Potential Novel Therapeutic Targets in Epilepsy from The View of Intestinal Comorbidities

Mi Jiang  
Central South University

Jia Li  
Guangzhou Medical University

Zhi Song  
Central South University

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Abstract

**Background:** Epilepsy is a complicated neurological disorder with almost 30% refractory. Recent years, several studies showed that epilepsy is associated with its comorbidities by shared molecular mechanisms. However, the association of epilepsy and digestive comorbidities are still unclear. In this study, we aim to explore the association between inflammatory bowel disease (IBD) and epilepsy, and to find promising therapeutic targets for refractory epilepsy.

**Methods:** Two gene expression profiles (GSE134697 and GSE59071) were selected from Gene Expression Omnibus (GEO) database. Differentially expressed genes (DEGs) were identified by GEO2R and the DESeq2 package. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of intersection DEGs and Gene Set Enrichment Analysis (GSEA) were conducted by clusterProfiler package. The protein-protein interactions (PPI) network was established by using STRING and visualized by Cytoscape. Genes in the most significant module identified by MCODE plug-in were considered as candidate hub genes. Validation of hub genes were performed by using the GSE143272 dataset.

**Results:** CXCL8, CXCR4 and ITGAX were identified as the hub genes.

**Conclusions:** CXCL8, CXCR4 and ITGAX were the shared molecular mechanism of epilepsy and IBD, which were potentially novel therapeutic targets in epilepsy.

1. Introduction

Epilepsy is a brain disorder characterized by an enduring predisposition to generate epileptic seizures [1]. Over 70 million people worldwide are affected by epilepsy and suffering various negative consequences from epileptic seizures, including disability and mortality [2, 3]. Although 70% of seizures could be controlled by using antiseizure medications (ASMs), 30% of were refractory that make epilepsy a burdensome disease [2-4]. Therefore, it is essential to explore novel therapy targets for epilepsy, especially for drug-resistant epilepsy [3, 5].

Recent studies showed that several diseases of different systems were found more common in people with epilepsy than in the general population, including neuropsychiatric, cardiovascular, digestive, and immune system diseases [6]. This is owing to a bidirectional factor between epilepsy and its comorbidities in mechanism, including genetic, environmental, structural, and physiological factors [6, 7]. It was found that epileptic seizures could be controlled by treating comorbidities [6, 8, 9], which potentially provided a novel treating idea for refractory epilepsy. Therefore, to explore shared molecular mechanisms of epilepsy and comorbid conditions is undoubtedly a fast and effective method to develop novel treatments for epilepsy [6]. Until now, some shared molecular mechanisms of epilepsy and neuropsychiatric comorbidities have been discovered [10-12], but the association of epilepsy and intestinal comorbidities are still unclear.

Inflammatory bowel disease (IBD) is a common intestinal comorbid condition of epilepsy, which are characterized by a chronic and recurrent gastrointestinal condition including ulcerative colitis (UC) and Crohn's disease (CD) [6, 13, 14]. IBD and epilepsy were found to be involved in the shared mechanisms in inflammatory, hypercoagulable, and genetic factors [13, 15]. However, the certain molecules acting in the shared mechanisms are unknown. In this study, we conducted a combined transcriptome analysis of epilepsy and IBD patients from Gene Expression Omnibus (GEO) database to identify the shared molecules mechanisms and determine the potential pathway by which develop novel therapeutic targets for epilepsy.

2. Materials And Methods

2.1. Data Collection

All microarray datasets were downloaded from the GEO database. We searched GEO database for microarray datasets using the keywords “epilepsy” and “IBD” (including “Crohn's disease (CD)” and “ulcerative colitis (UC)”). Datasets were recruited by the following criteria: (1) transcriptome data; (2) samples were derived from homo sapiens; (3) the count of samples was > 15; (4) including control groups. Finally, gene expression microarray datasets GSE134697 and GSE59071 were qualified to be selected. According to the IBD classification, GSE59071 was separated into two parts: GSE59071-UC and GSE59071-CD. The two datasets were based on the platforms of GPL16791 [Illumina HiSeq 2500 (Homo sapiens)], and GPL6244 (HuGene-1.0-st) Affymetrix Human Gene 1.0 ST Array [transcript (gene) version]], respectively.

The dataset GSE134697 contained 36 samples, including 17 hippocampal samples (the case group) obtained from patients with drug-resistant temporal lobe epilepsy, and 19 neocortex samples (the control group) obtained from 17 patients with drug-resistant temporal lobe epilepsy and 2 healthy individuals. The dataset GSE59071 contained 116 samples, including 105 affected intestinal mucosal samples (the case group) obtained from patients with IBD (consisting of 97 UC and 8 CD), and 11 intestinal mucosal samples (the control group) obtained from healthy individuals in the control group.

2.2. Identification of Differentially Expressed Genes (DEGs)

DEGs screenings of the two datasets GSE134697 and GSE59071 were conducted by the GEO2R online analysis tool (https://www.ncbi.nlm.nih.gov/geo/geo2r/) and the R package “DESeq2” [16], respectively. P-values were adjusted by using the false discovery rate (FDR) method. Genes with adjusted $P < 0.05$ and $|\log2$ fold change (FC) $| > 1$ were considered as DEGs. We used Venn diagram web tool (http://bioinformatics.psb.ugent.be/webtools/Venn/) to find the DEGs shared by both datasets.
2.3. Function Enrichment Analysis of DEGs

To explore the enriched biological pathways and annotations, we utilized the RStudio v4.0.5 to conduct the Gene Ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis by clusterProfiler package [17]. Adjust $P$-values $< 0.05$ were regarded as the cut-off criteria.

2.4. Gene Set Enrichment Analysis (GSEA) of Two Expression Profiles

To further reveal the common pathway between epilepsy and IBD, GSEA was performed based on each single expression matrix. R package "clusterProfiler" [17] was utilized to perform GSEA [18]. Enrichment analyses were conducted to determine whether a series of a priori-defined biological processes was enriched. The genes of two datasets were ranked according to the false discovery rate (FDR). $P < 0.05$ were considered statistically significant.

2.5. Protein-protein Interaction Network Construction, Significant Module Analysis and Candidate Hub Gene Identification

The protein-protein interactions (PPI) network of DEGs was established by using STRING v11.0 (https://string-db.org). A PPI network of the DEGs with combined score $> 0.4$ in STRING was considered as a functional link and was visualized by Cytoscape software v3.7.2. The Cytoscape's plug-in molecular complex detection technology (MCODE) was used to identify closely connected modules from the PPI network with MCODE score $> 4.5$. The GO enrichment analysis of the module genes was conducted by using the Database for Annotation, Visualization and Integrated Discovery (DAVID) v6.8 (https://david.abcc.ncifcrf.gov). Genes in the most significant module identified by MCODE plug-in were selected as candidate hub genes.

2.6. Validation of Candidate Hub Genes

We used GEO2R to identify the DEGs in the GSE143272 dataset [epilepsy response to valproate (VPA) treatment vs. healthy control]. The candidate hub genes that downregulated in this dataset were identified as hub genes.

3. Results

3.1. Identification of DEGs in Epilepsy and IBD

In the GSE59071 dataset, 1243 DEGs (UC tissues vs. control) and 697 DEGs (CD tissues vs. control) were identified. In the GSE134697 dataset, 1846 DEGs (hippocampus vs. control) were identified. The shared DEGs of datasets GSE134697 and GSE59071 were 78 genes, including 56 upregulated and 22 downregulated genes (Figure 1, Table 1).

3.2. GO Enrichment Analysis of DEGs

GO enrichment analysis showed that various DEGs were upregulated in the pathways of biological processes (BP), molecular functions (MF), and cellular components (CC). In BP upregulated DEGs were significantly enriched in the “regulation of vasculature development”, “response to molecule of bacterial origin”, “response to lipopolysaccharide”, “positive regulation of cytokine production”, and “positive regulation of cell-cell adhesion” (Figure 2a, Table 2). In MF, upregulated DEGs were enriched in the “glycosaminoglycan binding”, “cytokine activity”, “receptor ligand activity”, and “signaling receptor activator activity” (Figure 2b, Table 2). In CC, upregulated DEGs were significantly enriched in the “secretory granule membrane” and “collagen-containing extracellular” (Figure 2c, Table 2). There also various downregulated DEGs enriched in MF (Figure 2d, Table 2). More detailed GO enrichment results are shown in Table 2. The number of upregulated genes involved in the different processes of BP, CC, and MF was much more than that of downregulated genes. These results suggest that epilepsy and IBD may undergo common metabolic activities involving in cytokine associated inflammatory response and other complex biological process.

3.3. KEGG Enrichment Analysis of DEGs

KEGG enrichment analysis showed that upregulated genes were enriched in 26 pathways, such as rheumatoid arthritis, graft-versus-host disease, type 1 diabetes mellitus, hematopoietic cell lineage, leishmaniasis, intestinal immune network for IgA production, toll-like receptor signaling pathway, inflammatory bowel disease, and cytokine-cytokine receptor interaction pathway and so on (Table 3, Figure 3). These pathways are mainly involved in inflammatory or proinflammatory response. The downregulated genes were not enriched in any pathway (Table 3).

3.4. GSEA
GSEA showed that the dataset GSE134697 (epilepsy) is enriched in the pathways of antigen processing and presentation, cytokine-cytokine receptor interaction, graft-versus-host disease, hematopoietic cell lineage, and leishmaniasis infection. As for dataset GSE59071, the expression profiles of IBD samples were enriched in cell adhesion molecules cams, chemokine signaling pathway, complement and coagulation cascades, cytokine-cytokine receptor interaction, and ECM receptor interaction. The results indicated that the cytokine-cytokine receptor interaction pathway is the communal pathway between epilepsy and IBD (Figure 4a, 4b).

3.5. PPI Network Construction, Significant Module Analysis and Candidate Hub Gene Identification

We developed a PPI network containing 51 nodes and 162 edges and visualized by using Cytoscape software (Figure 5a). Nodes were drawn in different colors, representing the node degree (up or down). There were 56 upregulated genes and 22 downregulated genes. The most significant module with the highest score (module score: 9.111) was shown in Figure 5b, containing 10 genes in a network with 41 edges. GO analysis revealed that these genes were involved in chemokine-mediated signaling pathway, inflammatory response, and the other biological process were shown in Table 4. Genes in the most significant module were selected as candidate hub genes. These genes were all upregulated genes, as follows: CXCL8, CXCR4, ITGAX, CD80, SELL, CD44, CD69, IL1B, CD38, and CXCL2.

3.6. Validation of Candidate Hub genes

We finally identified three hub genes CXCL8, CXCR4 and ITGAX, which validated by using GSE143272 dataset [epilepsy response to VPA treatment vs. healthy control]. In the group of epilepsy to VPA treatment, CXCL8 was significantly downregulated (adjusted P < 0.05 and log2FC = -1.2911696), CXCR4 and ITGAX were slightly downregulated. The three genes are significantly upregulated in the case groups (untreated) of GSE134697 and GSE59071 datasets.

4. Discussion

Although previous studies pointed out that epilepsy and IBD are related, the mechanism of their association is not addressed [19-21]. In this study, we conducted a transcriptome analysis to explore the association of epilepsy and IBD, aiming to discover promising therapeutic targets for refractory epilepsy.

A total of 78 overlapping DEGs were identified based on GSE134697 and GSE59071, of which 56 genes were upregulated and 22 genes were downregulated. GO analysis revealed that DEGs were enriched in the pathways of regulation of vasculature development, response to molecule of bacterial origin, response to lipopolysaccharide, and positive regulation of cytokine production. KEGG analysis showed that the DEGs enriched in the pathways of rheumatoid arthritis, intestinal immune network for IgA production, and toll-like receptor signaling. GSEA showed that the gene expression profile of epilepsy was enriched in cytokine-cytokine receptor interaction pathway that was same as IBD. Previous study showed that central/peripheral inflammation played an important role in triggering or sustaining epileptic activity [8, 22-25]. Therefore, IBD may induce or aggravate seizures through the communal pathway and other inflammation/proinflammatory process. We identified 3 hub genes of CXCL8, CXCR4, and ITGAX, which were all upregulated in both epilepsy and IBD datasets. Additionally, CXCL8, CXCR4, and ITGAX were all downregulated in epilepsy under VPA treatment (dataset GSE143272), in which CXCL8 was downregulated most obviously. These findings suggested that the three hub genes, especially CXCL8, may be promising therapeutic targets for epilepsy.

Interleukin-8 (IL-8: CXCL8) is a chemotactic and inflammatory cytokine that involves in central nervous system (CNS) inflammation [26, 27]. Chemokines are small (8–12 kDa) chemotaxis proteins which play an important physiological role in immune system, mainly being responsible for guiding leukocyte to move to inflammatory sites [28]. Increased CXCL8 expression has been widely demonstrated in colonic mucosa of UC compared with normal control subjects, and upregulated CXCL8 concentration is correlated with the degree of inflammation [28]. There also some studies showed that the levels of CXCL8 transcripts were significantly higher in total epileptic patients compared with healthy subjects [29]. Elevated levels for CXCL8/IL-8 were reported in several different epilepsy etiologies and media [30], such as febrile infection-related epilepsy syndrome, and epileptic temporal lobe [31]. Thus, we supposed that CXCL8 may cause epilepsy by ways of immunoregulatory.

The chemokine CXC motif receptor 4 (CXCR4) is cognate with chemokine CXCL12. It is known as stromal cell derivedfactor-1 (SDF-1), which is highly expressed in the CNS and plays a crucial role in brain architecture [32-34]. Several studies indicated that the chemokine receptors were upregulated expressed in epilepsy and the active stage of UC [35-37], which was consistent with this study. Additionally, AMD3100, the antagonist of CXCR4, could reverse the neurogenesis promoted by enriched environment and suppresses long-term seizure activity [38, 39]. Animal experiments also showed that AMD-3100 can reduce colon injury in mice and CXCL12/CXCR4 blocking was beneficial in improving experimental colitis in rodent models [40-43].

ITGAX encodes the integrin alpha X chain protein (CD11c), which is a pan dendritic cells (DCs) marker. While normally residing in the meninges and choroid plexus, perivascular and intraparenchymal DCs can be detected in brain under several inflammatory conditions. The level of CD11c protein was higher after status epilepticus (SE), while there was no detectable expression of CD11c in control group [44].

The evidence above supported that the three hub genes (CXCL8, CXCR4 and ITGAX) found in this study were potentially the shared molecular mechanism of epilepsy and IBD. CXCL8, CXCR4 and ITGAX were discovered as potentially novel therapeutic targets in epilepsy from the view of intestinal comorbidities in this study. More details in mechanism warrant further experimental validation.

Declarations
Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests for this research.

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Author Contributions

Conceptualization, M.J. and Z.S.; Methodology, M.J. and J.L.; Software, M.J.; Validation, M.J., Z.S., and J.L.; Investigation, M.J. and Z.S.; Writing – Original Draft Preparation, M.J.; Writing – Review & Editing, M.J., Z.S., and J.L.; Visualization, M.J.; Supervision, Z.S.; Project Administration, Z.S.; Funding Acquisition, Z.S.

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**Tables**

**Table 1. Co-expression of differential genes**

| Group | Gene symbol |
|-------|-------------|
| Upregulated | PAD2, IFI44L, CAPN13, FPR1, HLA-DBP1, THBS6, ADGRE2, EGR1, HLA-DPA1, TREM1, STX11, PRRX1, ITGAX, CXCL2, PDK4, ABCA12, ANGPTL2, ADM, SCI1, MT1A, CXCR4, VCAN, RASGRF3, ENPP2, THEMIS2, IL1A, FGF7, SPP1, DMRT1, SELL, NPSR1, APLNR, BCL2A1, SPARC, SLC5A1, SLC11A1, CHI3L2, FOS, CD80, CD38, PCK1, CD69, GBA3, IL1B, SERPINE1, LIPG, CD44, CXCL8, RGS1, TNC, OSM, SERPINA3 |
| Downregulated | HSD17B2, SATB2-AS1, MUC5B, MT1H, SLC38A4, PTGDR, MEDAG, FAM20A, GLRA2, TRHDE, CEMIP, SLC04C1, CNTN3, COL3A1, OLFM4, CNTN4, ADGRL2, STRIP2, SLC9A2, NOS2, THRB, MGP |

**Table 2. GO enrichment analysis of DEGs**

**Table 2. GO enrichment analysis of DEGs (continued)**
| Category | Term | Description | Gene ID |
|----------|------|-------------|---------|
| **Upregulated BP** | GO:1901342 | regulation of vasculature development | CXCR4/IL1A/ENPP2/ITGAX/ADM/IL1B/ADAMTS9/APLNR/CXCL8/EGR1/THBS2/SERPINE1/SERPIE1 |
| | GO:0002237 | response to molecule of bacterial origin | IL1A/SLC11A1/CXCL2/ADM/IL1B/CXCL8/PCK1/CD80/DMBT1/FOS/SERPINE1/SPARC |
| | GO:0045765 | regulation of angiogenesis | CXCR4/IL1A/ENPP2/ITGAX/ADM/IL1B/ADAMTS9/APLNR/CXCL8/THBS2/SERPINE1/SPARC |
| | GO:0032496 | response to lipopolysaccharide | IL1A/SLC11A1/CXCL2/ADM/IL1B/CXCL8/PCK1/CD80/FOS/SERPINE1/SPARC |
| | GO:1904018 | positive regulation of vasculature development | CXCR4/IL1A/ITGAX/ADM/IL1B/APLNR/CXCL8/EGR1/SERPINE1 |
| | GO:0045766 | positive regulation of angiogenesis | CXCR4/IL1A/ITGAX/ADM/IL1B/APLNR/CXCL8/SERPINE1 |
| | GO:0001819 | positive regulation of cytokine production | IL1A/OSM/SLC11A1/HLLA-DPB1/IL1B/EGR1/HLLA-DPA1/ZBP1/CD80/SERPINE1 |
| | GO:0022409 | positive regulation of cell-cell adhesion | CD44/IL1A/HLLA-DPB1/IL1B/HLLA-DPA1/PCK1/PDPN/CD80 |
| | GO:0030198 | extracellular matrix organization | CD44/SPP1/ITGAX/VCAN/ADAMTS9/PDPN/TNC/SERPINE1/SPARC |
| | GO:0043062 | extracellular structure organization | CD44/SPP1/ITGAX/VCAN/ADAMTS9/PDPN/TNC/SERPINE1/SPARC |
| **MF** | GO:0005539 | glycosaminoglycan binding | CD44/SELL/ADGRE2/LIPG/VCAN/FGF7/THBS2 |
| | GO:005125 | cytokine activity | IL1A/SPP1/OSM/CXCL2/IL1B/CXCL8 |
| | GO:0048018 | receptor ligand activity | IL1A/SPP1/OSM/CXCL2/ADM/IL1B/CXCL8/FGF7 |
| | GO:0030546 | signaling receptor activator activity | IL1A/SPP1/OSM/CXCL2/ADM/IL1B/CXCL8/FGF7 |
| | GO:0050840 | extracellular matrix binding | SPP1/DMBT1/SPARC |
| | GO:0140375 | immune receptor activity | CD44/CXCR4/FPR1/HLLA-DPA1 |
| | GO:0005149 | interleukin-1 receptor binding | IL1A/IL1B |
| | GO:0008528 | G protein-coupled peptide receptor activity | CXCR4/FPR1/APLNR/NPSR1 |
| | GO:0001653 | peptide receptor activity | CXCR4/FPR1/APLNR/NPSR1 |
| | GO:01901681 | sulfur compound binding | SELL/ADGRE2/LIPG/FGF7/THBS2 |
| **CC** | GO:0030667 | secretory granule membrane | CD44/SELL/CD38/SLC11A1/FPR1/ITGAX/DMBT1/SPARC |
| | GO:0062023 | collagen-containing extracellular matrix | VCAN/SERPINA3/ADAMTS9/TNC/THBS2/SERPINE1/ANGPTL2/SPARC |
| Category   | Term                  | Description                                      | Gene ID                                    | Count | P- value  |
|------------|-----------------------|--------------------------------------------------|--------------------------------------------|-------|-----------|
| Upregulated| CC                    | platelet alpha granule                           | SERPINA3/THBS2/SERPINE1/SPARC              | 4     | 1.34E-04  |
|            | GO:0101003            | ficolin-1-rich granule membrane                   | SLC11A1/FPR1/ITGAX                        | 3     | 7.11E-04  |
|            | GO:0031093            | platelet alpha granule lumen                      | SERPINA3/SERPINE1/SPARC                   | 3     | 9.35E-04  |
|            | GO:0042613            | MHC class II protein complex                      | HLA-DPB1/HLA-DPA1                         | 2     | 9.42E-04  |
|            | GO:0030666            | endocytic vesicle membrane                        | SLC11A1/HLA-DPB1/HLA-DPA1/DMBT1           | 4     | 1.25E-03  |
|            | GO:0031258            | lamellipodium membrane                            | CD44/PDPN                                 | 2     | 1.79E-03  |
|            | GO:0030139            | endocytic vesicle                                 | SLC11A1/HLA-DPB1/HLA-DPA1/DMBT1/SPARC     | 5     | 1.99E-03  |
|            | GO:0042611            | MHC protein complex                               | HLA-DPB1/HLA-DPA1                         | 2     | 2.32E-03  |
| Downregulated| MF                    | anion transmembrane transporter activity          | SLC38A4/SLC9A2/GLRA2/SLCO4C1               | 4     | 5.33E-04  |
|            | GO:0031406            | carboxylic acid binding                           | NOS2/CEMIP/GLRA2                          | 3     | 1.50E-03  |
|            | GO:0043177            | organic acid binding                              | NOS2/CEMIP/GLRA2                          | 3     | 1.75E-03  |
|            | GO:0016597            | amino acid binding                                | NOS2/GLRA2                                | 2     | 1.86E-03  |
|            | GO:0015291            | secondary active transmembrane transporter activity| SLC38A4/SLC9A2/SLCO4C1                    | 3     | 2.04E-03  |
|            | GO:0008509            | anion transmembrane transporter activity          | SLC38A4/SLC9A2/GLRA2/SLCO4C1              | 4     | 5.33E-04  |

Note: GO, Gene Ontology; DEGs, differentially expressed genes; BP, biological processes; MF, molecular functions; CC, cellular components.

Table 3. The KEGG enrichment analysis of DEGs (top 10 terms according to P-value)

| ID        | Description                              | Genes                                                                 | Count | P-value  |
|-----------|------------------------------------------|------------------------------------------------------------------------|-------|-----------|
| hsa05323  | Rheumatoid arthritis                     | IL1A/CXCL2/HLA-DPB1/IL1B/CXCL8/HLA-DPA1/CD80/FOS                      | 8     | 1.26E-08  |
| hsa05332  | Graft-versus-host disease                 | IL1A/HLA-DPB1/IL1B/HLA-DPA1/CD80                                      | 5     | 1.68E-06  |
| hsa04940  | Type I diabetes mellitus                 | IL1A/HLA-DPB1/IL1B/HLA-DPA1/CD80                                      | 5     | 1.89E-06  |
| hsa04640  | Hematopoietic cell lineage                | CD44/CD38/HLA-DPA1/IL1A/HLA-DPB1                                      | 6     | 7.81E-06  |
| hsa05140  | Leishmaniasis                            | IL1A/HLA-DPB1/IL1B/HLA-DPA1/FOS                                       | 5     | 3.44E-05  |
| hsa04672  | Intestinal immune network for IgA production| CXCR4/HLA-DPB1/HLA-DPA1                                                | 4     | 9.17E-05  |
| hsa04933  | AGE-RAGE signaling pathway in diabetic complications | IL1A/IL1B/CXCL8/EGR1/SERPINE1                                      | 5     | 1.21E-04  |
| hsa04620  | Toll-like receptor signaling pathway      | SPP1/IL1B/CXCL8/HLA-DPA1/FOS                                           | 5     | 1.45E-04  |
| hsa05321  | Inflammatory bowel disease                | IL1A/HLA-DPB1/IL1B/HLA-DPA1                                            | 4     | 2.77E-04  |
| hsa05133  | Pertussis                                | IL1A/IL1B/CXCL8/FOS                                                   | 4     | 5.05E-04  |

Note: KEGG, Kyoto Encyclopedia of Genes and Genomes; DEGs, differentially expressed genes.

Table 4. The GO analysis of genes in the significant module (top 5 terms according to P-value)
| Category | Term | Description                                      | Gene ID                  | Count | P-value       |
|----------|------|--------------------------------------------------|--------------------------|-------|---------------|
| BP       | GO:0070098 | chemokine-mediated signaling pathway           | CXCL12, CXCL8, CXCR4   | 3     | 6.23E-04     |
|          | GO:0006954 | inflammatory response                         | CXCL12, CXCL8, IL1B, CXCR4 | 4     | 8.66E-04     |
|          | GO:0007155 | cell adhesion                                  | CXCL12, SELL, ITGAX, CD44 | 3     | 0.001507293  |
| CC       | GO:0009897 | external side of plasma membrane               | CXCL12, SELL, CD80, ITGAX, CD69 | 5     | 2.18E-06     |
|          | GO:0009896 | cell surface                                   | CD80, ITGAX, CD38, CXCR4, CD44 | 5     | 8.66E-05     |

Note: GO, Gene Ontology; BP, biological processes; CC, cellular components

Figures

**Figure 1**

Overlapping DEGs between epilepsy and inflammatory bowel disease (IBD).

A total of 78 overlapping DEGs of the epilepsy dataset (GSE134697) and IBD (UC and CD) dataset (GSE59071) were identified by the Venn web tool. DEG, differentially expression genes; UC, ulcerative colitis; CD, Crohn's disease.
Figure 2

GO enrichment analysis of DEGs.

(a) BP GO terms for upregulated DEGs; (b) MF GO terms for upregulated differentially expressed genes (DEGs); (c) CC GO terms for upregulated DEGs; (d) MF GO terms for downregulated DEGs. GO, Gene Ontology; DEGs, differentially expression genes; BP, biological process; MF, molecular function; CC, cellular component.
Figure 3

KEGG pathway enrichment analysis of DEGs.

The significant KEGG pathways for upregulated DEGs were shown. KEGG, Kyoto Encyclopedia of Genes and Genomes; DEG, differentially expression genes.

Figure 4

Gene Set Enrichment Analysis (GSEA).

(a) KEGG pathways enrichment in the gene expression profile of epilepsy (GSE134697), ranking by P-value; (b) KEGG pathways enrichment in the gene expression profile of IBD (GSE59071) ranking by P-value; KEGG, Kyoto Encyclopedia of Genes and Genomes; IBD, inflammatory bowel disease.
Figure 5

Constructed PPI networks of the DGEs and identified candidate hub genes.

(a) The PPI network of DEGs was constructed using Cytoscape. The nodes meant proteins; the edges meant the interaction of proteins. Upregulated genes are marked in light red; downregulated genes are marked in blue. (b) The most significant module of the PPI network was identified using molecular complex detection technology (MCODE) plug-in. Candidate hub genes were CXCL8, CXCR4, ITGAX, CD80, SELL, CD44, CD69, IL1B, CD38, and CXCL2. PPI, protein–protein interaction; DEGs, differentially expressed genes.