Integrative Bioinformatics
ISSN: 3078-7416
DOI: https://doi.org/10.61784/ib3002

ANALYSIS OF OXIDATIVE STRESS-RELATED GENES IN MAJOR DEPRESSION BASED ON BIOINFORMATICS AND SCREENING OF TARGETED PREVENTION AND TREATMENT OF TRADITIONAL CHINESE MEDICINES

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Abstract: Major Depressive Disorder (MDD) is a severe mental disorder with approximately 350 million patients worldwide. In recent years, oxidative stress has played an important role in the pathogenesis of depression. This study used bioinformatics methods to explore the expression patterns of oxidative stress-related differential genes in MDD and screen related traditional Chinese medicines, in order to provide more reference for clinical decision-making.
Keywords: Severe depression; Oxidative stress; Traditional Chinese medicine screening; Ginseng; tea tree root; Saffron

1 INTRODUCTION

Depression is a common mental disorder, with significant and persistent low mood and slow thinking as the main clinical manifestations. According to estimates by the World Health Organization (WHO), depression has become the fourth most common disease in the world. This study aims to explore the oxidative stress-related genes of MDD through bioinformatics analysis and screen out potential traditional Chinese medicine treatments [1].

2 MATERIALS AND METHODS

2.1 Data Collection

This study downloaded the data set GSE54562 from the Gene Expression Omnibus (GEO), which provides samples of the anterior cingulate cortex of 10 MDD patients and 10 normal individuals [2].

2.2 Screening of Differentially Expressed Genes (DEGs)

Use the limma package in the R program, set the filter conditions to $|\log2FC|\geq0.26$, correct $P<0.05$ for DEGs analysis, and draw heat maps and volcano maps.

2.3 Functional Enrichment Analysis of DEGs

To identify the biological properties of DEGs, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis of DEGs was performed using the R package [3].

2.4 Acquisition and Screening of Oxidative Stress-Related Genes

The GeneCards database was used to screen oxidative stress genes based on the criterion that the correlation score was greater than the average, and the intersection with the DEGs of the GSE54562 data set was used to obtain the oxidative stress-related DEGs of MDD.

2.5 Functional Enrichment Analysis of Oxidative Stress Differential Genes in MDD

Select $P<0.05$ as the screening criterion and use the clusterProfiler R software package to perform GO and KEGG enrichment analysis and perform visualization [4].

2.6 Protein-Protein Interaction (PPI) Network Construction and Screening of Key Genes

The STRING website was used to analyze and connect oxidative stress differential genes with strong correlation in MDD to form a PPI network. Put the oxidative stress differential genes in MDD into Cytoscape, and use the four algorithms in the Cytohubba plug-in: Degree, MCC, DMNC, and EPC to intersect the top 10 genes in various algorithms to obtain the key genes [5]. Then, the least absolute shrinkage and selection operator (LASSO) regression analysis modeling was performed, and the R language glmnet package was used as the analysis tool to obtain the characteristic hub genes.

2.7 Verification of Key Genes Related to Oxidative Stress in MDD

Use the "pROC" R package to draw the receiver operating (ROC) curve of key genes, and use the data set GSE39653 as a validation data set for key genes of MDD and oxidative stress.

2.8 Immune Infiltration Analysis

The CIBESORT function method of the R package was used to analyze the infiltration degree of 22 types of immune cells in the anterior cingulate cortex of the brain areas of the MDD group and the control group [6].

2.9 Correlation Analysis of Key Genes and Immune Infiltration

Use Pearson to perform correlation analysis between key genes and immune cell abundance.

2.10 Prediction of Traditional Chinese Medicines for the Prevention and Treatment of Key Genes Related to Oxidative Stress in MDD

Use the COREMINE Medical online database to predict the targeted prevention and treatment of traditional Chinese medicine that interacts with key genes of oxidative stress in MDD and the disease.

3 RESULTS

3.1 Screening of DEGs

The results of GSE54562 gene differential expression analysis showed that there were 202 DEGs in the MDD group and the normal control group. The volcano plot and heat map showed that 113 genes were significantly up-regulated and 89 genes were significantly down-regulated.

3.2 Functional Enrichment Analysis of DEGs

GO analysis showed that genes in the anterior cingulate cortex brain area were enriched in different signaling pathways, mainly in nervous system development, oligodendrocyte differentiation, and central nervous system myelination signaling pathways [7]. MDD is mainly localized in cellular components such as myelin, plasma membrane parts, membrane components, neuronal projections, and whole membranes. Participates in endoribonuclease activity and produces 3'-phosphate monoester, double-stranded RNA binding, cyclic nucleotide binding, nucleotide diphosphatase activity, integrin binding and other molecular functions [8].
KEGG analysis results showed that MDD differential genes were mainly enriched in phagosomes, ether lipid metabolism, histidine metabolism, endocytosis, cell adhesion molecules, etc.

3.3 Functional Enrichment Analysis and Functional Module Analysis of Oxidative Stress DEGs in MDD

Wayne analysis was performed on the 202 DEGs of GSE54562 and the 3962 oxidative stress-related genes screened, and 47 oxidative stress differential genes in MDD were obtained.

3.4 PPI Network Construction

In order to explore the interactions between proteins encoded by DEGs, the STRING database was used to connect 47 oxidative stress differential genes to each other to form a PPI network diagram.

3.5 Key Gene Screening

Using Cytoscape's 4 algorithms, we calculated the genes with the highest scores and took the intersection to obtain 8 key genes: myelin protein (PLP1), myelin oligodendrocyte glycoprotein (MOG), 2', 3'- Cyclic nucleotide 3' phosphodiesterase (CNP), recombinant rabbit monoclonal antibody to transcription factor SOX10 (SOX10), ionized calcium adapter protein antibody (AIF1), contact protein 2 (CNTN2), integrin subunit β2 (ITGB2) , G protein-coupled receptor 37 (GPR37).

3.6 Verification of Key Genes Related to MDD and Oxidative Stress

A ROC curve was drawn using the R package and the expression of two key genes to evaluate the diagnostic accuracy. The two key genes have high diagnostic value, and the AUC values corresponding to the genes MOG and AIF1 were 0.850 and 0.760, respectively.

3.7 Immune Infiltration Analysis Results

Immune infiltration analysis was performed based on CIBESORT. The boxplot showed that compared with the normal

group, resting natural killer (NK) cells were significantly increased and T follicular helper cells (Tfh) were significantly decreased [9].

3.8 Results of Correlation Analysis between Key Genes and Immune Infiltration

Conduct correlation analysis between the selected key genes and immune cells with differential changes. MOG has a moderate positive correlation with resting NK cells, and AIF1 has a strong positive correlation with T follicular helper cells.

3.9 MDD Traditional Chinese Medicine Forecast

Screen traditional Chinese medicines that are related to key genes of MDD, and standardize the names of relevant traditional Chinese medicines by consulting the 2020 edition of the Chinese Pharmacopoeia [10].

4 DISCUSSION

Research shows that oxidative stress can cause damage to neurons and neural circuits, cause neuroinflammation, destroy brain function, and lead to depression. There is a mutually reinforcing relationship between oxidative stress and inflammatory response, and oxidative stress can activate inflammatory response. Inflammatory factors are closely related to the pathogenesis of depression [11]. Inflammatory factors in the brain regulate neurotransmitters related to mood regulation, upregulating pro-inflammatory factors and promoting depression.

GO analysis results showed that MDD differential genes were mainly enriched in nervous system development, oligodendrocyte differentiation, and central nervous system myelination signaling pathways. MDD is mainly involved in molecular functions such as cyclic nucleotide binding and integrin binding. Abnormal development of interneurons is closely associated with depression, and myelin and oligodendrocyte lineage cells play a damaging role in depression and stress-related diseases [12].

KEGG analysis results showed that MDD differential genes were mainly enriched in pathways such as ether lipid metabolism, histidine metabolism, phagosomes, cytokines, and cell adhesion molecules. MDD differential genes are enriched in ether lipid metabolism, affecting neurotransmitter homeostasis and release, and changes in their composition are often related to neurological and psychiatric diseases. MDD differential genes are enriched in histidine metabolism. Elderly women with moderate depressive symptoms show a deficiency of essential amino acids involved in inflammation and neurotransmission, one of which is characterized by lower L-histidine levels [13].

Eight key genes of MDD oxidative stress were obtained through screening. There are three myelin proteins (i.e., PLP1, CNPase, MOG) in the white matter of the ventral prefrontal cortex in MDD. PLP1 is the main component of myelin. In the PLP1 overexpression model, microglia are activated and pro-inflammatory cytokines are upregulated in the brain. , PLP1 overexpression is associated with defects in oxidative stress homeostasis and may exacerbate the development of MDD.

AIF1 allograft inflammatory factor 1, gene encoding an actin- and calcium-binding protein that enhances membrane ruffling and RAC activation, plays a role in RAC signaling and phagocytosis, enhances actin bundling of LCP1 active [14]. Under the induction of cytokines and interferons, AIF1 can promote the activation and growth of some immune cells, affecting various physiological processes such as oxidative stress, inflammation and immunity.

MDD is closely related to immune system abnormalities. This study conducted immune infiltration analysis based on CIBESORT and found that compared with the normal group, resting NK cells were significantly increased and T follicular helper cells were significantly decreased. Studies have confirmed that lymphocyte subsets are closely related to immune activation in MDD.

Traditional Chinese medicine's understanding of depression originally came from the ancient medical document "Huangdi Neijing". Traditional Chinese medicine believes that the occurrence of depression is related to the dysfunction of the internal organs and the imbalance of qi, blood, yin and yang [15]. Therefore, it should

Choose traditional Chinese medicine that nourishes the liver, kidneys, blood and spleen. Coremine Medical's predicted results are tea tree root, honey, saffron, floating wheat, ginseng, ginseng flower, ginseng reed, ginseng leaf, hemp seed, gastrodia elata, turnip, castor bean, zombie silkworm, zombie pupa and other traditional Chinese medicines.

5 CONCLUSION

The oxidative stress differential genes of MDD were obtained through bioinformatics analysis, and 14 preferred traditional Chinese medicines for the treatment of MDD were predicted, such as honey, ginseng, tea tree roots, etc. This provides important significance for the traditional Chinese medicine prevention and treatment of MDD [16].

COMPETING INTERESTS

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

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