Integrative Analysis of Key Candidate Genes and Signaling Pathways in Alzheimer's disease Related to Chronic Periodontitis Based on Analysis of GEO Dataset and Text Mining

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Research

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Abstract

Background: Although chronic periodontitis has been confirmed to be related to Alzheimer's disease, the pathogenesis between the two is unclear. Herein, we analyzed and screened out the prospective molecular marker.

Methods: To explore the candidate genes, as well as signaling cascades involved in Alzheimer's disease and mild cognitive impairment (MCI) related to chronic periodontitis, we extracted the integrated differentially expressed genes (DEGs) from the intersection of genes from the Gene Expression Omnibus (GEO) cohorts and text mining, followed by enrichment of the matching cell signal cascade through DAVID analysis. Moreover, the MCODE of Cytoscape software was employed to uncover the protein-protein interaction (PPI) network and the matching hub gene.

Results: A total of 305 and 100 integrated human DEGs in AD and MCI group associated with chronic periodontitis were uncovered, respectively, that met the criteria of $|\log 2 \text{ changes}| \geq 2$, adjusted $P < 0.01$. After PPI network construction, the top five hub genes associated with AD were extracted, including IL6, VEGFA, AKT1, MAPK3, and ALB, whereas those associated with MCI were EGFR, IL10, IGF1, BMP2, and LDLR.

Conclusions: The establishment of the above-mentioned candidate key genes, as well as the enriched signaling cascades provides promising molecular marker for chronic periodontitis-related cognitive decline, especially AD, which may help the diagnosis and treatment of AD patients in the future.

1. Introduction

Periodontitis constitutes a chronic inflammatory disease. During the development of periodontitis, associated complications such as alveolar bone destruction, as well as the loss of attachment of collagen fibers to periodontal ligament will occur, eventually leading to tooth loss[1]. A large number of recent reports have shown that chronic periodontitis comprises a risk factor for neurodegenerative diseases such as cognitive decline. Among them, in the study of Cestari et al., it was found that the levels of inflammatory cytokines in individuals with Alzheimer's disease (AD) /Mild Cognitive Impairment (MCI) were remarkably correlated with periodontitis [2].

AD constitutes a progressive neurodegenerative disease. Its clinical indications primarily include cognitive decline, which eventually develops into AD. It has a place in diseases that threaten the lifespan of the elderly. A large number of previous studies have confirmed that immune factors, depression, genetic factors, etc. could be remarkably positively correlated with the incidence and development of AD[3-8]. Despite the huge advancements in AD research, the current AD treatments can only improve and relieve patient conditions to some level [9]. As the threat of AD to the elderly becomes greater and greater, it is imperative for us to establish the etiology, as well as the molecular features of AD disease. Therefore, we explore the molecular biomarkers by studying the correlation between chronic periodontitis and AD disease to provide evidence for early diagnosis, prevention, as well as the treatment of this disease.

At present, high-throughput sequencing techniques, such as molecular diagnosis, prognosis estimation, as well as drug target discovery, and, which can be employed to assess the gene expression differences, as well as the variable splicing variation, are gradually considered to have important clinical significance in disease research. The Integrated Gene Expression Database (GEO), a publicly available websites supported by the National Center for Biotechnology Information (NCBI), harbors dozens of basic experimental disease gene expression patterns and is extensively employed to explore key genes and prospective mechanisms of disease onset and development[10]. Though the pathogenesis of chronic periodontitis has been found to be related to AD recently, its pathogenesis, as well as the molecular mechanism remain unknown. Hence, we need to utilize the gene expression chip in the bulletin database and analyze its data through modern software to find new diagnostic markers and therapeutic targets[11].

In this study, we retrieved GSE5281 and GSE18309, the human AD and MCI gene expression patterns, respectively, from the GEO website. After that, R software (version 3.6.3) installed Limma package was utilized to screen the differentially expressed genes (DEGs)[12,13]. Text mining about chronic periodontitis was then carried out by the pubmed2ensembl online tool [14]. After the data obtained from microarray, as well as the text mining were intersected to obtain the common gene, GO enrichment and KEGG pathway assessment were performed on the obtained DEGs [15]. Finally, the protein-protein interaction (PPI) network was developed using the Search Tool for the Retrieval of Interacting Genes (STRING) and Cytoscape software to screen candidate hub genes, as well as the highly relevant functional modules.

2. Methods

2.1 Data Abstraction

We abstracted the gene expression chip data GSE5281[16] and GSE18309 from the NCBI Gene Expression Comprehensive (GEO) web resource (https://www.ncbi.nlm.nih.gov/geo/) [10,17]. The GSE5281 cohort contains ten euthyroid and ten AD samples, while the GSE18309 dataset includes three normal control and three MCI samples.

2.2 Identification of DEGs

The core R package was used to process the downloaded matrix files. After normalization, the differences between ad or MCI and the control group were determined by truncation criteria (|log2 fold change (FC)| ≥ 2, adjusted $P < 0.05$), and selected the remarkable DEGs for downstream analyses [18].

2.3 Text mining

We carried out the text mining based on the pubmed2ensembl public tool (http://pubmed2ensembl.ls. manchester.ac.uk/). When manipulated, pubmed2ensembl retrieves all the gene names found in the existing literature relevant to the search topic. We searched for the concept of chronic periodontitis. We then screened all the genes associated with the topic from the results. Finally, we used the gene set obtained by text mining and the previously obtained differential gene set for the next step of analysis after the intersection.

2.4 Gene Ontology Analysis of DEGs and KEGG pathway analysis

The obtained DEGs were imported to David V. 6.8 (https://david.ncifcrf.gov/). The GO annotation and KEGG pathway enrichment were carried out in the web resource, which provided a sequence of functional annotation tools for systematic analysis of biological significance of gene lists. The above gene tables were analyzed with $P < 0.05$ as the significant threshold.

2.5 Assessment of the PPI network of the DEGs

We used the STRING online search tool to analyze the protein-protein interaction (PPI) data encoded by DEGs [19], and only the combination score >0.6 was considered significant. Then, the PPI network was analyzed and visualized by using Cytoscape, and the first five hub genes were determined as per the connectivity between des. The standard default setting of the mcode parameter is except for k-core = 5. The function enrichment of DEGs of each module was analyzed by $P < 0.05$ as the cutoff standard.

3. Results

3.1 DEGs identification

Firstly, 5672 DEGs were selected from AD samples and normal controls in the GSE5281 data set through limma package screening of R software. Of these, 3804 upregulated genes and 1868 downregulated genes were selected. At the same time, 1596 differentially expressed genes, including 706 upregulated genes and 890 downregulated genes, were obtained by analyzing the MCI samples in the GSE18309 data set and the normal control group. Then, the overall distribution of the two data sets and the first 100 DEGs are represented by volcano map and heat map respectively (Fig. 1A-D). Using $|\log2$ fold change $(FC)| \geq 2$ criteria and adjusted $P < 0.05$.

Through text mining, 1096 human genes associated with chronic periodontitis (S. s 1). After the DEGs in the microarray data were crossed, the intersection of selected genes was obtained, and 305 genes involved in AD group and 100 genes involved in MCI group were obtained (Fig. 2A-B).

3.2 Function and Signal Pathway Enrichment Analysis

After introducing the DEGs obtained above into DAVID, we subjected them to GO and KEGG enrichment analysis. The purpose of this study is to study the biological functions of DEGs integrated in AD and MCI associated with chronic periodontitis. In the GO analysis results, 519 biological process terms (BP), 67 cell component terms (CC), and 95 molecular function terms (MF) were uncovered in the DEGs integrated by AD. The $P < 0.05$ signified threshold significance. Overall, 39 genes were primarily abundant in BP term to “inflammatory response”, 95 genes are located in the “extracellular space” of CC term, and 226 genes were abundant in the MF term “protein binding” as indicated in Fig. 3. For MCI, integrated DEGs were remarkably abundant in 325 GO terms consisting of 239 BP terms, 37 CC terms, as well as 49 MF terms. Besides, the genes were majorly abundant in the following terms: modulation of inflammatory response in BP, extracellular space in CC, as well as protein binding in MF, which constituted the top 3 GO annotation terms, in which the integrated genes were most remarkably enriched (Fig. 4).

The KEGG enrichment assessment demonstrated that the integrated DEGs were remarkably enriched in the KEGG cascade Proteoglycans in cancer, PI3K-Akt signaling cascade and Influenza A in AD group and Cytokine-cytokine receptor crosstalk, Type I diabetes mellitus and Inflammatory bowel disease in the MCI group (Fig. 3-4).

3.3 Module screening from the PPI network

Based on the 305 AD group genes and the 100 MCI group genes, the Cytoscape publicly available platform and the STRING resource were employed to develop the PPI network, perform module analysis, as well as visualization. Consequently, we developed a PPI network bearing 1494 crosstalk based on 247 integrated DEGs related to AD (Fig. 5A). Moreover, we developed a PPI network in the MCI group containing 64 integrated DEGs (Fig. 6A). Based on the degree value, the top five hub genes extracted from the AD group consisted of IL6 (Interleukin-6), MAPK3 (Mitogen-activated protein kinase 3), VEGFA (Vascular endothelial growth factor A), AKT1 (Threonine kinase 1), and ALB (Albumin). On the contrary, in the MCI group, the top five hub genes were EGFR (Epidermal growth factor receptor), IL10 (Interleukin-10), IGF1 (Insulin-like growth factor I), BMP2 (Bone morphogenetic protein 2), and LDLR (Low-density lipoprotein receptor) (Table 1)

We employed the MCODE algorithm to determine highly interconnected subnets, which are frequently protein complexes, as well as components of cascades as per the topological structure. We selected the two most important modules from AD group and MCI group respectively for further analysis (Fig 5B-C, Fig 6B-C). Additional functional enrichment assessment of the established modules demonstrated that genes in the AD module were majorly abundant in the GO terms of “inflammatory response”, “extracellular space”, “heparin binding”, as well as KEGG cascade of “PI3K-Akt signaling pathway” (Fig 7A-B). Genes in the module of MCI primarily were abundant in the GO terms of “inflammatory response”, “extracellular space”, “chemokine activity” and KEGG pathway of “Proteoglycans in cancer” (Fig 8A-B).

Discussion

In many epidemiological studies, chronic periodontitis may be the result of the gradual deterioration of neuronal function during aging. Therefore, a new potential treatment method for preventing the progression of AD has emerged, that is, delaying or preventing chronic inflammatory diseases. However, at present, the pathogenesis and effective treatment of chronic periodontitis for cognitive decline remain unclear. Hence, it is imperative to explore the molecular mechanism of the cognitive decline after chronic periodontitis to determine efficient biomarkers and effective approaches for the diagnosis, monitoring, as well as treatment of patients.

Herein, 305 genes in the AD and 100 genes in MCI linked to chronic periodontitis were uncovered for functional analysis using the GO, as well as the KEGG enrichment assessments. The data from the GO annotation suggested that the uncovered DEGs primarily participated in protein docking, apoptosis, as well as immune modulation. It is critical to point out that MAPK3 constitutes a prevalent gene in most of the rich KEGG pathways in AD. Additionally, the MAPK3 gene comprised one of the hub genes uncovered by the PPI network. MAPK3 referred to as the mitogen-activated protein kinase 3, is a MAP kinase family member and participates in an extensive array of biological processes, including cell proliferation, as well as angiogenesis. MAPK3 may serve as the intrafollicular mediators that trigger the expansion of the cumulus cell-oocyte complex (COC), as well as the maturation of the oocytes [20-22]. The extracellular, as well as intracellular mitogenic stimuli activate the MAPK3 cascade, which has pivotal functions in cellular differentiation, proliferation and survival [23]. The study of colorectal cancer by Schmitz et al. showed that the expression of MAPK3 is related to poor prognosis [24].

At the same time, IL10 is a common gene in most of the rich KEGG pathways in MCI, and also one of the hub genes uncovered in PPI network. Interleukin-10 (IL-10) is a key immunomodulatory cytokine, which is involved in the inflammatory response [25-27]. Among them, the research results of Guillot-Sestier et al. propose that the re-balancing of innate immunity via blocking of the IL-10 anti-inflammatory response may be linked to the treatment of AD [28]. Similarly, many studies have shown abnormal increases in IL-10 signaling in the brains of AD patients. Numerous results confirm and extend other studies that have reported elevated IL-10 levels in serum, as well as the brain extracts from individuals with AD [29-31].

Through the establishment of the PPI network, the functional enrichment assessment of the greatly integrated modules demonstrated that the AD module genes were majorly abundant in the KEGG PI3K-Akt signaling cascade term. Phosphatidylinositol 3 -kinase (PI3K) is involved in the formation of phosphatidylinositol 3, 4, 5-trisphosphate, a second messenger, which is crucial in the Akt (protein kinase B) translocation. The activation of the Akt participates in important cellular roles, including cell survival, as well as cell proliferation. The PI3K-Akt cascade is related to the progression of numerous diseases, e.g., cancer, autoimmunity, as well as diabetes mellitus [32]. Moreover, five hub genes with the highest degree of connectivity were separately identified from the AD and MCI. The top five hub genes linked to AD are IL6, VEGFA, AKT1, MAPK3, and ALB, whereas those associated with MCI are EGFR, IL10, IGF1, BMP2, and LDLR.

VEGFA is a growth factor released by tumor cells. It participates in tumorigenesis and development. It can trigger the germination of existing vascular endothelial cells to form a new vascular system [33]. It is reported that VEGFA is abnormally regulated in various cancers and promote tumor progression [34]. According to reports, a variety of miRNAs inhibits tumor growth, angiogenesis, as well as metastasis by suppressing the expression of its target gene VEGFA [35,36]. In addition to its widely described growth factor function, VEGFA also acts as a neurotrophic factor [37-39], and interestingly, VEGFA also serves a critical role in hippocampal neurogenesis [40,41]. Recent studies have found that considerable evidence suggests that insufficient neuroprotection of VEGFA can lead to neurodegenerative diseases [42-44].

IL-6 constitutes a pleiotropic pro-inflammatory cytokine. The deregulation of IL-6 is linked to chronic inflammation, as well as multifactorial auto-immune disorders. The study of Gurel et al. found that IL6 is involved in iron homeostasis and inflammation, and IL6 was found to be elevated in the hippocampus of 5XFAD mice [45]. A large number of studies have found that IL-6 increases with age and is associated with loss of motor function [46-48]. Meanwhile, in many mental diseases, such as obsessive-compulsive disorder, acute psychosis, schizophrenia, panic disorder, as well as post-traumatic stress disorder (PTSD), IL-6 expression has been found to be significantly increased [49-54].

AKT1 comprises a redox-sensitive protein and its kinase activity is modulated by the redox milieu [55,56]. The results of Karege et al. [57] showed that the polymorphism of the AKT1 gene seems to have an impact on mental symptoms such as schizophrenia. Devaney et al. [58] documented that AKT1 is a risk factor of metabolic syndrome, as well as insulin resistance. Interestingly, a large number of studies have found that abnormalities in Akt1 signal have been observed in the brain tissues and animal models of AD patients [59-63].

EGFR functioning as a protein tyrosine kinase receptor, not only serves important functions in cell differentiation, cell growth, as well as tissue development and function, serving as an integrator at the convergence of the extracellular growth and survival signals, which are transformed into intracellular outputs [64,65]. In addition, EFGR serves a vital role in the development of human cell transformation and cancer [64,65]. The function of EGFR is obviously related to a series of neurometabolic disorders, such as diabetes, AD, as well as aging [64,66].

ALB (albumin) constitutes a multifunctional plasma protein found in large Numbers in human blood [67]. In addition, albumin is also involved in stabilizing colloidal osmotic pressure, removing free radicals and protecting nerve cells, and is significantly related to systemic nutritional status and inflammation [68]. The study of Lei et al. found that albumin concentration can be used as an independent prognostic factor for patients with endometrial cancer [69].

The IGF1 signaling pathway is ubiquitous in the aging process, so it is called the somatotropic axis [70,71]. Similarly, low levels of serum IGF1 can reduce the incidence of cognitive impairment in women after the age of 10 [72].

Low-density lipoprotein receptor (LDLR) can regulate the level of peripheral and central nervous system (CNS) lipoproteins, so it is known as an important receptor that inhibits amyloid deposition [73,74]. Yao et al. found that polyphenol-mediated regulation of LDLR expression may be a safe and effective treatment for AD disease, which can accelerate the clearance rate of AD [75].

Conclusions

By employing a sequence of bioinformatics tools for gene expression profiling, we established the core function of candidate key genes, including MAPK3 and IL10, and the enriched signaling cascades constituting the PI3K-Akt axis in the molecular modulation network of cognitive decline via integrated bioinformatic analysis. This provided the prospective targets for the future diagnosis, as well as clinical treatment of AD. However, in vitro, as well as in vivo studies should be conducted to verify our findings.

Declarations

Compliance with ethical standards

Competing of interests

The authors declare that they have no competing interests.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate

Not applicable.

Consent for publication

All authors consent to the publication of this study.

Availability of data and material

All data is available under reasonable request.

Code availability

Not applicable.

Authors' contributions

ZJ, BZ, YZ and YS conceived and designed this study. ZJ wrote this manuscript. ZW revised this manuscript. ZJ made these figures with the help of YS, YX, WZ, LW and GT.

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Tables

Table 1. Top five hub genes identified from the PPI networks

Unstable angina related genes		Myocardial infarction related genes	
Gene	Node	Gene	Node
IL6	91	EGFR	17
VEGFA	73	IL10	16
AKT1	69	IGF1	15
MAPK3	55	BMP2	8
ALB	55	LDLR	7

Figures

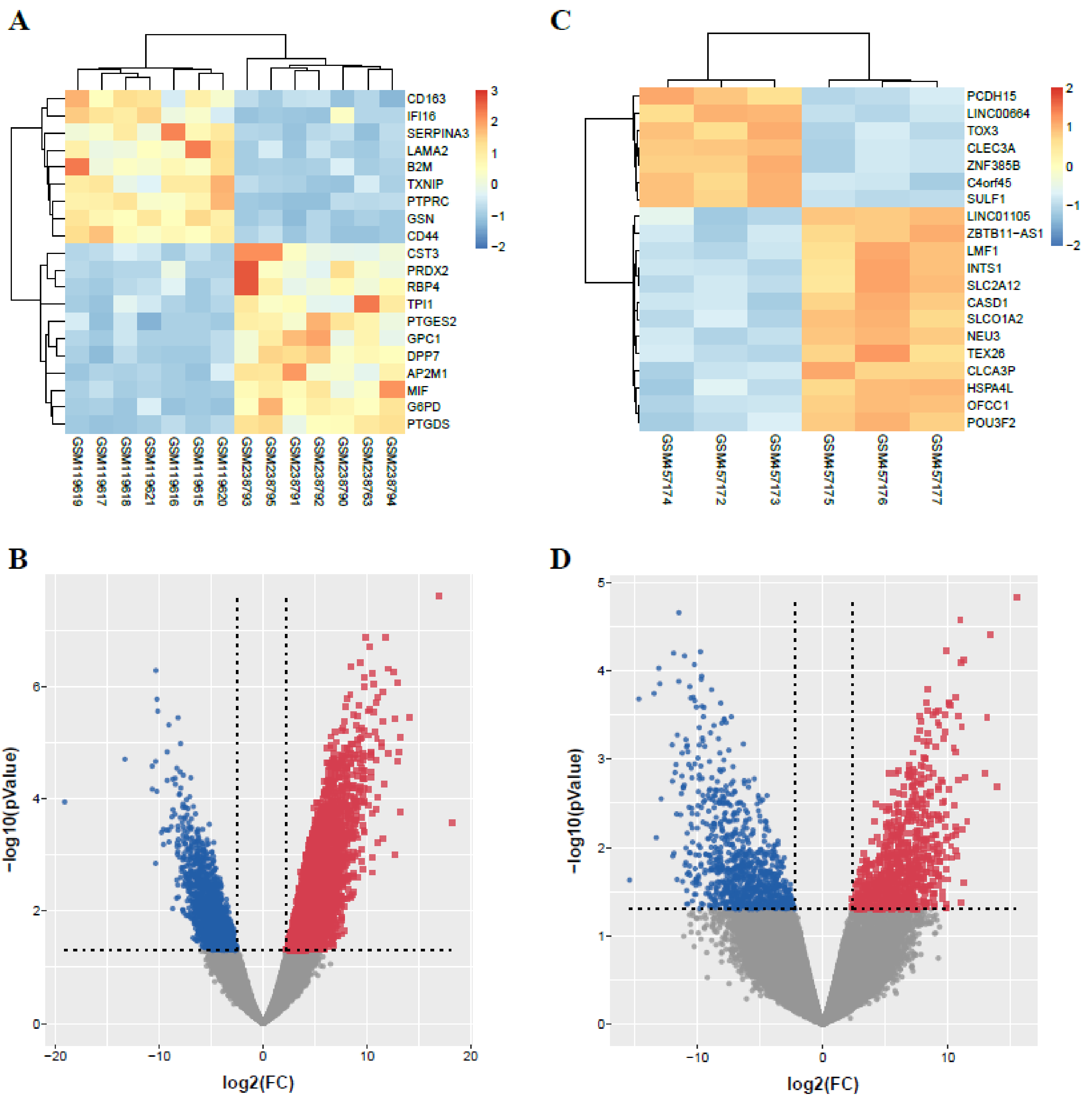

Figure 1

Differentially expressed genes between Alzheimer disease/mild cognitive impairment and control groups. A, B Volcano plot and cluster heat map of the top 20 differentially expressed genes from GSE5281. C, D Volcano plot and cluster heat map of the top 20 differentially expressed genes from GSE18309. Red represents the upregulated genes based on |log2FC|>1 and P value < 0.05 and blue represents the downregulated genes based on the same statistical requirements.

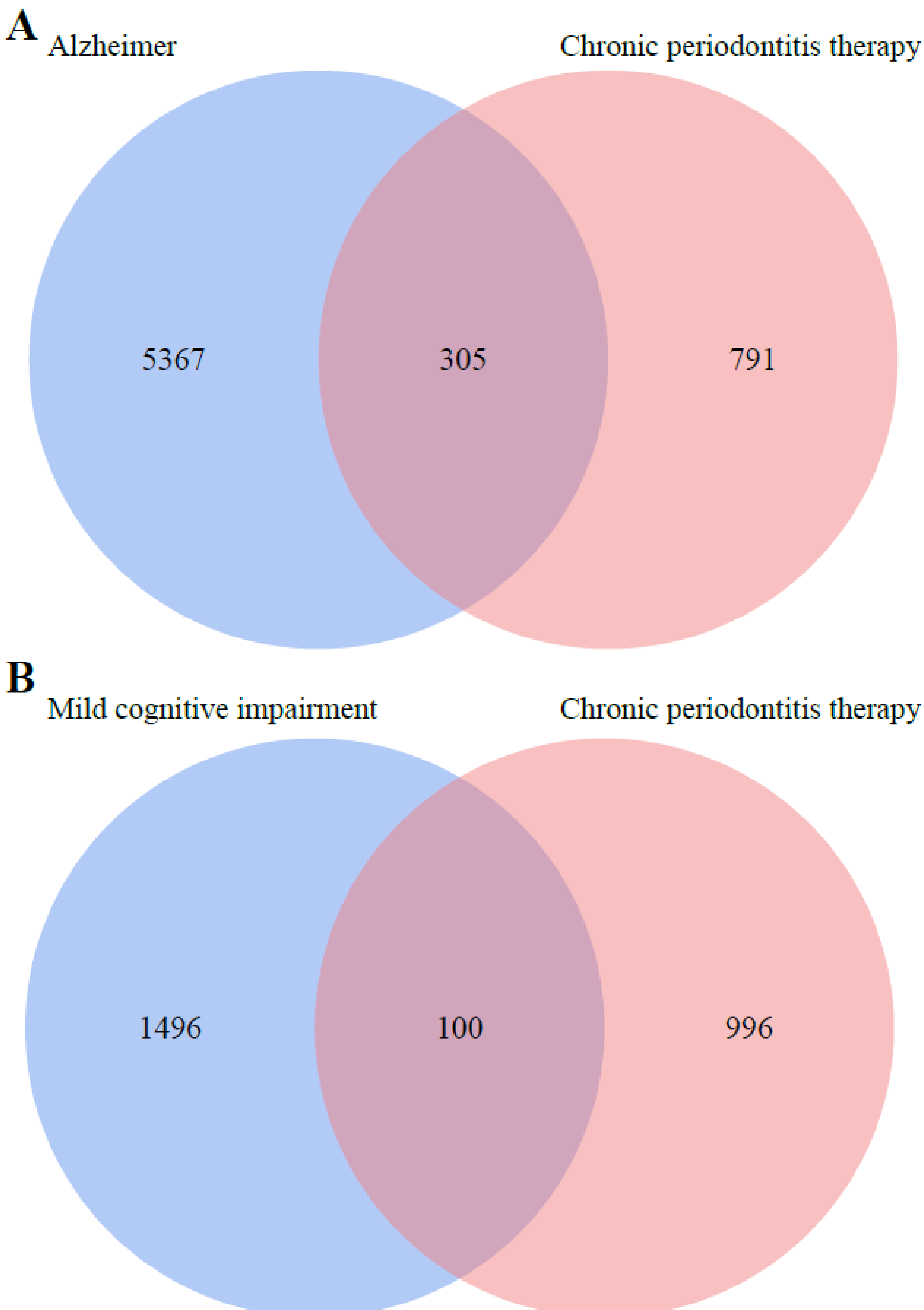

Figure 2

Venn diagram of DEGs from microarray data and genes list from text mining. A Intersection of genes between DEGs generated from GSE5281 and chronic periodontitis gene list from text mining. B Intersection of genes between DEGs generated from GSE18309 and chronic periodontitis gene list from text mining. DEGs, differentially expressed genes.

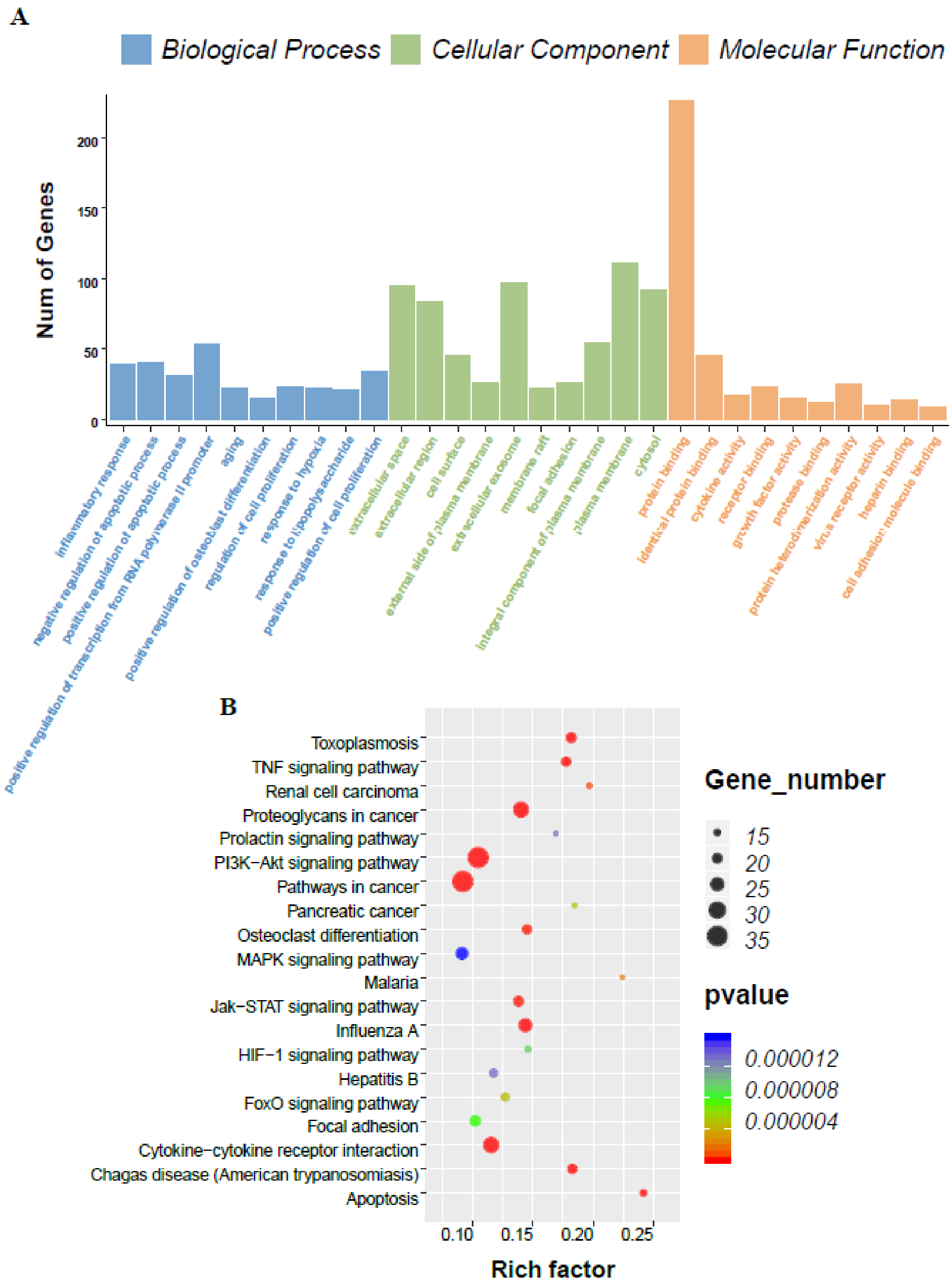

Figure 3

GO term and KEGG pathway analysis for DEGs significantly associated with Alzheimer disease and chronic periodontitis. A Top 10 GO terms. Number of gene of GO analysis was acquired from DAVID functional annotation tool. p <0.05. (B) KEGG pathway.

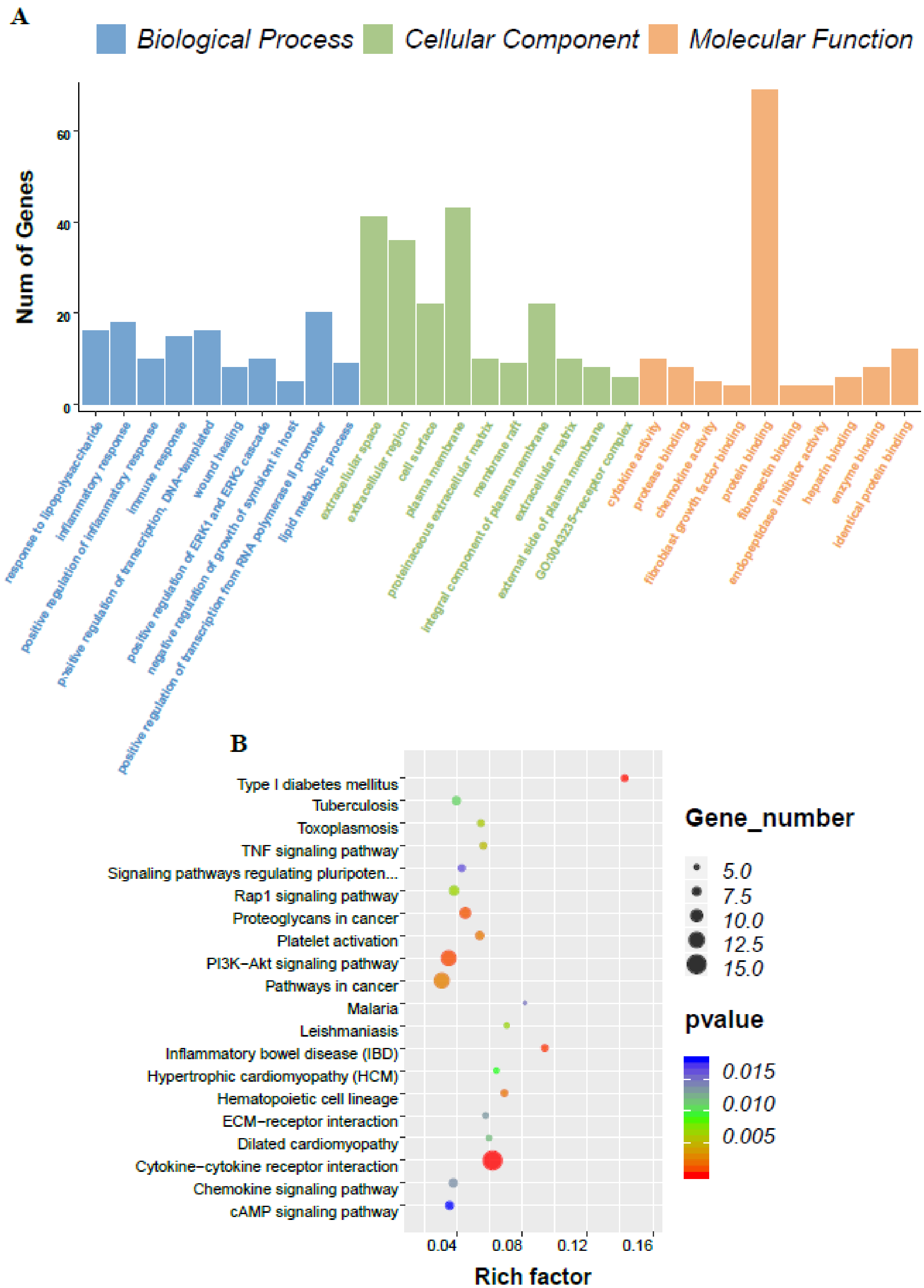

Figure 4

GO term and KEGG pathway analysis for DEGs significantly associated with mild cognitive impairment and chronic periodontitis. A Top 10 GO terms. Number of gene of GO analysis was acquired from DAVID functional annotation tool. p <0.05. (B) KEGG pathway.

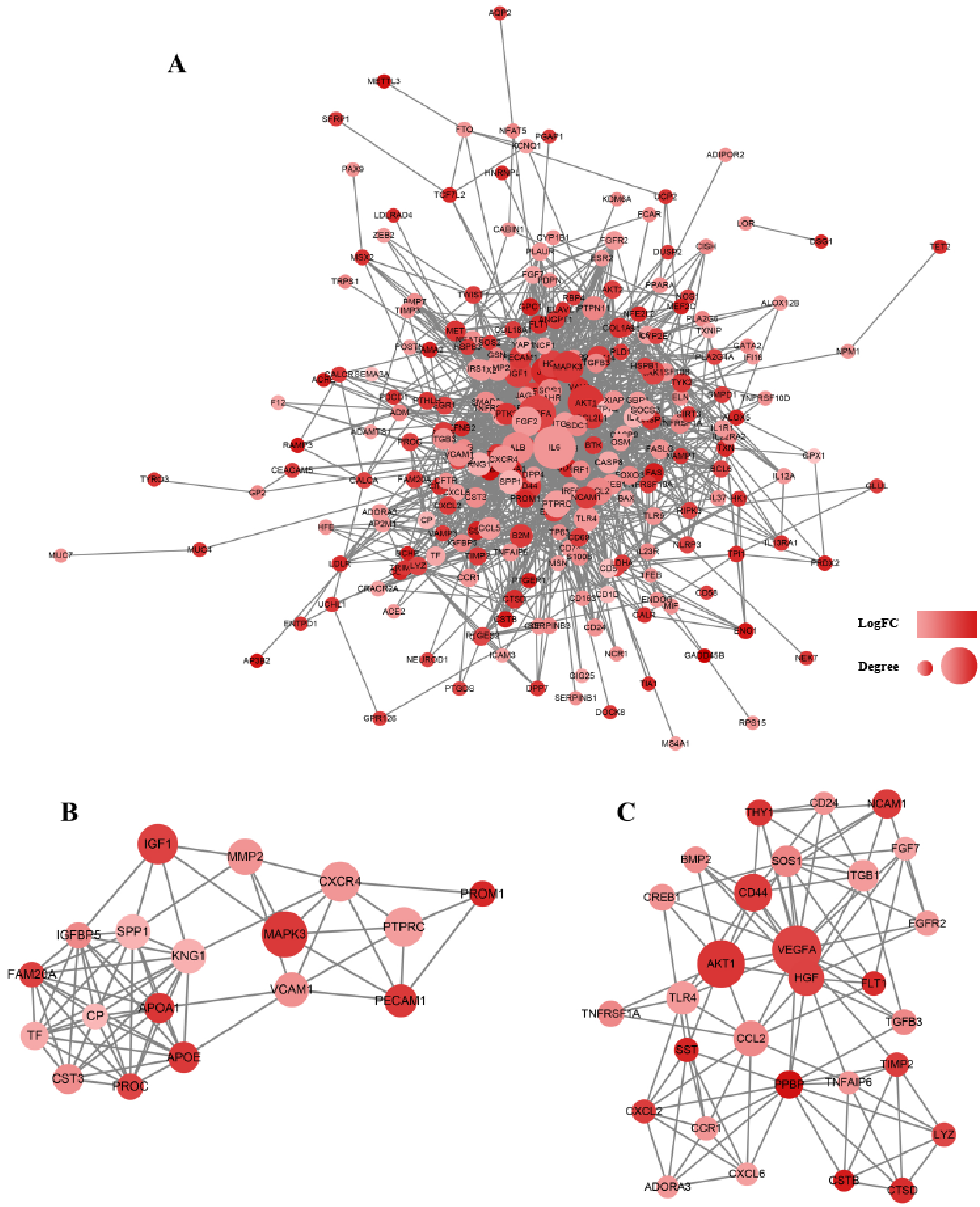

Figure 5

A Based on the STRING online database, 247 genes/node were filtered into the DEG PPI network. B The most significant module 1 from the PPI network. C The second significant module 2 from the PPI network. The color of a node in the PPI network reflects the log (FC) value of the Z score of gene expression, and the size of node indicates the number of interacting proteins with the designated protein.

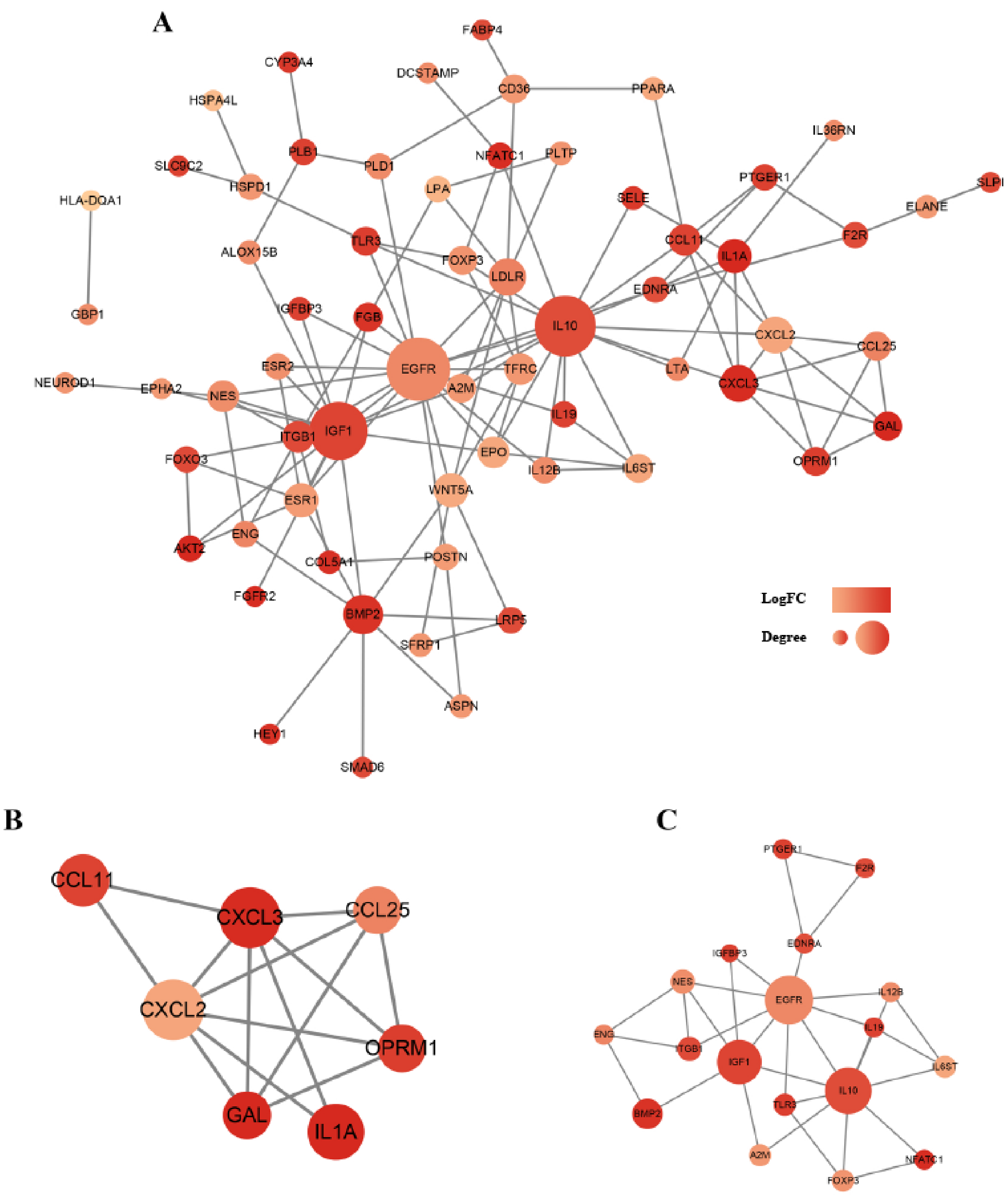

Figure 6

A Based on the STRING online database, 64 genes/node were filtered into the DEG PPI network. B The most significant module 1 from the PPI network. C The second significant module 2 from the PPI network. The color of a node in the PPI network reflects the log (FC) value of the Z score of gene expression, and the size of node indicates the number of interacting proteins with the designated protein.

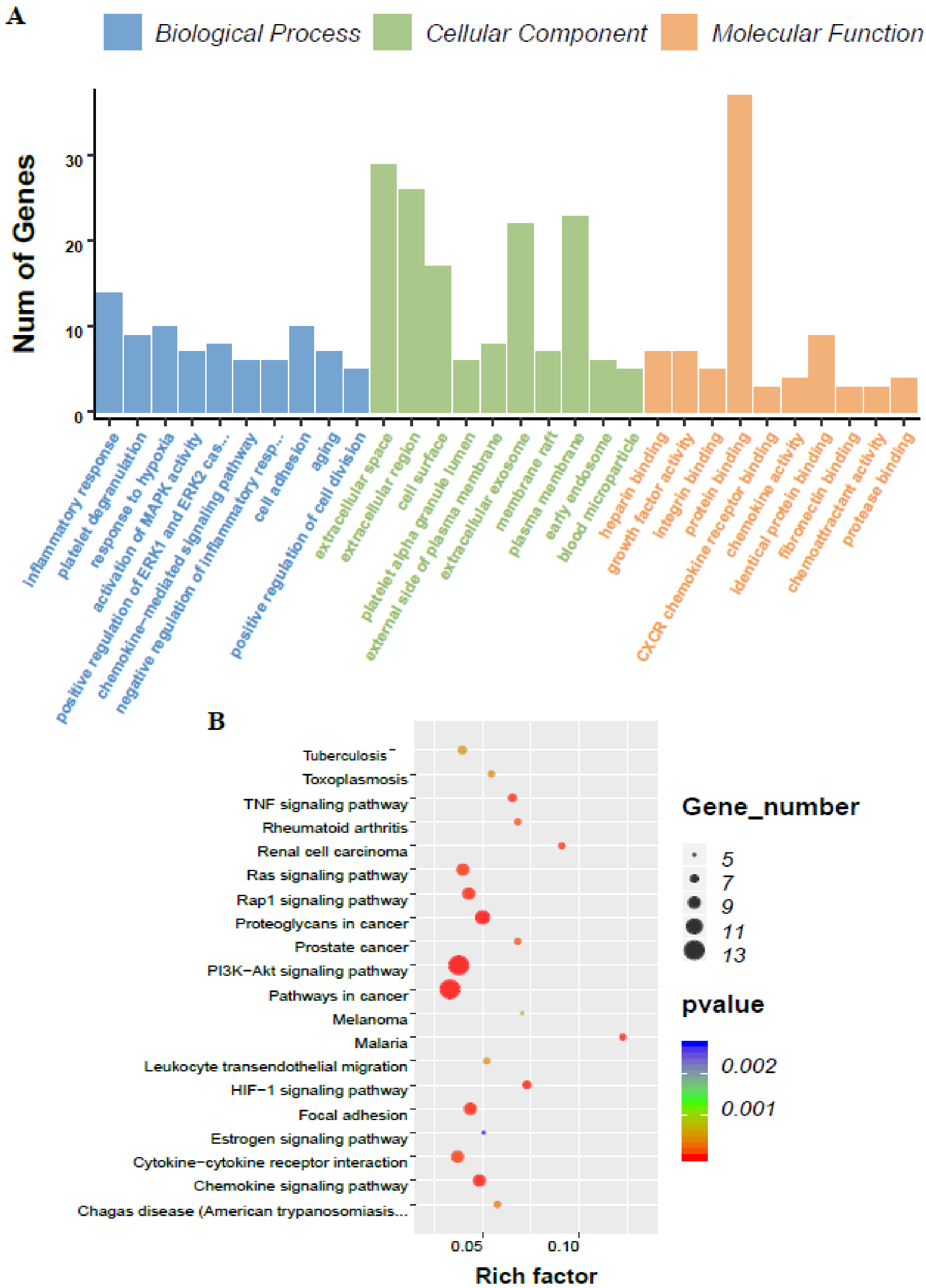

Figure 7

Functional enrichment analysis of genes from the highly interconnected modules of Alzheimer disease. A Top 10 GO terms. Number of gene of GO analysis was acquired from DAVID functional annotation tool. p <0.05. (B) KEGG pathway.

Figure 8

Functional enrichment analysis of genes from the highly interconnected modules of mild cognitive impairment. A Top 10 GO terms. Number of gene of GO analysis was acquired from DAVID functional annotation tool. p <0.05. (B) KEGG pathway.