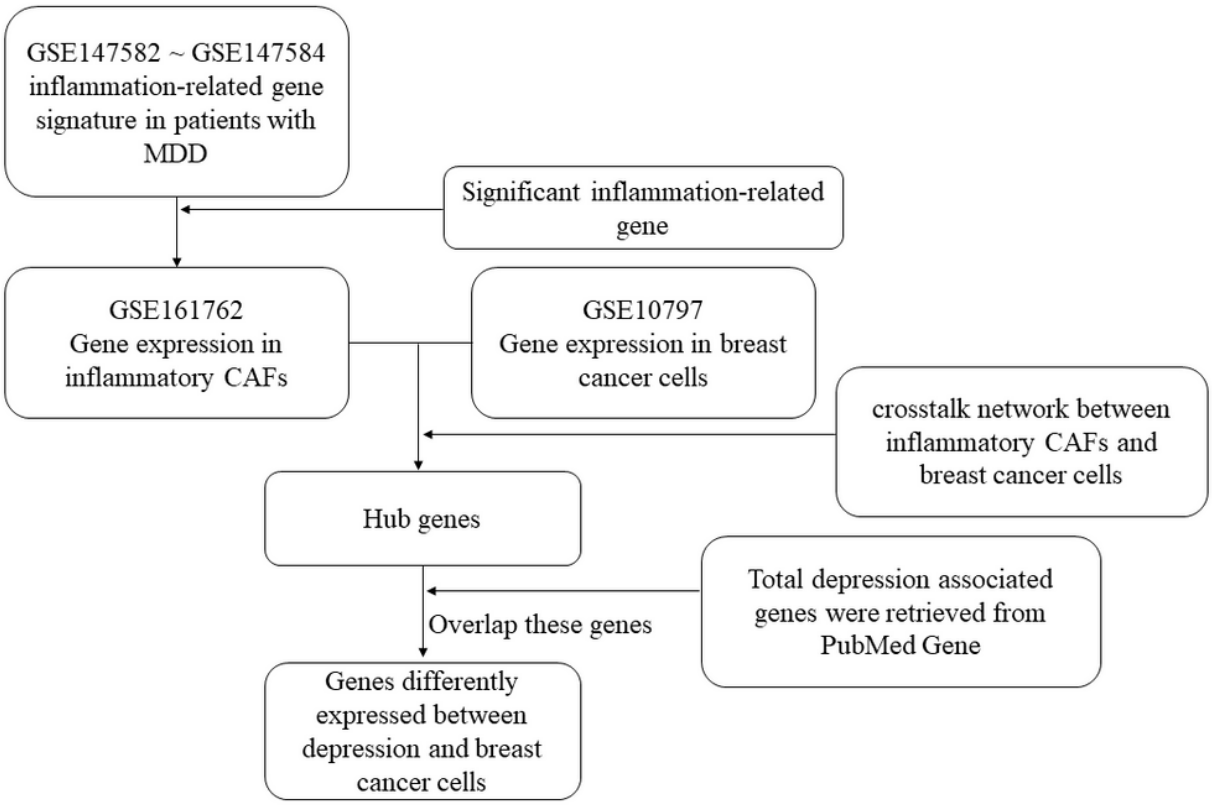

Figure 1

Flow chart. The flow chart provided detailed step of the bioinformatic mining

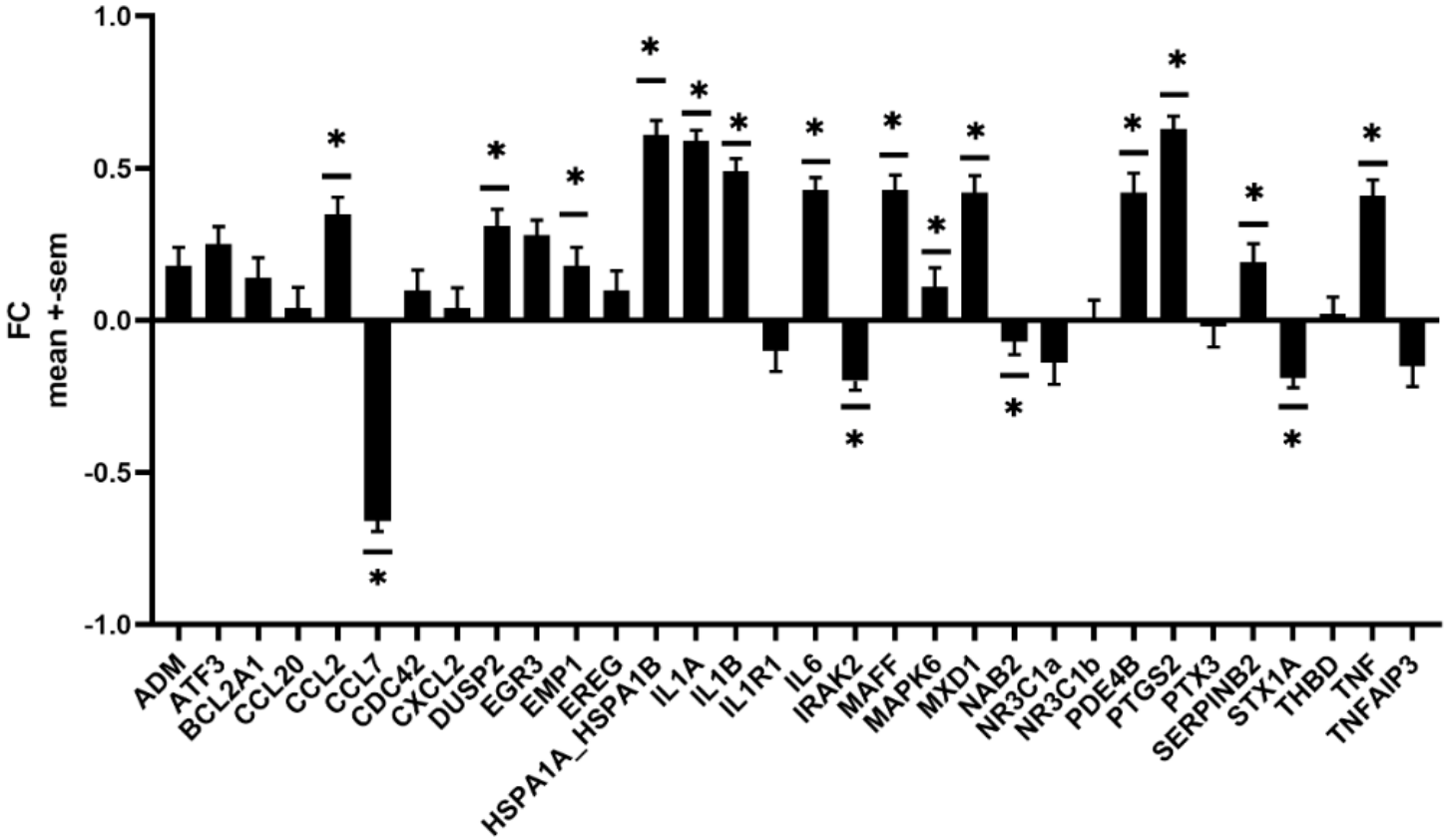

Figure 2

The inflammation-related genes expression pattern in monocytes of MDD patients

The fold change (FC) values between MDD patients (n = 197) and health controls (n = 95) are displayed. *p 0.05

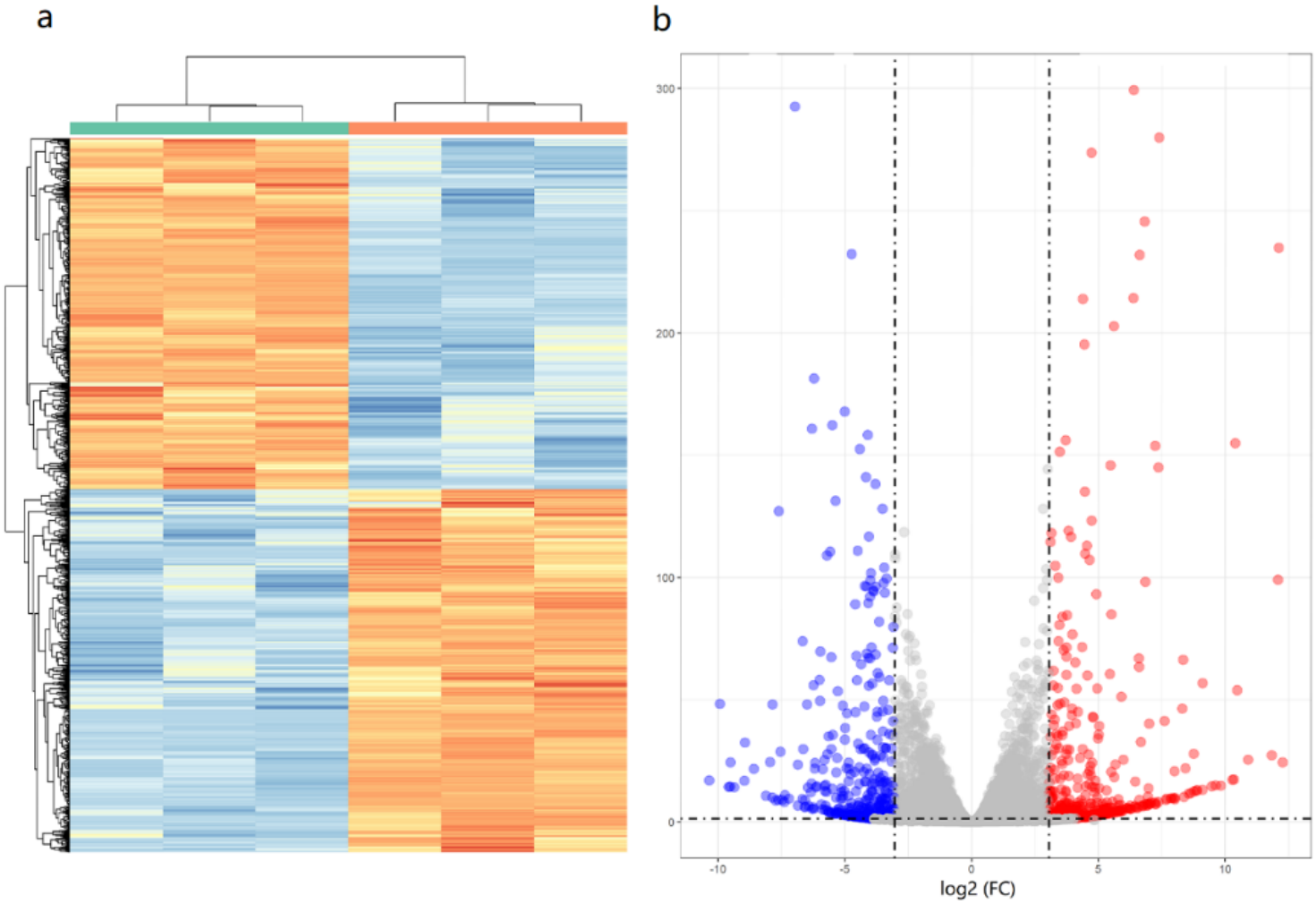

Figure 3

Differentially expressed genes in inflammatory CAFs

A: Heatmap presented the differential expressed genes. B: volcano plot showed the up-regulated (showed in red) and down-regulated (showed in blue) genes. |log2(FC)|>2 and P<0.05 were statistically significant. FC: Fold Change.

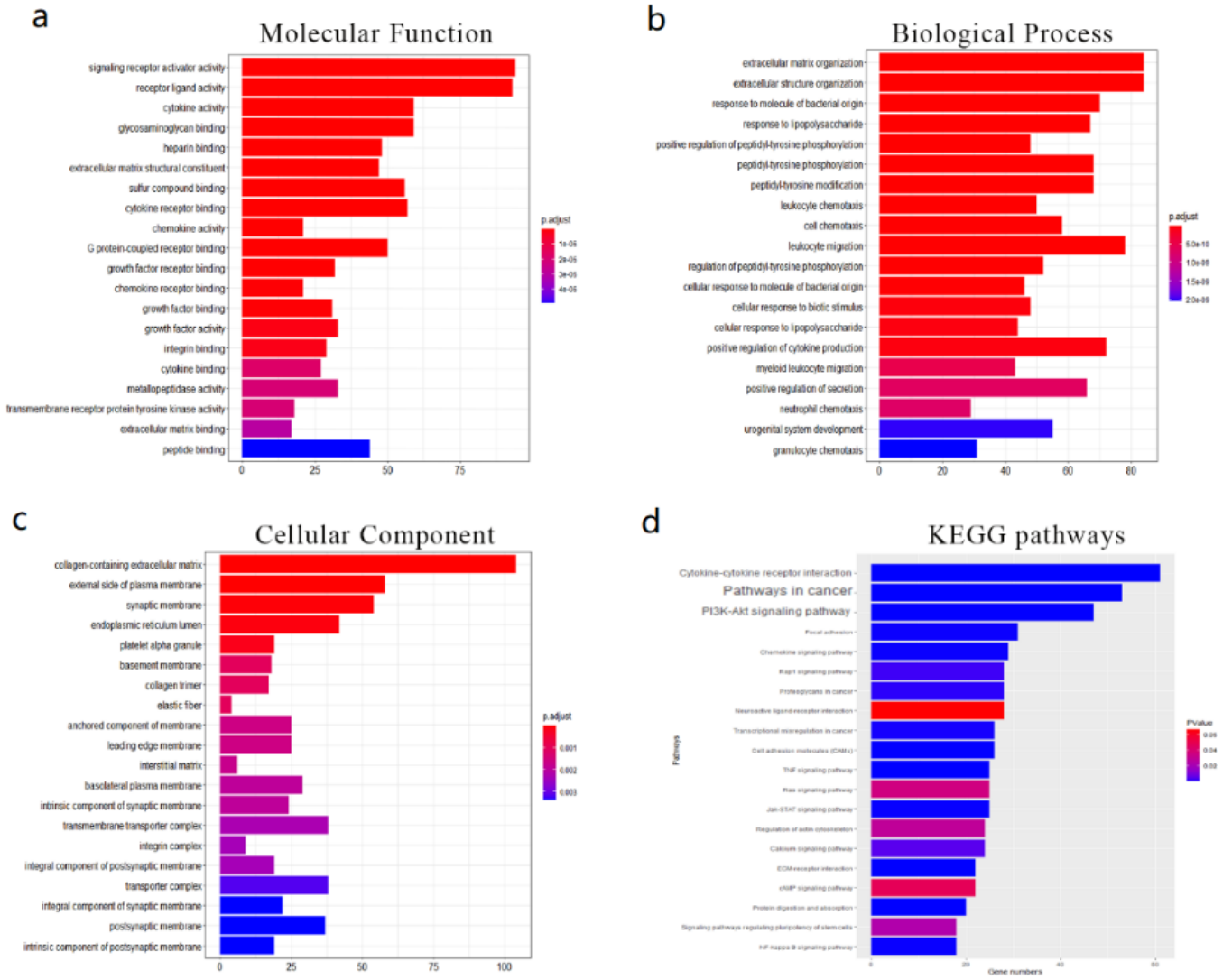

Figure 4

Gene Ontology (GO) analysis and KEGG pathway of differentially expressed genes in inflammatory CAF

A: Biological Process, B: Cellular Components, C: Molecular Functions of GO analysis. D: KEGG pathway

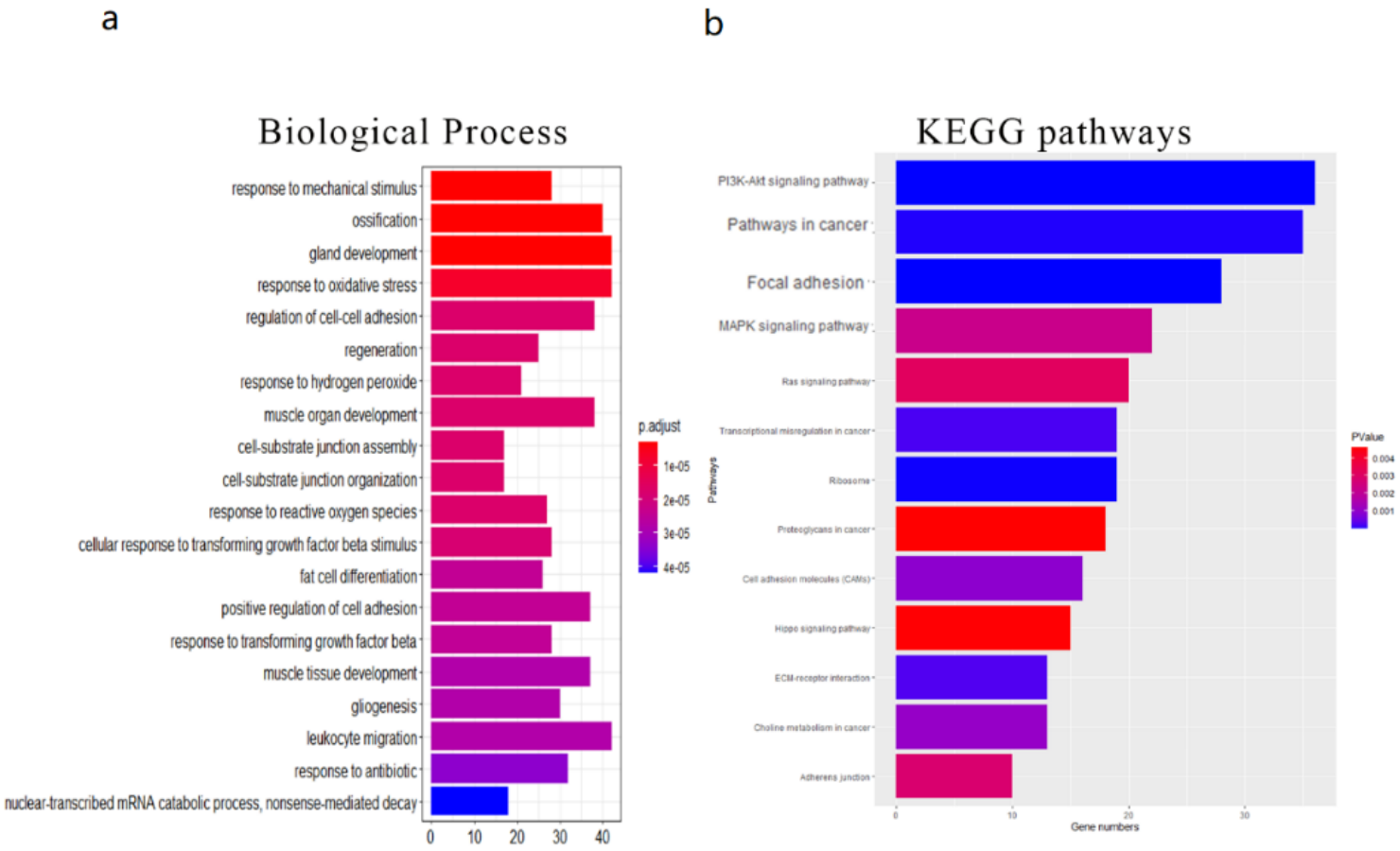

Figure 5

Gene Ontology (GO) analysis and KEGG pathway of differentially expressed genes in breast tumor cells. (A) Biological Process, (B) KEGG pathway

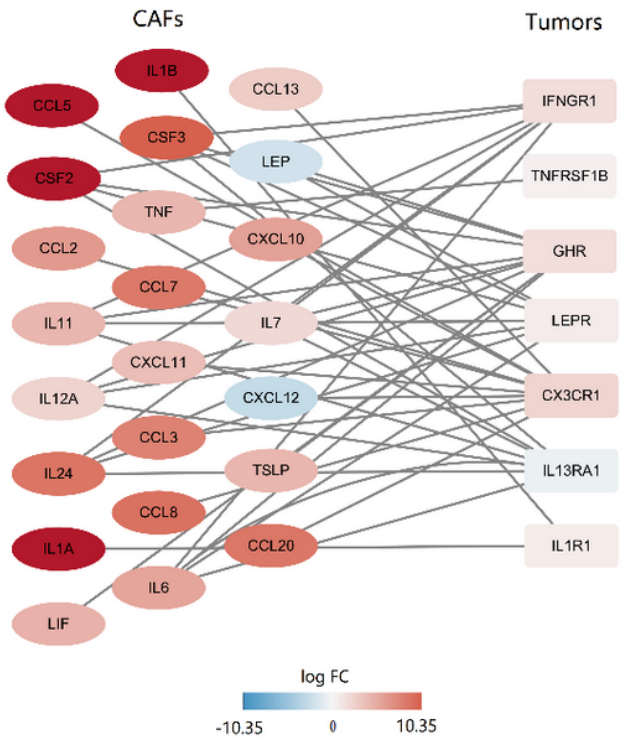

Figure 6

The crosstalk between breast cancer cells and inflammatory CAFs