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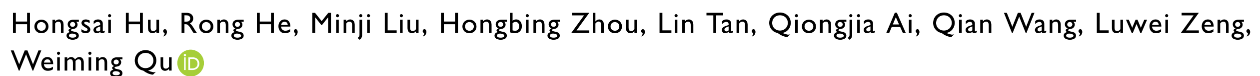
ORIGINAL RESEARCH

C-X-C Motif Chemokine 12 Was Identified as a Potential Gene Target in the Treatment of Crohn's Disease



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Object: The present study aimed to identify hub genes associated with the treatment and control of active and inactive Crohn's disease (CD).

Methods: Differentially expressed genes (DEGs) were identified in normal, active CD, and inactive CD samples from GSE95095 dataset. Intersection genes screened by Venn diagram in DEGs. Subsequently, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses were conducted on the intersection genes. The protein-protein interaction (PPI) network was used to screen of hub gene. The expression and mRNA levels of CXCL12 in CD and ROC curves in GSE95095 dataset. Signaling pathways of hub genes and their correlation with immune cells were analyzed by gene set enrichment analysis (GSEA), EPIC, and ESTIMATE, respectively. Finally, immunohistochemistry (IHC) and Reverse Transcription-Polymerase Chain Reaction (RT-PCR) were used to detect the expression of the hub gene in normal, inactive, and active CD tissues.

Results: In GSE95095 dataset, CXCL12 was identified as the most hub gene by limma analysis, Venn diagram and A protein-protein interaction (PPI) network. CXCL12 expression was highest in active CD ($p < 0.001$) followed by inactive CD ($p < 0.01$). Subsequently, it was validated through IHC and RT-PCR in normal intestinal mucosal, active CD, and inactive CD. *CXCL12* was overexpressed in active and inactive CD (IHC: $p < 0.001$ and RT-PCR: $p < 0.001$, respectively). CXCL12 expression in active CD was determined via analysis with receiver operating characteristic (ROC) curves. The specificity and sensitivity were 0.875 and 0.625, respectively, the accuracy was 72.92%, the area under the curve (AUC) was 0.780, and the 95% confidence interval (CI) was in the range of 0.648–0.912. CXCL12 expression was closely correlated with various immune cells.

Conclusion: CXCL12 is overexpressed in active CD and is closely correlated with various immune cells. We propose that *CXCL12* as a potential target genes for the treatment and management of both active and inactive CD.

Keywords: Crohn's disease, C-X-C motif chemokine 12, gene target, immune cell

Introduction

Crohn's disease (CD) is also known as localized or regional enteritis. The precise etiology of this intestinal inflammatory disease is unknown. This condition can occur in any part of the gastrointestinal tract.[1] However, it is most often confined to the terminal ileum and right colon.[2] CD and chronic nonspecific ulcerative colitis (UC) are collectively designated inflammatory bowel disease (IBD).[3] In the United States, the incidence of CD is ~58/100,000 children and 119–241/100,000 adults.[4,5] CD can affect people of any age and may have a negative impact on the quality of life (QoL).[4,6] Clinical symptoms of CD include abdominal pain, diarrhea, intestinal obstruction, and extraintestinal manifestations such as fever and nutritional disorders.[7,8] Though there is currently no specific therapy for CD, common treatment approaches include the control of disease progression and the management of symptoms.[9] Nevertheless, certain patients with CD require surgical resection of the diseased intestinal tract to help prevent deterioration of overall function.[10] The rate of

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CD recurrence is associated with the extent of the lesion, severity of disease progression, prolongation of disease course, and patient age.[11] CD may be the result of exposure to a combination of environmental, immunological, and microbiological factors in genetically susceptible populations.[12]

Though CD is immune-related, it is not an autoimmune disease.[13] At present, it is known that the inflammatory response caused by abnormal immune system reactions in the intestinal mucosa plays an important role in the pathogenesis of IBD. The immune response is related to the release of inflammatory mediators, including cytokines, interleukins, tumor necrosis factor, and the melanocortin system.[14,15] Approximately half the total risk of developing CD is related to genetics, and > 70 genes have been linked to CD onset and progression.[16] Lifestyle and environmental factors also have significant impacts on CD, such as smoking and regular physical activity.[17,18] Smokers are twice as likely to develop CD as non-smokers, and regular physical exercise can improve the condition of mild to moderate CD.[17,18] However, patients with CD often exhibit poor adherence to this type of exercise.[18] CD is detected and diagnosed mainly through colonoscopy and biopsy.[19] The various available treatment options aim to alleviate symptoms and reduce the risk of recurrence.[1,5,8] In newly diagnosed patients, corticosteroids may rapidly alleviate inflammation-related symptoms while methotrexate or thiopurine may lower the risk of recurrence.[5,8] The most important metric in CD management is the duration of therapeutic activity. Current research focuses mainly on CD therapy including the identification of CD-associated genes and drugs that target active CD.

The present study analyzed the DEGs in active CD, inactive CD, and normal tissue samples, screened the hub gene from the DEGs through a PPI network, analyzed hub gene expression, and evaluated the correlation between the hub gene and the immune cells in the GSE95095 dataset.

Methods and Materials

Data Collection and Workflow

The mRNA transcriptome data for CD were obtained using the GSE95095 dataset from the GEO database (https://www.ncbi.nlm.nih.gov/geo/). The GSE95095 dataset included 6 normal, 24 inactive CD, and 24 active CD tissue samples, and the workflow is illustrated in Figure 1.

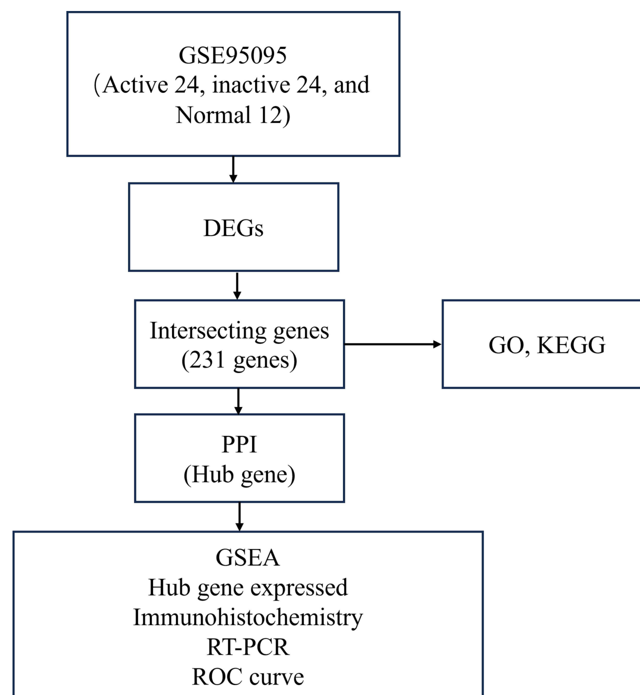

Figure 1 The workflow is illustrated.

DEG and Intersection Gene Screening

The gene profile of the GSE95095 dataset was obtained using the cluster profile package in R v. 4.0.2 (http://www.r-project.org/). Limma v. 3.40.6 (https://bioconductor.org/packages/release/bioc/html/limma.html) was used to analyze the DEGs, and the thresholds were false discovery rate (FDR) < 0.01 and |log2 (fold change [FC])| ≥ 1.5. The intersection genes were obtained by plotting the DEGs from all three groups in a Venn diagram.

GO and KEGG Pathway Analyses

The GO functional enrichment analysis includes biological process (BP), molecular function (MF), and cellular component (CC). KEGG analyzes advanced molecular-level functions and mechanisms in biological systems. The Database for Annotation, Visualization, and Integrated Discovery (DAVID) online tool (http://david.ncifcrf.gov/) was used to perform the GO and KEGG pathway analysis of the key genes in the module. The enrichment results were then downloaded and mapped in R software, and P < 0.05 and FDR < 0.25 indicated statistical significance.

PPI Network

A PPI network of the intersection genes was constructed using the STRING protein database (http://string-db.org/). The network was analyzed and visualized with Cytoscape v. 3.6.1 (http://www.cytoscape.org/). The degree value for each gene was calculated using the network analyzer tool built into Cytoscape, and the hub gene was obtained based on the betweenness centrality (BC) value.

EPIC and ESTIMATE

The immune cell deconvolution method EPIC was performed using the IOBR v. 0.99.9 package in R (https://www.ncbi.nlm.nih.gov/pmc/articles/pmc8283787/). B cells, cancer-associated fibroblasts (CAFs), CD4_T cells, CD8_T cells, endothelial cells, macrophages, natural killer (NK) cells, and other immunocytes in the GSE95095 dataset were detected. ESTIMATE v. 1.0.13 https://bioinformatics.mdanderson.org/publicsoftware/estimate/) was then run to detect the presence of infiltrating immune cells. The stromal, immune, and ESTIMATE scores were calculated for each sample based on the hub gene expression in the GSE95095 dataset.

ROC Curve

The ROC diagnosis was conducted using pROC v. 1.18.0 (https://packages.debian.org/bookworm/r-cran-proc) and ggplot2 v. 3.3.6 (https://ggplot2.tidyverse.org/) in R v. 4.0.2. The specificity, sensitivity, AUC, and CI for the hub gene in the GSE95095 dataset were then evaluated.

Tissue Collection

Twelve active CD, 12 inactive CD, and six normal intestinal tissues were collected by colonoscopy and frozen at −80 °C until the subsequent IHC and RT-PCR. Two pathologists independently confirmed the specimens through IHC. All tissues were collected between January and June 2023 at Zhuzhou Central Hospital, Tianyuan District, Zhuzhou, Hunan, China. The tissue harvest methodology was approved by the Ethics Committee of Zhuzhou Central Hospital (No. 20231072), and each eligible participant provided written informed consent (Clinical information of 30 fresh tissue samples is provided in Supplementary Table 1).

IHC and RT-PCR

For the IHC, fresh tissue was fixed with 4% (v/v) formaldehyde, dehydrated, and subjected to high-pressure antigen repair. The samples were then blocked with goat serum and incubated overnight with primary antibody (No. ab185966; 1:400; Abcam, Cambridge, UK). The next day, the tissues were exposed to secondary antibody, and color development was performed with a diaminobenzidine (DAB) chromogen kit. *CXCL12* immunohistochemical analysis: observed and photographed under a high-power microscope (20x), and the color of CD1a positive is brown. The Image J1.5 software measures the integrated option density (IOD) and area value of each image, and then calculates the mean density value (mean density=IOD/area), which reflects the unit area concentration of *CXCL12* protein.

Table 1 RT-PCR Primer Information

Gene name	Primer sequence (5′-3′)
GAPDH-F	ACAGCCTCAAGATCATCAGC
GAPDH-R	GGTCATGAGTCCTTCCACGAT
CXCL12-F	TGCCCTTCAGATTGTAGCCC
CXCL12-R	GCCCTTCCCTAACACTGGTT

For the RT-PCR, total RNA was extracted by the TRIzol method and reverse-transcribed into cDNA with a reverse transcription kit (TaKaRa, Dalian, China) according to the manufacturer's instructions. The cDNA was then integrated into the RT-PCR system along with the primers listed in Table 1. Fold change *CXCL12* expression was compared between the experimental and control groups by the $2^{-\Delta\Delta Ct}$ method.

Statistical Analysis

Student's *t*-test was conducted using the *t*-test function (https://www.statmethods.net/stats/ttest.html) in R to detect significant differences between the experimental and control groups, and $p < 0.05$ was considered statistically significant. All graphs were plotted using the ggplot2 package in R software.

Results

DEGs in Active and Inactive CD Were Screened

The DEGs of the active and inactive CD tissues in the GSE95095 dataset were screened. In the active CD vs inactive CD tissue sample comparison, there were 928 upregulated and 847 downregulated genes. In the inactive CD vs normal tissue sample comparison, there were 188 upregulated and 683 downregulated genes. In the active CD vs normal tissue sample comparison, there were 3,217 upregulated and 1,423 downregulated genes (Figure 2A–F). A Venn diagram analysis of the

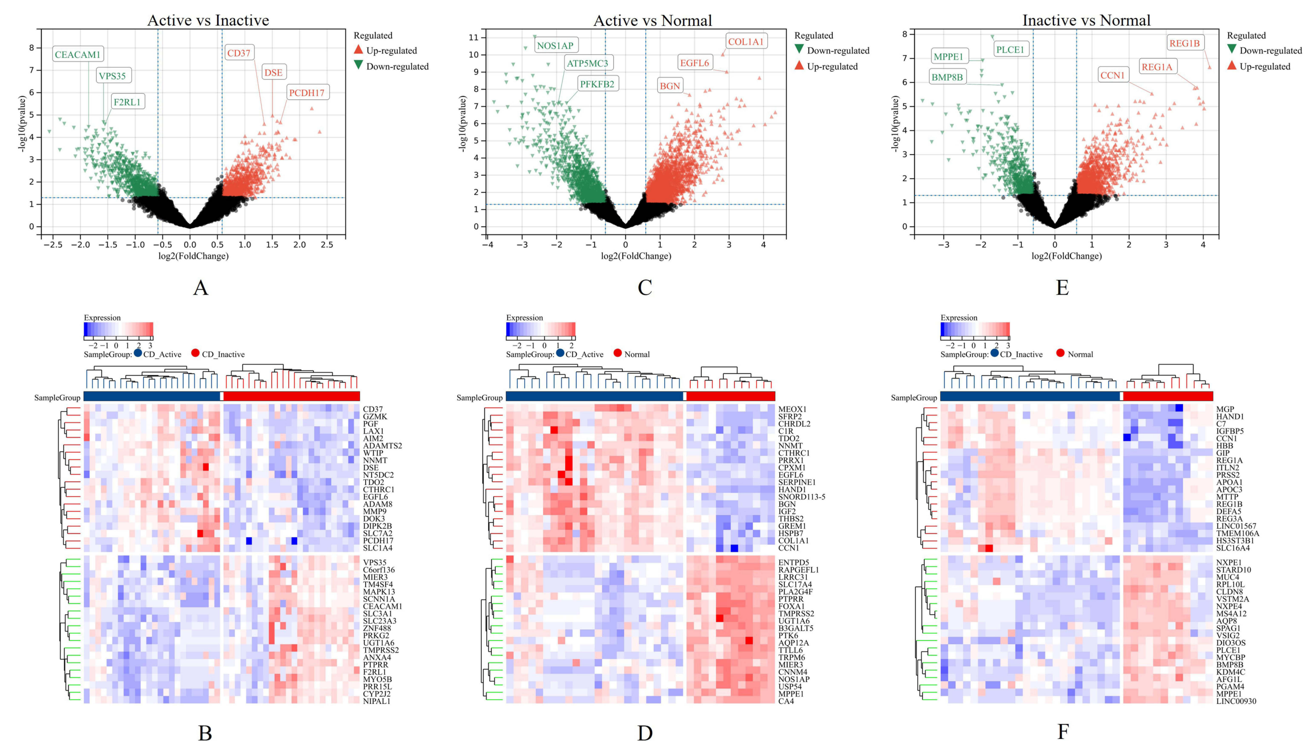

Figure 2 Screening for differential gene expression (DEGs) and Key genes in GSE95095 dataset. (**A, C**, and **E**) The volcano plot of DEGs in inflamed and uninflamed of CD from GSE179285 dataset. (**B, D**, and **F**) The heatmap of the DEGs and the top 40 genes were showed.

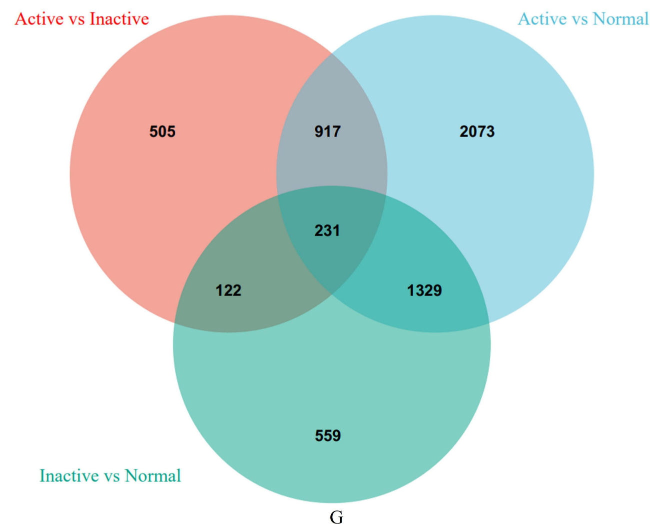

Figure 3 A Venn diagram identified the intersection genes for the three DEGs groups.

DEGs in the active CD, inactive CD, and normal tissue samples revealed 231 key intersection genes (Figure 3 and Supplementary Table 2).

GO and KEGG Pathway Analyses of Key Genes

DAVID software was used to perform the GO enrichment and KEGG pathway analyses of the 231 key genes. The GO functions included multicellular organismal process, cell migration, locomotion, sulfur compound binding, molecular function regulator, and structural molecule activity conferring elasticity ($p < 0.05$; Figure 4A–C). The KEGG analysis included the Interleukin (IL)-17 and Peroxisome proliferator-activated receptor (PPAR) signaling pathways, Fc gamma R-mediated phagocytosis, and Proteoglycans in cancer ($p < 0.05$; Figure 4D).

PPI Network Identification and GSEA of Hub Genes

The STRING online website analyzed the protein network nodes for 274 key genes. The PPI results were then analyzed with Cytoscape, its cytohubba plugin was used to estimate the node degree value, the latter identified *CXCL12* as the hub gene in the GSE95095 dataset (Figure 5A), and *CXCL12* was then subjected to GSEA. *CXCL12* was significantly associated with the enrichment of BUTANOATE_METABOLISM (ES = −0.4971, NP = 0.0309), CELL_ADHESION_MOLECULES_CAMS (ES = 0.4338, NP = 0.01), GLYCOSPHINGOLIPID_BIOSYNTHESIS_LACTO_AND_NEOLACTO_SERIES = −0.5527, NP = 0.0245), STEROID_BIOSYNTHESIS (ES = −0.5264, NP = 0.0451), CALCIUM_SIGNALING_PATHWAY (ES = 0.3535, NP = 0.0376), T_CELL_RECEPTOR_SIGNALING_PATHWAY (ES = 0.4009, NP = 0.0373), MAPK_SIGNALING_PATHWAY (ES = 0.3370, NP = 0.0253), and NOD_LIKE_RECEPTOR_SIGNALING_PATHWAY (ES = 0.4961, NP = 0.0208) (Figure 5B).

CXCL12 Was Overexpressed and Closely Associated with Inflammation in CD

CXCL12 was overexpressed in the active CD tissue samples from the GSE95095 and GSE179285 datasets ($p < 0.001$, Figure 6A). The specificity and sensitivity of *CXCL12* in CD were determined through ROC curves and found to be 0.875 and 0.625, respectively. The accuracy rate was 72.92%, and the AUC = 0.780 (95% CI = 0.648–0.912) (Figure 6B). Six normal intestinal mucosal and 24 CD tissues were identified by IHC and RT-PCR. *CXCL12* was overexpressed in active and inactive CD ($p < 0.001$ and $p < 0.001$, respectively; Figure 6C and D).

Correlation Between CXCL12 Expression and Immune Infiltration Cell

The correlation between *CXCL12* and immune cell infiltration in the GSE95095 dataset was then analyzed. Significant differences were detected between *CXCL12* and the stromal ($p < 0.0001$), immune ($p < 0.05$), and ESTIMATE scores

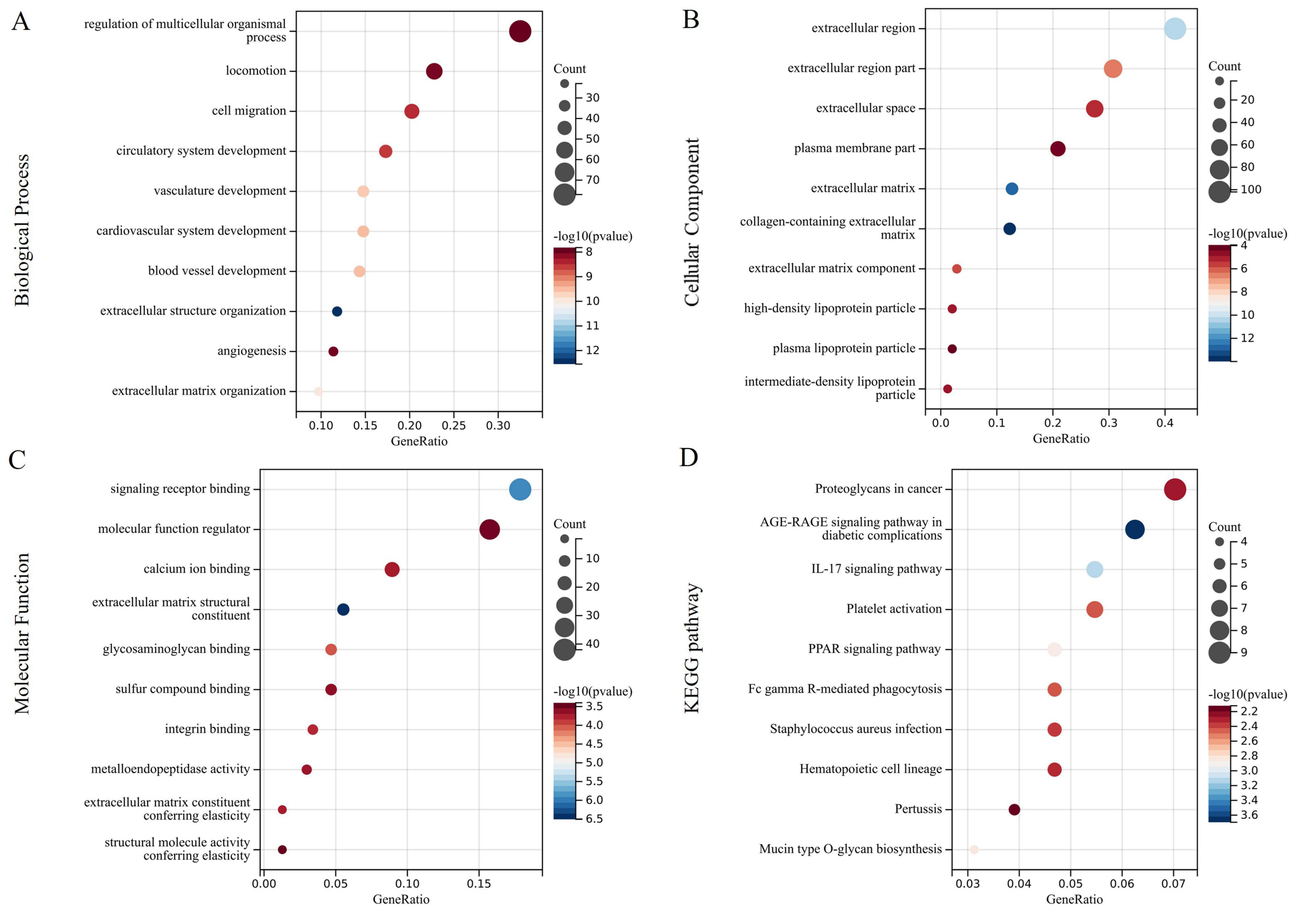

Figure 4 GO and KEGG pathway analysis. (**A**) biological process; (**B**) cellular component; (**C**) molecular function; (**D**) KEGG pathway.

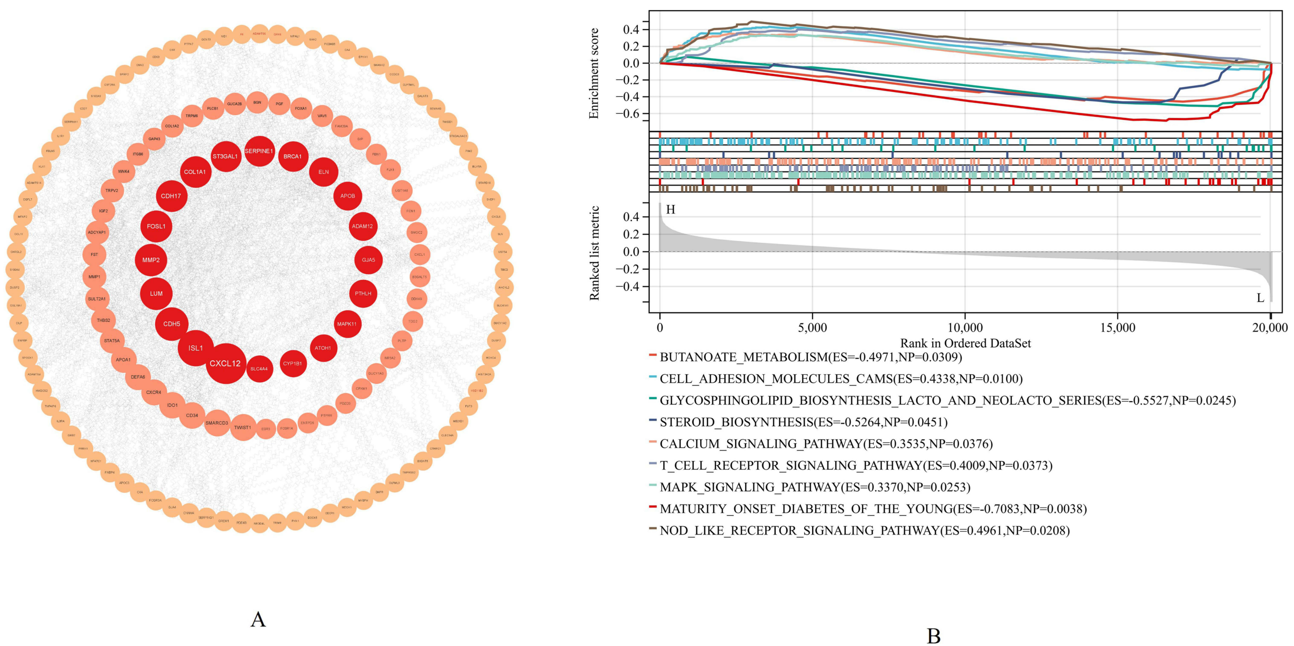

Figure 5 Protein-Protein Interaction (PPI) networks identify and gene set enrichment analysis (GSEA) of hub gene. (**A**) PPI networks identified CXCL12 as a hub gene. (**B**) CXCL12 was analyzed by GSEA in GSE95095 dataset.

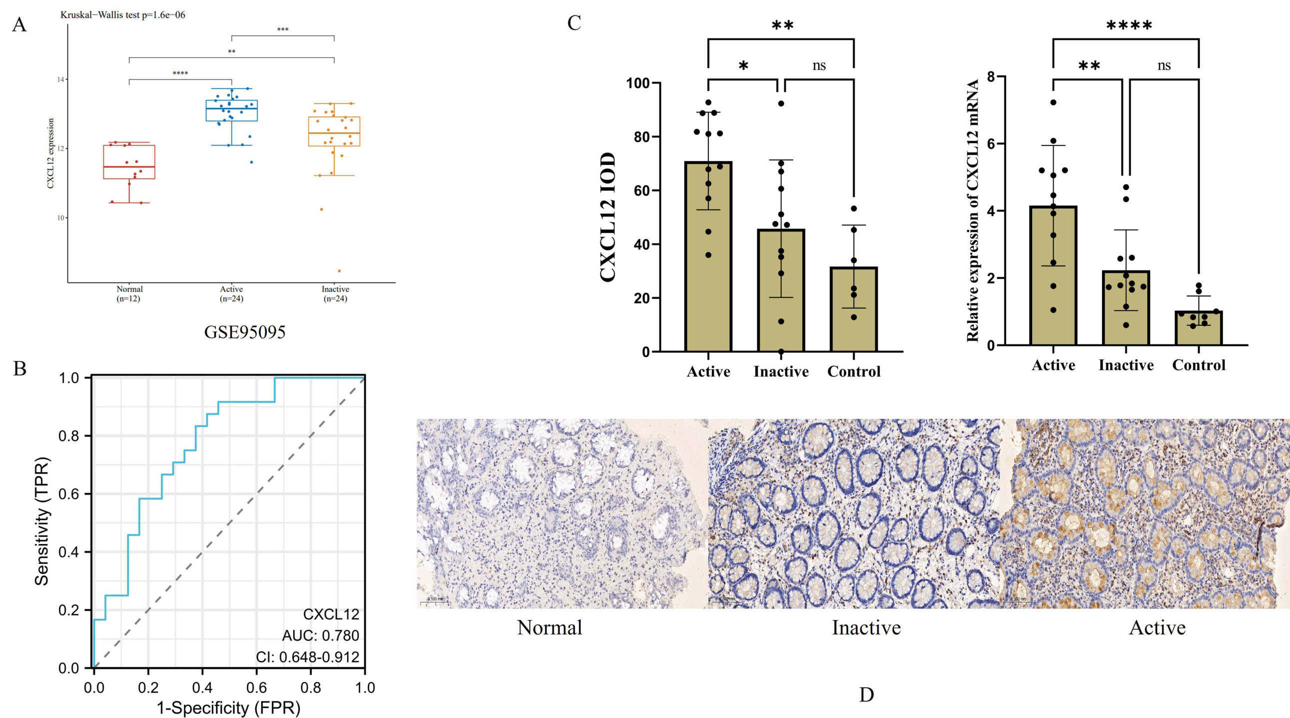

Figure 6 The expression and mRNA levels of CXCL12 in CD and ROC curves. (**A**) CXCL12 was overexpression in inflamed CD in GSE95095 dataset. (**B**) The specificity and sensitivity of CXCL12 was analyzed by ROC curves in inflamed CD. (**C**) The IOD and the mRNA levels of CXCL12 was significantly overexpression in CD tissues. (**D**) Immunohistochemistry of CXCL12 in CD and normal intestinal mucosal tissues (Brown color indicates expression of CXCL12). (*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001).

(p < 0.0001) (Figure 7A). The EPIC method was used to analyze *CXCL12* and the immune cells and disclosed significant correlations among them (Figure 7B). The immunocytes include B cells (p < 0.01), CAFs (p < 0.0001), CD4_T cells (p < 0.05), endothelial macrophages (p < 0.0001), and others cells (p < 0.0001) (Figure 7B).

Discussion

The current therapeutic approach for CD focuses on controlling its symptoms and transforming active CD into inactive CD.[20] However, it does not prevent CD-related intestinal damage.[20] Up to one-half of all patients with CD in clinical remission continue to present inflammation.[21] Hence, novel treatment methods for CD should primarily control inflammation rather than merely ameliorate symptoms.[22]

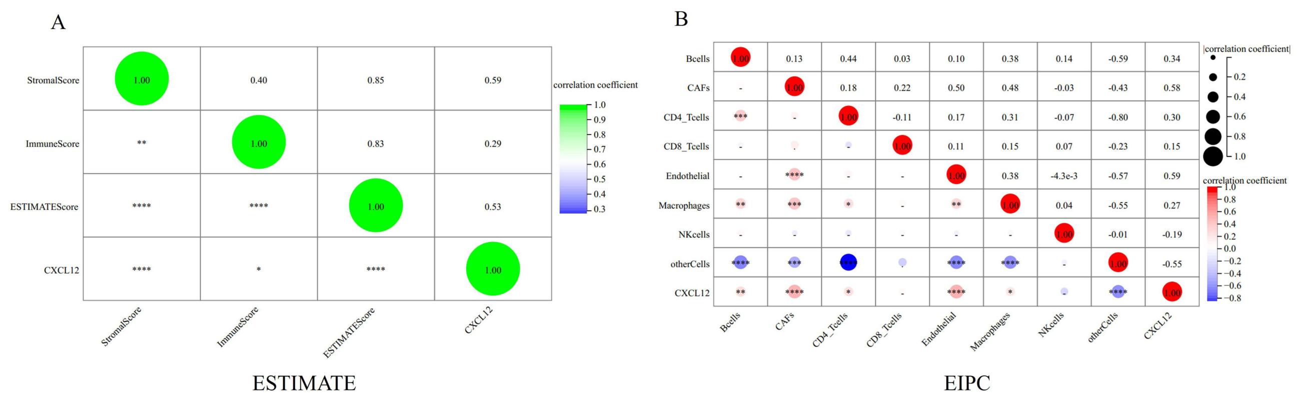

Figure 7 Correlation between CXCL12 and immune infiltrating cells. (**A**) There was a significantly negative correlation between CXCL12 and Stromal Score, Immune Score, and ESTIMATE Score. (**B**) The EPIC method analyzed the association between CXCL12 and immune cells, revealing significant correlations, including B cells, CAFs, CD4 T cells, endothelial macrophages, and other immune cells. (*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001).

Here, we identified the DEGs of active and inactive CD in the GSE95095 dataset and screened hub genes among the DEGs. *CXCL12* was deemed the hub gene common to both active and inactive CD. It was overexpressed in the active CD tissue samples from both the GSE95095 and GSE179285 datasets. IHC and RT-PCR were used to analyze 6, 12, and 12 normal intestinal mucosal, active CD, and inactive CD tissues, respectively, and validated that *CXCL12* was overexpressed in CD.

CXCL12, also known as stromal-derived factor-1 (SDF-1), is a CXC subfamily chemokine member. It is designated a pre-B-cell growth-stimulating factor (PBSF) as it plays an important role in pre-B cell proliferation and differentiation.[23] Unlike other inflammation-induced chemokines, *CXCL12* is stably expressed in the body in the absence of any pathogen invasion.[24] It is expressed in the liver, lungs, heart, kidneys, bone marrow, lymph nodes, vascular endothelial cells, interstitial fibroblasts, and osteoblasts. All the foregoing organs, tissues, and cells may secrete CXCL12 constitutively.[25] *CXCL12* participates in numerous pathophysiological processes.[23] It regulates homeostasis, inflammation, wound healing, and tissue repair.[24] Dotan et al[26] reported that intestinal epithelial cells (ICES) in normal intestinal mucosae express *CXCL12. CXCL12* expression is higher and more widely distributed in the ICES of patients with IBD than in those of normal controls. Zheng et al[27] identified essential genes and performed drug discovery for IBD via text mining and bioinformatics analysis. They identified *CXCL12* as a potential key gene implicated in CD and found that it targeted 26 existing drugs administered as CD therapy. Linares et al[28] biopsied normal, slightly inflamed, and severely inflamed ileal tissues, measured their chemokine and receptor expression levels, and conducted functional enrichment analyses on them. The monoclonal antibody adalimumab and the integrin blocker vedolizumab significantly inhibited *CXCL12*-promoting antigen presentation by dendritic cells (DCs) as well as the initiation of leukocyte extravasation.[28] The results of the foregoing studies were consistent with our observation that *CXCL12* was overexpressed in active CD.

Neutrophils, monocytes, macrophages, DCs, innate lymphoid cells, and NK cells mediate intestinal innate immunity.[29] Innate immune cells resist the invasion of intestinal microbial pathogens and remove them as well.[30] Innate immune cells constitute part of the first line of defense and initiate adaptive immunity. Changes to the preceding equilibrium may trigger intestinal inflammation and IBD.[30] Innate immune cells may produce both cytokines and chemokines such as *CXCL12* which have several functions in the immune system.[31]

The present study disclosed a correlation between *CXCL12* expression and immune cell infiltration. It also showed that *CXCL12* is closely associated with various different immunocytes including B cells, CAFs, CD4 T cells, endothelial macrophages, and other immune cells. An animal experiment revealed that silencing *CXCL12* fortified the immunosuppressive tumor microenvironment (TME) and increased immune cell infiltration.[32] The CXCR4/CXCL12 axis biases the TME mainly towards dampening the immune responses.[33] *CXCL12* may inhibit T cell infiltration in tumors, and blocking the CXCL12/CXCR4 pathway improves the prophylactic and therapeutic efficacy of immune checkpoint inhibitors (ICIs).[34,35] Therefore, the aforementioned combination is promising a cancer treatment strategy.

The results of the present work and those of earlier studies indicate that the chemokine *CXCL12* modulates the equilibrium between microbial pathogens and the normal microflora in the gut by regulating innate immune cells. In this manner, *CXCL12* may induce IBD and prolong or exacerbate the inflammation that characterizes it. We propose that *CXCL12* as a potential target genes for the treatment and management of both active and inactive CD.

Data Sharing Statement

All data may be obtained by contacting the corresponding author (Weiming Qu) via e-mail at qwmq2q2@163.com.

Ethics Approval and Consent to Participate

The study protocol was approved by Zhuzhou Central Hospital (Tianyuan District, Zhuzhou, Hunan, China) affiliated with Xiangya Medical College, Central South University (Changsha, Hunan, China).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no competing interests to declare.

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