Identification of Potential Signal Pathways and Immune Disorders in Crohn's Disease

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Abstract

Background: In recent years, the number of visits to Crohn's disease (CD) has gradually increased, but its pathogenesis is still unclear¹. This research aimed to explore the potential molecular pathways and immune disorders of CD.

Methods: The two gene datasets of GSE83448 and GSE95095 were used to identify differentially expressed genes (DEGs) in our study. We also carried out the function enrichment analyses of DEGs between the CD group and the control group. xCell is used to identify the types of lymphocytes in the microenvironment. Subsequently, the correlation analysis between potential enrichment pathways and lymphocyte infiltration in the microenvironment was performed. We mined 944 DEGs (321 up-regulated and 623 down-regulated) and 1467 DEGs (781 up-regulated and 686 down-regulated) in the GSE83448 and GSE95095 datasets, respectively.

Results: Comprehensive analysis shows that: the Focal adhesion and ECM-receptor interaction are the main significant enrichment pathways. xCell analysis identified significantly altered immune cells in CD, Th17 cells, included pDC, Th1 cells, Blood vessels, Macrophages, NK CD56dim cells, Tem, NK cells, NK CD56bright cells, Lymph vessels. The enrichment scores of Focal adhesion and ECM-receptor interaction signaling pathways in the CD intestinal mucosa were significantly correlated with the abundance of immune cells in the two sets of data.

Conclusions: These data suggest the important role of Focal adhesion and ECM-receptor interaction signal transduction pathways in CD, and the intimate relationship between these two pathways and specific types of immune cell infiltration. This study confirmed the potential molecular pathways and immune disorders in CD.

Introduction

CD is a chronic, repetitive, gastrointestinal inflammatory disease with a tendency to relapse throughout life, which may affect any part of the gastrointestinal tract². Genetic, environmental, immunological, and bacterial factors are all deemed to contribute to the disease³⁻⁵. The CD is a non-autoimmune immune-related disease⁶ and the exact underlying immune problem has not been identified. CD often occurs after gastroenteritis, suggesting that maintaining gastrointestinal mucosal barrier homeostasis is essential. Multiple components are collectively involved in the intestinal mucosal barrier⁷: intestinal epithelial cell subsets form a physical barrier, and a robust junction complex between epithelial cells consisting of tight junctions and adherent junctions, which are reinforced by the cytoskeleton⁸. Mucus secreted by goblet cells isolates the epithelial layer from gut microbiota⁹. In addition, complicated and multiple mucosal immune systems provide tolerance to food and antigens while maintaining due immune response capabilities¹⁰. The destruction of intestinal barrier integrity produces "intestinal leakage effect", which leads to abnormal interaction between luminal contents and immune system. This reaction persists in genetically susceptible patients, leading to abnormal local immune responses, and ultimately to CD¹¹. As

we all know, mucosal healing is the key to the treatment of CD. Insufficient wound healing (abscess, fistula) or excessive healing (fibrous stenosis) is the primary indication for surgery in CD patients^{12,13}. However, when the "intestinal leakage effect" occurs, we still don't know which molecular signals and pathways will cause abnormal healing. Similarly, the types of immune cells involved in the abnormal immune response and the specific mechanisms are also unknown. The abnormal immune response and chronic aberrant healing together promotes repeated and uncontrollable intestinal inflammation. In our research, we use bioinformatics methods to identify the DEGs between the CD group and Control group, as well as the correlation between the enrichment pathways of the DEGs and the infiltration of immune cells in the microenvironment, and to further explore the potential molecular pathways and immune disorders of CD.

Materials And Methods

Data processing. Two gene datasets (GSE95095 and GSE83448) were available from GEO (www.ncbi.nlm.nih.gov/gds). GSE95095 had 60 samples, including 48 CD intestinal mucosal tissues and 12 control intestinal mucosal tissues. GSE83448 had 53 samples, including 39 CD intestinal mucosal tissues and 14 control intestinal mucosal tissues. The GSE95095 sample came from the Southern Hospital of Southern Medical University and the GSE83448 sample came from the Wald Hebron Hospital Research Institute. All datasets had been standardized by the uploader.

Identify differentially expressed genes (DEGs). R's limma software was used to identify differentially expressed genes (DEG) between the CD group and control group by using the unpaired Student's t-test¹⁴.

Functional enrichment analyses of DEGs. The R package clusterProfiler software¹⁵ was utilized to analyze and visualize functional profiles of gene and gene clusters from GO¹⁶ and KEGG¹⁷. KEGG pathway enrichment analysis for DEGs was also performed using clusterProfiler package. A false discovery rate (FDR) of < 0.05 was considered a significant GO function and KEGG pathway.

Protein-protein interaction (PPI). To evaluate the interactions between DEGs associated with CD in depth, a PPI network was built by utilising the search tool for searching interacting genes (STRING)¹⁸⁻²⁰, which is the interaction of known and predicted proteins database. Interactions with a threshold composite score ≥ 0.4 are extracted. Cytoscape 3.8.2 software (<http://www.cytoscape.org/>)^{21,22} makes PPI network visualization.

Immune infiltrating cell analysis. xCell²³ web tools were used to infer 28 immune cell types. We further compared the abundance of 28 immune cells in CD and control intestinal mucosa samples²⁴. The cutoff value for cell analysis was $p < 0.05$.

Gene set enrichment analyses and gene set variation analyses. Gene Set Variation Analyses (GSVA)²⁵ was used to analyze datasets for KEGG enriched pathways. Gene set enrichment analyses (GSEA)¹⁹ were performed to identify enriched immune-related signaling pathways in CD. Spearman

correlation analysis and linear regression analysis were used to analyze the correlation between immune cells and key KEGG pathways.

Statistical analyses. All statistical analyses were performed using the R software version 4.0.2. $P < 0.05$ was considered statistically significant.

Results

Identification of DEGs between CD and Control

As displayed in Fig. 1A and B: a total of 944 DEGs (321 up-regulated and 623 down-regulated) were identified in the GSE95095 dataset. Additionally, 1467 DEGs (781 up-regulated and 686 down-regulated) were observed in the GSE83448 dataset (Fig. 1C, D).

PPI network construction.

As shown in the Fig. 2A: there are 781 up-regulated differential genes in the GSE84338 database, and 321 up-regulated differential genes in the GSE95095 database. The common up-regulated differential genes of these databases are 80. As shown in the Fig. 2B: there are 686 down-regulated differential genes in the GSE84338 database, and 623 down-regulated differential genes in the GSE95095 database. The common down-regulated differential genes of these databases are 82. To obtain the interactions between the 162 common DEGs, a PPI network was constructed using the STRING database and visualized by cytoscape software. As displayed in Fig. 3, the network included 103 nodes and 246 edges. Red nodes indicate up-regulated genes and light blue nodes indicate down-regulated genes.

Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) enrichment analyses of common DEGs.

GO terms with significant enrichment of the common DEGs are shown in Fig. 4. The most enriched GO terms in cellular component category was “endoplasmic reticulum lumen” (Fig. 4A), in the biological process category was “extracellular matrix organization” (Fig. 4B), and in molecular function category was “extracellular matrix structural constituent” (Fig. 4C). Significantly enriched KEGG pathways were “Focal adhesion signaling pathway” and “ECM-receptor interaction signaling pathway”, which were involved in the mechanism of the CD. (Fig. 4D)

Gene Set Enrichment Analysis (Gsea)

GSEA was used to screen biological differences between CD intestinal mucosal tissue and normal intestinal mucosal tissues. The GSEA results showed that the Focal adhesion signaling pathway and ECM-receptor interaction signaling pathway were enriched in CD samples in the both datasets. (Fig. 5)

Immune And Stromal Cells Deconvolution Analyses

XCell was used to identify the cell types potentially involved in the CD. The cell types that were significantly different in the CD intestinal mucosa tissue in the GSE83448 dataset are shown in Fig. 6 and those in the GSE95095 dataset are shown in Fig. 7. As shown in the Fig. 8, there were 10 significantly different immune cell types in the GSE84338 and GSE95095 datasets. Among these immune cell types, the cell abundance of pDC, Th1 cells, blood vessels, macrophages, NK CD56dim cells, Tem, NK cells, NK CD56bright cells and lymphatic vessels increased in the CD group, while the abundance of TH17 cells decreased.

Correlation Between Focal Adhesion Signaling Pathway And Immune Cells

GSVA enrichment scores of the Focal adhesion signaling pathways were correlated with the proportion of immune cell infiltration by Spearman correlation analysis. We further identified the correlation between infiltrated cell types with the Focal adhesion and ECM-receptor interaction signaling pathway. We observed significant correlation between 6 types of immune cells with these pathways (Fig. 9-Fig. 10).

Discussion

In this study, we found that the signal transduction pathway of focal adhesion and ECM-receptor interaction is up-regulated in CD. In addition, the abundance of specific types of immune cells in CD intestinal mucosal tissue will change. The abundance of these immune cells is significantly increased, such as TH1 cells, NK cells, macrophages, TEM cells and lymphatic cells, while the abundance of TH17 cells decreases. This means that there may be some potential pathogenic factors during CD, including but not limited to gene expression, downstream pathways of protein function, and immune cell infiltration.

The two databases contain 113 samples. We confirmed 944 DEGs in GSE95095 and 1467 DEGs in GSE83448. A total of 162 the common DEGs, including 82 up-regulated genes and 80 down-regulated genes, were noted in the CD group. KEGG pathway analysis manifested that the DEGs were mainly involved in the 'Focal adhesion', 'Protein digestion and absorption', 'ECM – receptor interaction' and 'Leukocyte transendothelial migration' pathways. Meanwhile, GSVA and GSEA reveal that two signaling pathways are up-regulated in intestinal mucosal tissue of CD, including Focal adhesion signaling pathway and its upstream pathway ECM – receptor interaction signaling pathway. In addition, when we accomplished correlation analyses of immune cell infiltration in the intestinal mucosa of CD with the Focal adhesion signaling pathway, as well as the ECM – receptor interaction signaling pathway, we found that TH17 cells, TH1 cells, NK cells, macrophages, TEM cells and lymphatic cells, which were closely associated with immune responses of CD.

Through integrins or other receptor modules (such as a cluster of differentiation 47 (CD47)), focal adhesion mechanically connects and transduces signals from the extracellular matrix (ECM) to the intracellular environment²⁶. The specific interaction between cells and ECM directly or indirectly controls cell activities, such as adhesion, migration, differentiation, proliferation and apoptosis. Although more and more studies have shown that focused adhesion plays an important role in maintaining the mucosal epithelial barrier^{27–30}, the specific molecular mechanism of how to regulate and maintain the mucosal epithelial barrier still lacks characteristics. The adhesion and collective migration of epithelial cells is crucial in the process of mucosal wound closure³¹. The assembly process requires the dynamic regulation of β -1 integrin signals, which can guide the rapid formation and dissolution of focal adhesions^{32–34}. Similarly, poor wound repair after CD47 loss is related to the reduction of epithelial β 1 integrin and focal adhesion signals³⁵. Inna Grosheva and colleagues⁷ verified that putrescine can cause "exudative enteritis" in the process of autoinflammation or infection in the intestine of mice. The co-administration of the stabilizer taurine significantly reversed the destructive effect of putrescine on the intestinal barrier function during intestinal infection, indicating that the therapeutic application of novel epithelial barrier stabilizers can be used to prevent or treat inflammatory diseases associated with intestinal barrier failure. Obviously, the mucosal epithelium is located at the junction of the external environment containing bacteria and antigens and the internal tissue compartment. Therefore, the repair of the mucosal surface will not occur in a sterile environment, and the body will initiate an immune response when the intestinal mucosal barrier is broken. Generally, intestinal mucosal epithelial cells enhance the intestinal physical barrier (first layer barrier) by producing mucus, antimicrobial proteins, and IgA to minimize the contact between the gut microbiota and its surface. When the first barrier is broken by microbes, the body can rely on rapid detection and killing of microbes that penetrate outside epithelial cells. Such immune mechanisms include innate immune cell uptake and phagocytosis of microorganisms, and T cell-mediated responses. Microorganisms that escape the second barrier are ingested by dendritic cells³⁶. Depending on limited bactericidal activity and limited life span of dendritic cells³⁷, symbiotic microorganisms can be confined to the intestinal cavity without excessive inflammation, while maintaining the ability to remove intestinal infection. CD4 positive T helper cells can be functionally divided into Th1–Th2–Treg–Th17–Tfh and Th9 cells³⁸. Generally, Treg governs the activity of Th1 and Th17, preventing uninhibited inflammation. Studies³⁹ have shown that TH17 and TH1 cells are infiltrated in the lamina propria of the intestinal mucosa of CD. The response of these effector cells to bacteria or fungi is related to the pathogenesis of the disease. Similarly, there are reports that the functional activity of intestinal Treg cells is impaired in CD⁴⁰. When the immune homeostasis of the intestinal mucosa is broken, the intraluminal microbiota promotes an excessive immune response through the extraction of dendritic cells and the stimulation of inflammatory macrophages. The regulatory capacity of Treg is surpassed by the inflammatory activity of Th1 and Th17. In this study, we found that the abundance of immune cells in the intestinal mucosal tissue of CD increased: TH17, NK cells, macrophages, TEM cells and lymphatic cells, while the abundance of TH1 cells decreased. In addition, correlation analysis suggests that the type of specific immune cells infiltration was closely related to the Focal adhesion and the ECM-receptor interaction signaling pathway.

In short, we have studied a large number of gene profiles of CD to clarify its potential molecular pathways and immune disorders gene expression patterns. Our results show that the Focal signaling pathway and ECM – receptor interaction signaling pathway are the main pathways involved in the CD, and these pathways are closely related to the infiltration of specific immune cell types. Our data provide reliable insights into the pathogenesis and potential therapeutic targets of CD.

Declarations

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

LXP designed the study and revised the manuscript. ZQY and LWY analyzed the data and wrote the manuscript. LXD, LGF, CRY, and ZLL assisted with analyzing the data and writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests. References.

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Figures

Figure 1

DEGs. Heat maps of potential differentially expressed genes between CD intestinal mucosal tissues and 14 controls intestinal mucosal tissues in the GSE95095 and GSE83448 datasets(A–C). Volcano plot of potential differentially abundance proteins between Crohn's disease intestinal mucosal tissues and 14 controls intestinal mucosal tissues in the GSE95095 and GSE83448 datasets (B–D).

A graphical representation of the protein-protein interaction network based on genes differentially expressed between Crohn's disease and the control group. Red nodes indicate genes up-regulated in the Crohn's disease group, light blue nodes indicate down-regulated genes.

Figure 4

Annotation of the statistical significant enriched Gene Ontology and KEGG pathways of common differentially expressed genes between the GSE83448 dataset and GES95095 datasets: (A) Cellular component, (B) biological process, (C) molecular function and (D) KEGG pathway analysis. KEGG, Kyoto Encyclopedia of Genes and Genomes.

Figure 5

GSEA for significantly enriched pathways in the CD group.

Fig6

Figure 6

The xCell scores of 28 cell types between Crohn's disease intestinal mucosa tissue and the control intestinal mucosa tissue in the GSE83448 dataset.

Figure 7

ThexCell scores of 28 cell types between Crohn's disease intestinal mucosa tissue and the control intestinal mucosa tissue in the GSE95095 dataset.

GSE83448

GSE95095

Figure 8

Differential cell types common to the GSE83448 dataset and GSE95095 datasets

GSE95095

GSE83448

Figure 9

Correlation between pivotal pathways and immune cells. Significantly correlated immune cells in Focal adhesion signaling pathway in the GSE83448 dataset and GSE95095 datasets.

GSE95095

GSE83448

Figure 10

Correlation between pivotal pathways and immune cells. Significantly correlated immune cells in ECM-receptor interaction signaling pathway in the GSE83448 dataset and GSE95095 datasets.