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Original Article

Identification of key genes associated with sepsis patients infected by staphylococcus aureus through weighted gene co-expression network analysis

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Abstract: The prevention and treatment of staphylococcus aureus septicemia is one of the thorniest problems in modern medicine. However, as the underlying pathogenesis of sepsis is still unclear, there is currently no golden standard for clinical diagnosis. In this study, we used GSE33341 dataset for differentially expressed gene (DEG) analysis and screened out 857 differentially expressed genes associated with staphylococcus aureus infection. The module having the highest correlation with clinical features of sepsis was screened by weighted gene co-expression network analysis (WGCNA). The genes in the selected module and the differentially expressed genes were represented in Venn diagram, and 59 pathogenic genes at the intersection were obtained. GO and KEGG analysis showed that these genes were mainly related to aerobic respiration, cellular stress response, mitochondrial electron transport, mitochondrial transport, oxidative phosphorylation. Kaplan-Meier was used to analyze the influence of the top 10 key genes on the prognosis of sepsis patients. The results showed that the high expression of NDUFA4, NDUFB3, COX7A2, ATP5J and COX7C was significantly correlated with the poor overall survival (OS) in patients with bacterial sepsis. These findings may potentially provide a reference for the diagnosis and treatment of bacterial septicemia.

Keywords: Bacterial sepsis, staphylococcus aureus, weighted gene coexpression network, differential analysis, survival analysis

Introduction

Sepsis is a systemic inflammatory response syndrome in which the host response is dysregulated by infection [1]. Septic shock and multiple organ dysfunction syndrome are among the most serious complications of critical conditions such as trauma, burns, and shock [2]. Sepsis is also the leading cause of death in non-cardiac patients in intensive care units (ICU) [3]. About 30 million patients worldwide suffer from sepsis every year, with a mortality rate of 30-70% [4]. Although the diagnosis and treatment techniques in this field have been improving in recent years, the incidence and mortality are still on the rise [5]. Early diagnosis and comprehensive treatment are the key to enhancing the prognosis of sepsis [6].

The pathogenic bacteria of sepsis include staphylococcus aureus, coagulase negative staphylococcus, Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, Acinetobacter baumannii, Enterococcus faecium, Serratia marcescens and Enterobacter cloacae [7]. Both clinical and epidemiological data imply that Staphylococcus aureus (SA) accounts for the highest proportion among these pathogens [8]. Due to its complex pathogenic mechanism and the emerging drug resistance, especially vancomycin-resistance, the prevention and treatment of Staphylococcus aureus sepsis have become

increasingly nettlesome [9]. Thus, finding relevant markers that can be used to assist the diagnosis, prognosis and treatment of sepsis quickly and effectively is imperative, and may contribute new ideas to the clinical treatment of sepsis [10].

Previous research had pointed out that during the occurrence and development of sepsis, the body produces a continuous and excessive inflammatory response to infection, and the interactions among various cytokines, chemokines and neuroendocrine factors combine to form a complex molecular biology network [11, 12]. Therefore, we can try to elucidate the pathogenesis of sepsis by analyzing the complex interactions among various factors. As a comprehensive analysis technique based on biological network, weighted gene co-expression network analysis (WGCNA) can identify a class of genes (or proteins) that are co-expressed, associate clustering modules with phenotypes through algorithms, and explore the core of the gene (or protein) modules [13]. Meanwhile, the protein interaction network is composed of the interactions among various proteins possibly participating in biological signal transmission, gene expression regulation, material metabolism and other life processes [14]. In this study, we used a high-throughput Gene Expression Omnibus (GEO) dataset containing staphylococcus aureus infection samples (GSE33341). By combining weighted gene co-expression network analysis (WGCNA) and differentially expressed gene (DEG) analysis, we screened out the key genes related to a high risk of sepsis. Pathway enrichment analysis was performed to provide a reference for the diagnosis and treatment of sepsis caused by Staphylococcus aureus infection.

Materials and methods

Data collection and processing

In order to study the pathogenic mechanism of sepsis caused by staphylococcus aureus infection, dataset GSE33341 was downloaded from Gene Expression Omnibus (GEO) database. It contains the gene expression profiles of peripheral blood samples from 32 staphylococcus aureus infection subjects and 43 healthy subjects. The probes were converted into corresponding gene symbols by referring to the annotated information of GPL571 ([HG-U133A_2] Affymetrix Human Genome U133A 2.0 Array) platform. Then the data was normalized by Limma software package for further analysis. Moreover, the Robust Multichip Average (RMA) generated by Affymetrix Expression Console software was used for data processing.

This study used the publicly available dataset GSE54514 from GEO database. The database contained blood samples from 96 non-fatal sepsis cases and 31 fatal cases. The collected cases in the dataset have been confirmed as bacterial infections by microbiological pathology results. And the consulting physicians agreed that sepsis was the reason for the patients to be admitted to ICU.

DEG analysis

R package Limma was used to identify the differentially expressed genes (DEG) in the normalized peripheral blood samples of healthy subjects and staphylococcus aureus infected patients [15]. t-tests were performed to determine the level of differential expression between the two groups. |log2FC| >1 and Benjamini-Hochberg adjusted *P*-value <0.05 was taken as the thresholds of statistical significance. Additionally, a volcano map was constructed using the R packages *ggpubr* and *ggthemes*, and a heatmap was drawn using R package *pheatmap* based on the results of DEG analysis.

Construction of weighted gene co-expression network analysis

To explore modules and genes related to clinical characteristics staphylococcus aureus infection, genes with mean FPKM >8 were selected for sample clustering and outlier elimination. The *pickSoftThreshold* function in WGCNA package was used to calculate the correlation coefficient of β value and the mean value of gene connectivity, which were used as the soft threshold for subsequent network construction. Then, the *blockwiseModules* function was used to construct topological overlap matrix (TOM), and dynamic tree shearing algorithm was used for clustering. Genes with similar expression patterns were grouped into the same co-expression module, and different colors were assigned to each module for differentiation. The minimum number of genes in mod-

ules was set to 30, the threshold for merging similar modules was set to 0.25, and the rest of the default parameters were retained. Finally, gene significance (GS) and Module membership (MM) were calculated, associating modules with clinical traits. By setting |MM| >0.8 and |GS| >0.2, the module having the highest correlation with sepsis was selected, and genes within the module were chosen for the next phase of analysis. Genes in the co-expression module exhibit high connectivity, while genes in the same module may have similar biological functions.

Screening key genes responsible for high risk of sepsis

High-risk differentially expressed genes were defined as those pathogenic genes existing in both the modules screened by WGCNA and the results of DEG analysis. Venn plots (http://bioinformatics.psb.ugent.be/webtools/Venn/) were used to show all high-risk differentially expressed genes. Then, String functional enrichment analysis (https://www.string-db.org/) was used to analyze the interaction network of proteins in significantly correlated modules. In this study, Cytoscape11 was used for network analysis, Net Work Analyze was used to assess the related topological properties of the network, and CytoHubba plug-in was used to screen the top 10 genes in the module with MCC algorithm.

Enrichment analysis of genes in the selected modules

Enrichment analysis was conducted on the high-risk differentially expressed genes to further explore their biological functions. Metascape was used for GO (gene ontology) and KEGG (kyoto encyclopedia of genes and genomes) analysis [16]. The Benjamini-Hochberg adjusted *P*-value <0.05 was adopted as the significance threshold. GO analysis was used to annotates the function of genes and their products in biological processes (BP), molecular functions (MF) and cellular components (CC). Meanwhile, KEGG database served as a collection of genes, proteins, chemical compositions and their interaction, reaction and relationship network. It was used to annotate and analyze gene functions and metabolic pathways. Those pathways with adjusted *P*-value <0.01 were selected from the results of both analyses.

Kaplan-Meier survival curve analysis

GSE54514 dataset was selected from GEO database, Survival analysis was conducted using the Kaplan-Meier method, and the survival curve was drawn with R packages *Survival* and *SurvMiner*. Log-rank test was then used to assess the statistical significance of the difference in survival between the two groups.

Results

Screening for differentially expressed genes

R package Limma was used to screen the differentially expressed genes. Based on the threshold of |log2FC| >1 and adjusted P<0.05, the differentially expressed genes in the samples of Staphylococcus aureus infected patients and healthy subjects in GSE33341 dataset were selected. A total of 857 genes were found to be differentially expressed genes, among which 461 genes were up-regulated and 396 genes were down-regulated (**Figure 1A**). The results of DEG analysis were used to construct a volcano map in which up-regulated genes were represented in red and down-regulated genes were represented in green. At the same time, a heat map was drawn, in which high gene expression level was denoted in red and low gene expression level was denoted in green. Each column of the heat map represents a sample, and each row represents a gene. Similar samples and similar genes are clustered in the abscissa and ordinate respectively. As a result, we were able to observe that the expression patterns of functionally related genes are also similar (**Figure 1B**).

Constructing the co-expression module

After the height was set to 65, the outlier samples GSM824729 and GSM824730 were removed, and the remaining samples were reserved for further analysis (**Figure 2A**). When the scale-free topology fitting index R2 reaches 0.9, the appropriate β value is 5 (**Figure 2B**). Dynamic clipping tree algorithm was used to segment modules and construct the network graph (**Figure 2C**). Cluster analysis was performed on modules, and modules with similar distances were merged into new modules.

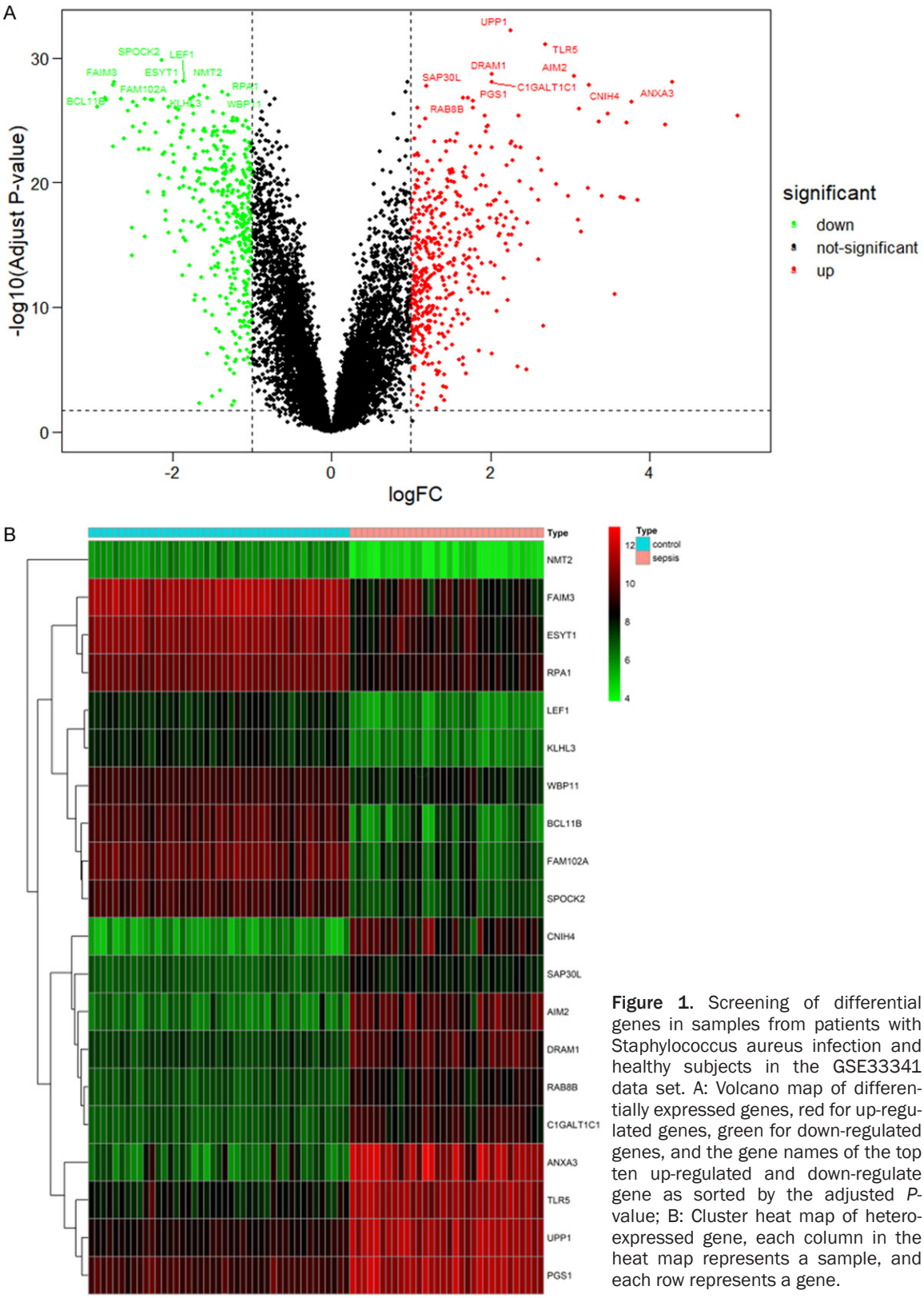


Figure 1. Screening of differential genes in samples from patients with Staphylococcus aureus infection and healthy subjects in the GSE33341 data set. A: Volcano map of differentially expressed genes, red for up-regulated genes, green for down-regulated genes, and the gene names of the top ten up-regulated and down-regulate gene as sorted by the adjusted *P*-value; B: Cluster heat map of hetero-expressed gene, each column in the heat map represents a sample, and each row represents a gene.

Among these modules, the smallest one had 30 genes and a clipping height of 0.25. A heat map (**Figure 2D**) was used to illustrate the topological overlap matrix between all genes, with

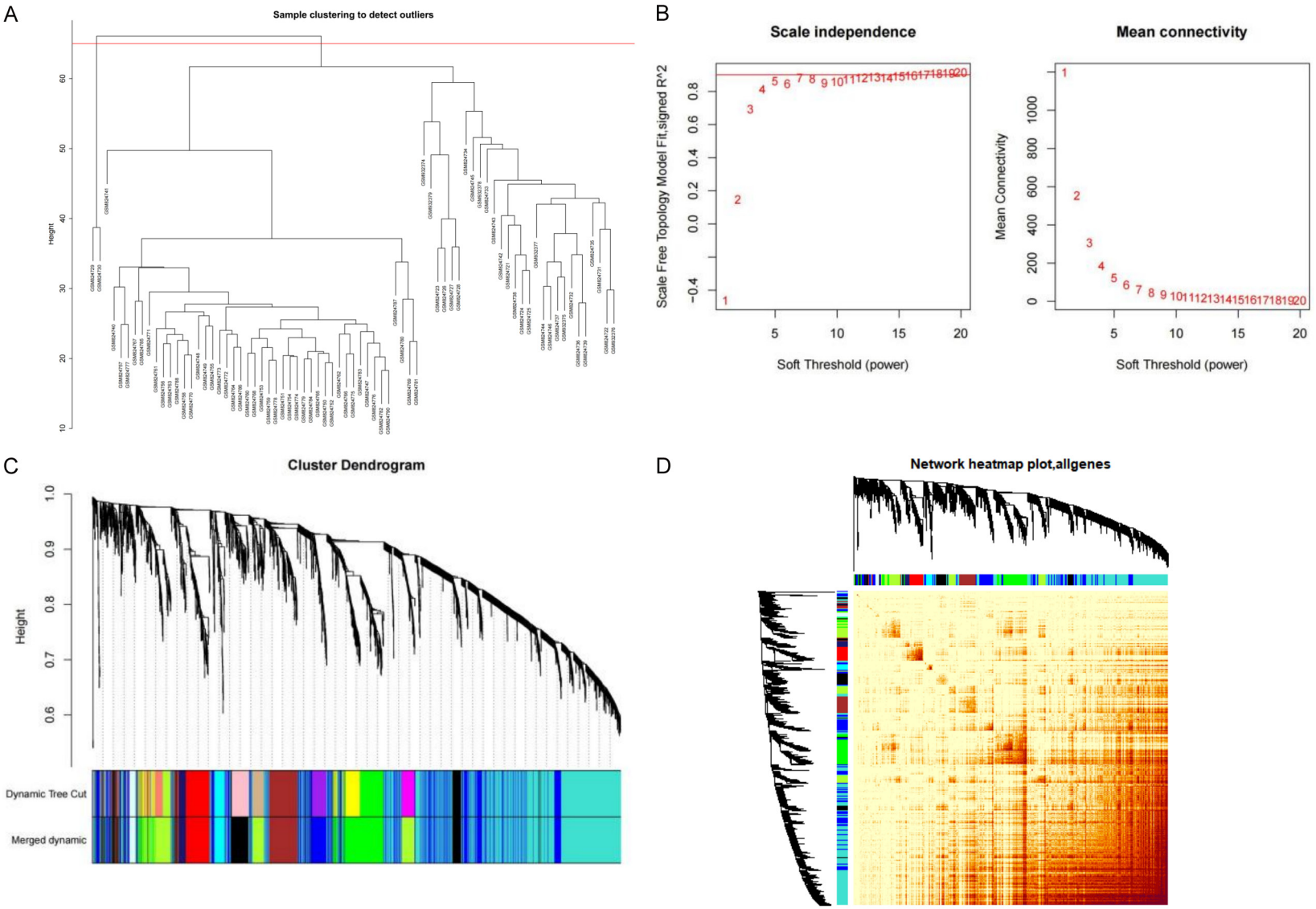


Figure 2. Construction of co-expression modules related to sepsis. A: Set the height to 65 to remove outliers; B: Determine the best soft threshold; C: Hierarchical data clustering to detect co-expression clusters with corresponding color assignments; D: Draw TOM heat map, perform topological overlap matrix of genes analyzed by WGCNA.

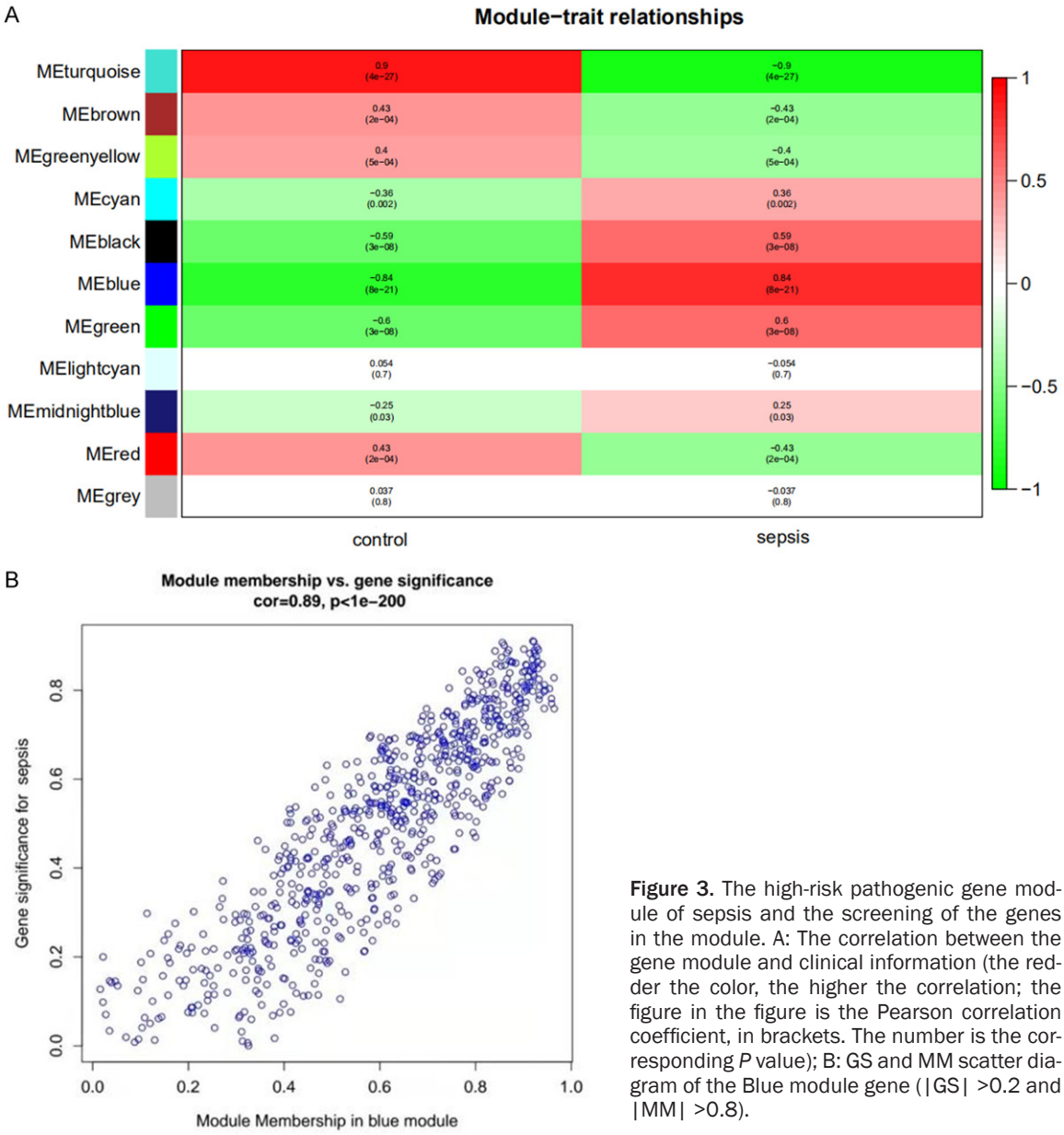
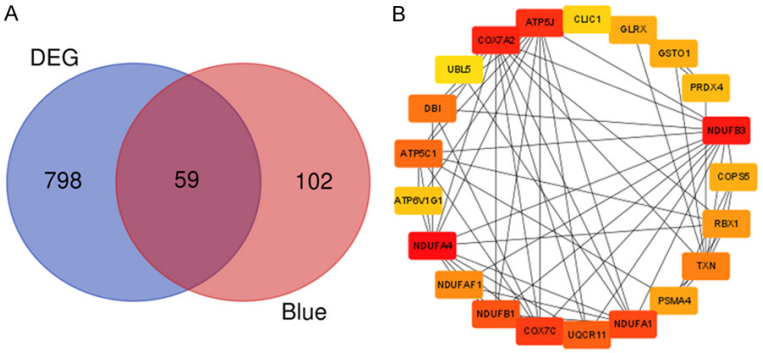


Figure 3. The high-risk pathogenic gene module of sepsis and the screening of the genes in the module. A: The correlation between the gene module and clinical information (the redder the color, the higher the correlation; the figure in the figure is the Pearson correlation coefficient, in brackets. The number is the corresponding *P* value); B: GS and MM scatter diagram of the Blue module gene (|GS| >0.2 and |MM| >0.8).

light colors representing small overlaps and darkening red colors representing large overlaps.

Screening of high-risk pathogenic gene modules for sepsis and the genes in the modules

On the basis of previous steps, WGCNA was used to conduct modular enrichment analysis of genes to examine the relationship between sample characteristics and modules. The corresponding colors of modules are black, blue, brown, green, grey, red, turquoise, green-yellow, cyan, light cyan, and light blue. The number of genes in modules ranges from 46 to 738 (**Figure 3A**). The grey module refers to genes that cannot be clustered to other modules, so it was excluded in subsequent analysis. Then GO/KEGG enrichment analysis was performed on genes contained in each module (Figures S1, S2, S3, S4, S5, S6, S7, S8, S9, S10), and key modules were identified according to the correlation coefficient between module characteristics and traits. The blue module had the highest correlation coefficient (COR=0.89, P<1E-200), and the genes of the blue module were enriched in cellular stress response, oxidative phosphorylation and other pathways.



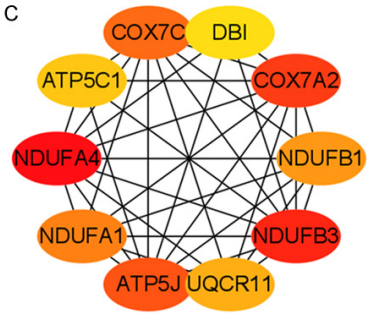


Figure 4. Screening of high-risk pathogenic genes for sepsis. A: Venn diagram to screen common pathogenic genes; B: Protein interaction network diagram of common pathogenic genes; C: Key genes screened by Cytol Hubba plug-in.

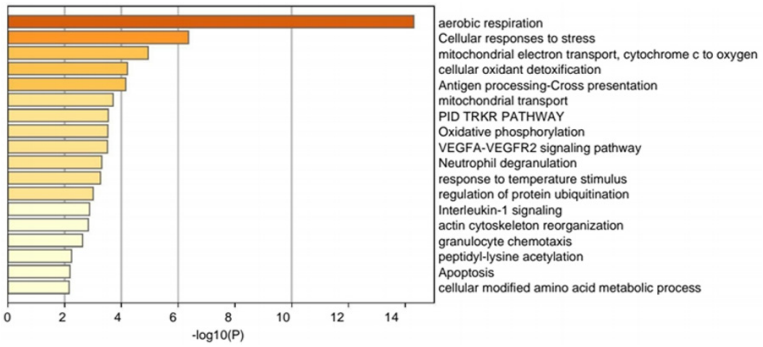


Figure 5. Using Metascape to perform GO and KEGG enrichment analysis on the common high-risk genes in the Wayne diagram.

Therefore, the blue module was identified to be the module having the highest degree of correlation with sepsis. After that, the key genes in the blue module were selected by setting |GS| >0.2 and |MM| >0.8. And finally, 161 key genes were reserved for the next step of screening (**Figure 3B**).

Selecting of high-risk pathogenic genes for sepsis

Next, Venn diagram (**Figure 4A**) was used to demonstrate the intersection of the 161 key genes in the blue module and the 857 differentially expressed genes obtained by DEG analysis to search for the pathogenic genes present in both analysis results. Then, the differentially expressed genes were made into a protein-protein interaction network (PPI) map using the online database STRING (**Figure 4B**). The threshold for the weighted edge was set to be 0.4. And the map included a total of 58 points and 97 edges. Subsequently, CytoHubba plug-in in Cytoscape was used to select the top 10 genes in MCC algorithm. These 10 genes, including NDUFA4, NDUFB3, COX7A2, ATP5J, COX7C, NDUFA1, NDUFB1, UQCR11, ATP5C1 and DBI are defined as the key genes (**Figure 4C**).

GO and KEGG enrichment analysis

GO and KEGG analyses of common high-risk genes from Venn diagrams were performed using Meta-scape (**Figure 5**). The results showed that the high-risk genes were mainly concentrated in aerobic respiration, cellular stress response, mitochondrial electron transport, mitochondrial transport and oxidative phosphorylation.

Survival analysis of key genes

To further verify the effect of the expression levels of the top ten key genes selected through the previous experiments on the occurrence and development of sepsis, we selected the GSE54514 dataset from the GEO database, which included blood samples from 96 non-deceased sepsis patients and 31 deceased sepsis patients. Kaplan-Meier curve was then used to evaluate whether the genes NDUFA4, NDUFB3, COX7A2, ATP5J, COX7C, NDUFA1, NDUFB1, UQCR11, ATP5C1 and DBI had an impact on the prognosis of patients with sepsis. The expression level of genes was divided into high and low expression groups according to the median of the expression quantities to draw the Kaplan-Meier curve (**Figure 6A-E**). The results showed that in the GSE54514 dataset, the overall survival

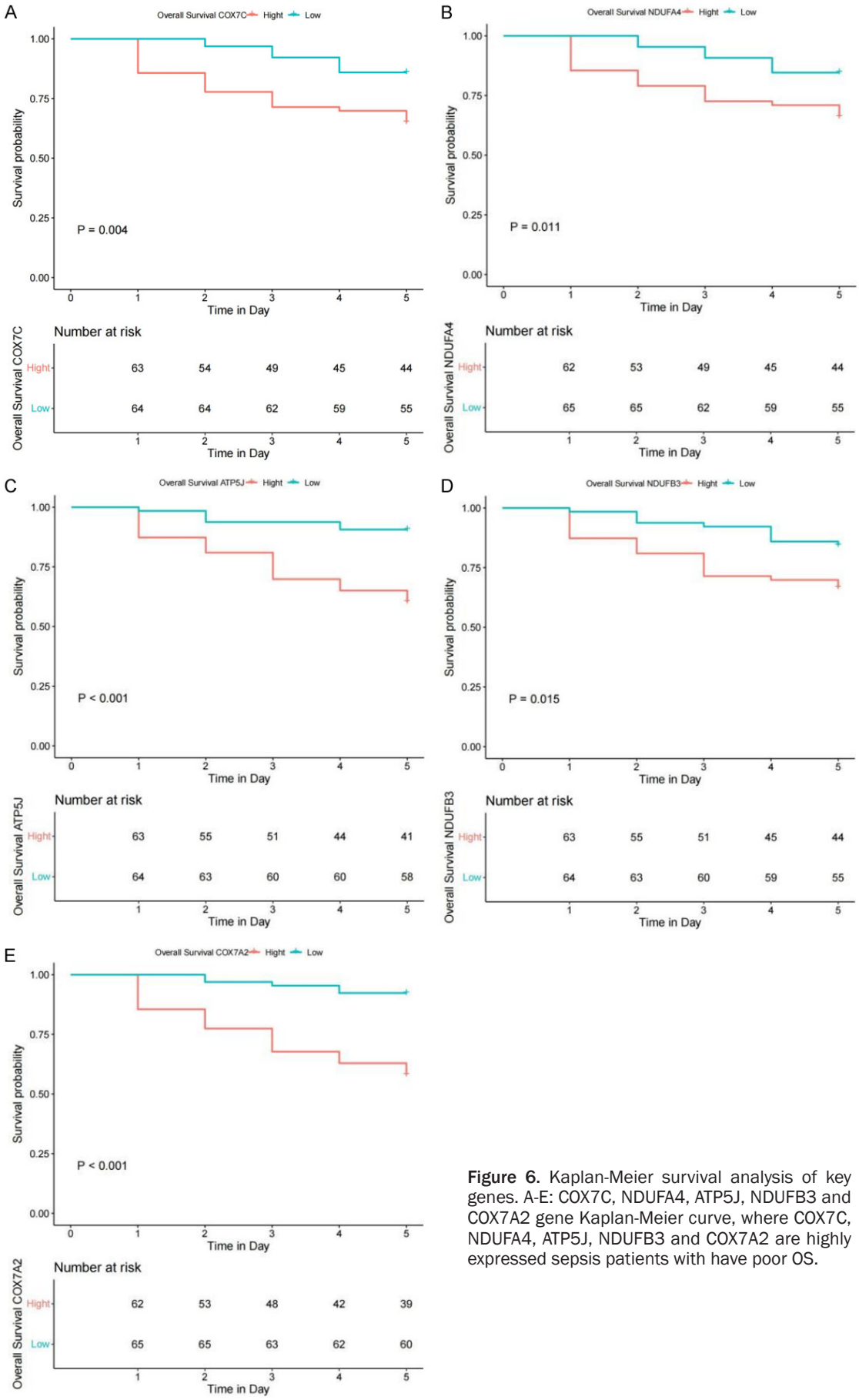


Figure 6. Kaplan-Meier survival analysis of key genes. A-E: COX7C, NDUFA4, ATP5J, NDUFB3 and COX7A2 gene Kaplan-Meier curve, where COX7C, NDUFA4, ATP5J, NDUFB3 and COX7A2 are highly expressed sepsis patients with have poor OS.

(OS) of sepsis patients with high expression of COX7C, NDUFA4, ATP5J, NDUFB3 and COX7A2 was poor (log-rank test $P<0.05$). Such results indicate that the high expression of those genes is significantly related to adverse OS impact on patients with sepsis, which is worthy of further investigation.

Discussion

The underlying pathogenesis of sepsis is not yet clear [17]. As a result, there is no gold standard for clinical diagnosis. Diagnosis can only be made based on abnormal indicators and combined with specific changes in clinical conditions. It is therefore necessary to develop new biomarkers and potential targets for the prevention and treatment of sepsis at the molecular level [17]. In this study, using GSE33341 dataset in GEO database, 59 high-risk pathogenic genes related to sepsis were screened by WGCNA analysis combined with DEG analysis using R package Limma. The GO enrichment analysis showed that the above-mentioned high-risk pathogenic genes were mainly enriched in pathways such as aerobic respiration, cellular stress response, mitochondrial electron transport, mitochondrial transport, and oxidative phosphorylation. Studies have shown that an important feature of sepsis is inflammation [18]. Cytokines produced by severe inflammation can activate neutrophils and cause excessive production of reactive oxygen species (ROS) [19]. The massive accumulation of ROS in the body leads to oxidative damage to cells [20]. This indicates that changes in partial oxidative respiration and cellular emergency response in the course of sepsis can be used as diagnostic indicators for early sepsis.

At the same time, we finally determined the first 10 key genes in MCC algorithm by Cytoscape plug-in: NDUFA4, NDUFB3, COX7A2, ATP5J, COX7C, NDUFA1, NDUFB1, UQCR11, ATP5C1, DBI. Combined with GO enrichment analysis, we found that these genes can be enriched in aerobic respiration, cellular stress response, mitochondrial electron transport, mitochondrial transport and oxidative phosphorylation pathways. This result indicates that multiple genes screened by us are high-risk genes associated with sepsis, and these genes may affect the occurrence and development of sepsis through aerobic respiration, cellular stress response and other pathways. In the future, we will further verify the mechanism of these genes in related pathways through experiments, so as to provide some theoretical basis for elucidating the pathogenesis of sepsis.

We defined the above genes as high-risk genes associated with sepsis, so it is still unknown what clinical value these genes have and whether they can be used to guide the diagnosis and treatment of bacterial sepsis. In order to verify the role of the above genes in the clinical treatment of bacterial sepsis, we screened the GSE54514 data set containing the survival information of patients with bacterial sepsis within five days through GEO database, and drew kaplan-Meier curve to evaluate the influence of the high-risk genes on the prognosis of patients with bacterial sepsis, the results showed that the high expression of NDUFA4, NDUFB3, COX7A2, ATP5J and COX7C was significantly correlated with the bad OS in sepsis patients, and most of the above genes were mitochondria related proteins. Previous studies have shown that in sepsis induced myocardial dysfunction (SIMD), MIR-210-3p can promote the pathogenesis of SIMD by targeting NDUFA4 to enhance myocardial cell apoptosis and damage mitochondrial function [21]. In addition, ATP5J is an important nuclear encoding gene of the F0 subunit of ATP synthase [22]. ATP5J expression is related to ATP synthase and mitochondrial ATP synthesis [23]. Studies have shown that in fluorine-induced mitochondrial dysfunction in cardiomyocytes, increased ATP5J expression compensates for mitochondrial dysfunction, further leading to reduced ATP synthesis [24]. The above results indicate that the sepsis-related genes we screened by bioinformatics methods have a high correlation with the occurrence and development of sepsis, and are significantly related to the poor OS of patients with bacterial sepsis. Therefore, the above genes can provide a reference for the diagnosis and treatment of sepsis patients with Staphylococcus aureus infection.

However, this study also has certain limitations. Due to the small sample size of the GSE54514 dataset, it is possible that it does not give a comprehensive representation of all the sepsis patients. we will further excavate relevant sample data of sepsis patients with different types,

and validate whether the screened key genes have specificity for evaluating sepsis patients with staphylococcus aureus infection. Moreover, the correlation between some key genes and the occurrence and development of sepsis has not yet been verified by biological experiments. In the follow-up study, experimental verification will be carried out to reveal the relationship between key genes and sepsis. In this way, we can determine whether these genes are suitable to be used as new diagnostic and therapeutic targets, providing theoretical basis for the clinical diagnosis and treatment of staphylococcus aureus sepsis.

Acknowledgements

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Disclosure of conflict of interest

None.

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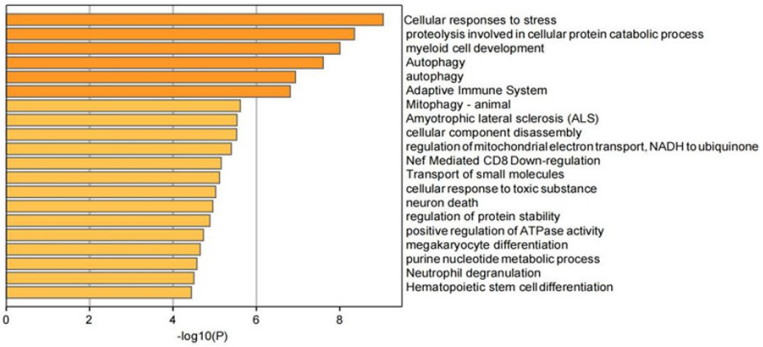

Figure S1. GO/KEGG enrichment analysis of the turquiose module.

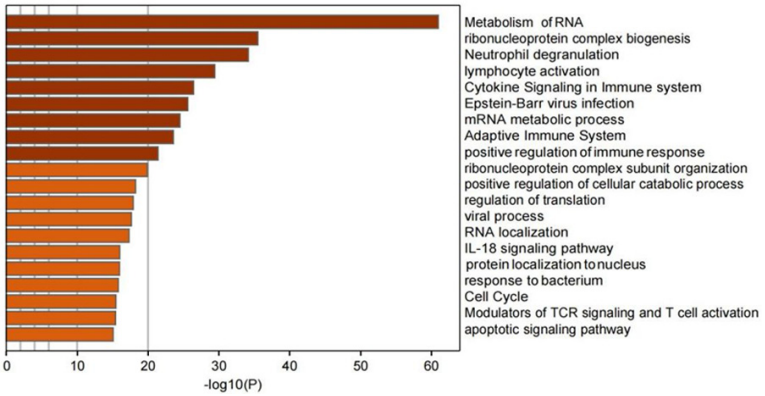

Figure S2. GO/KEGG enrichment analysis of the red module.

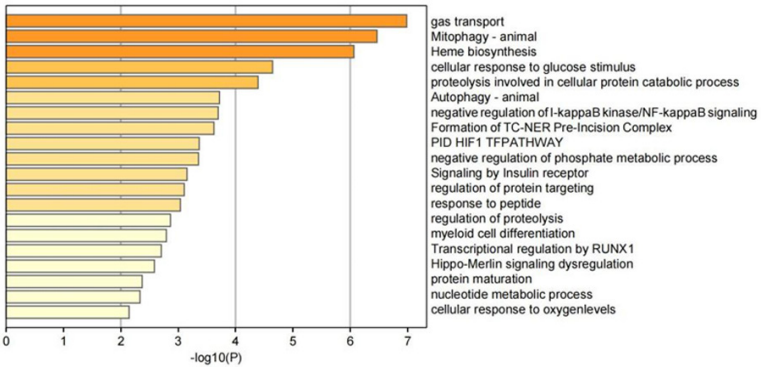

Figure S3. GO/KEGG enrichment analysis of the Midnight blue module.

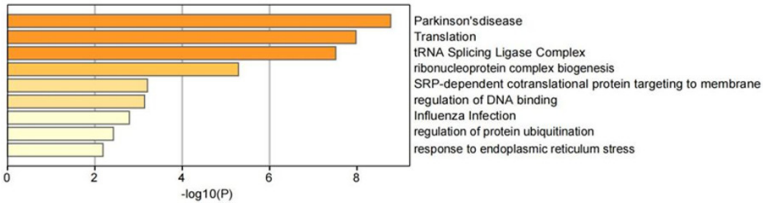

Figure S4. GO/KEGG enrichment analysis of the Light cyan module.

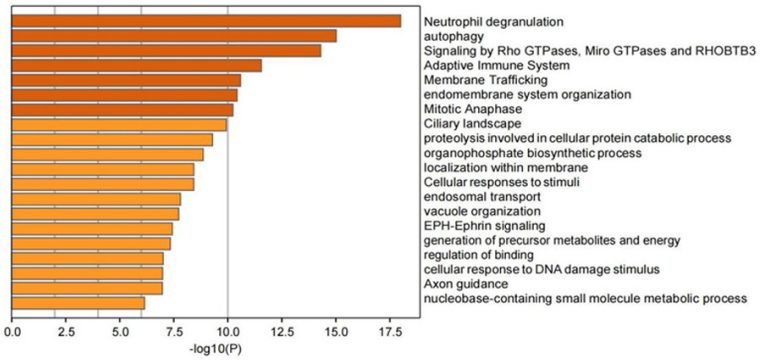

Figure S5. GO/KEGG enrichment analysis of the Green module.

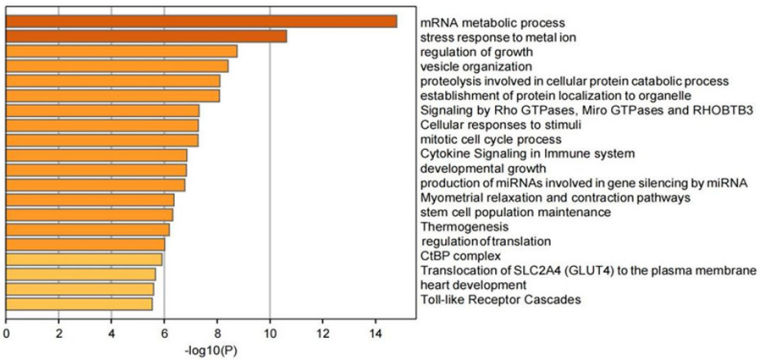

Figure S6. GO/KEGG enrichment analysis of the green yellow module.

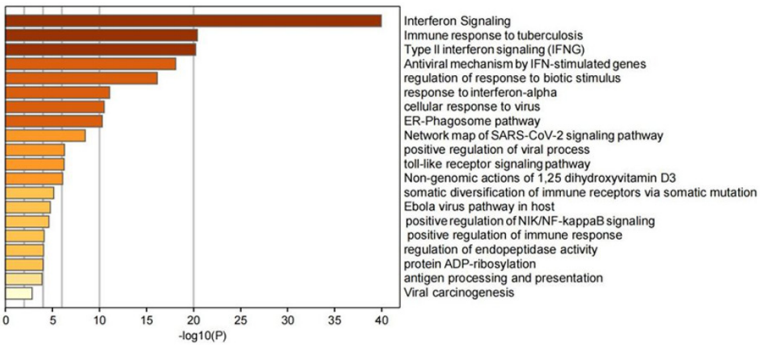

Figure S7. GO/KEGG enrichment analysis of the Cyan yellow module.

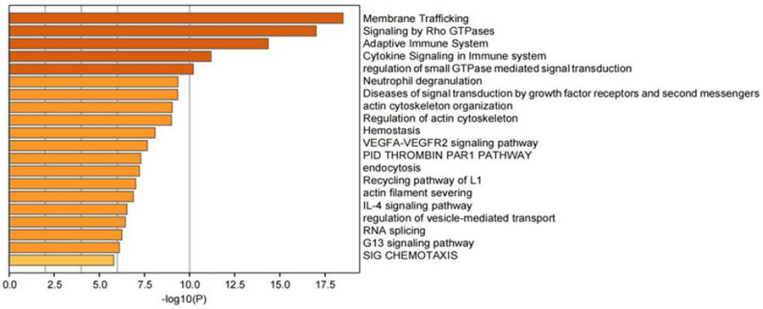

Figure S8. GO/KEGG enrichment analysis of the Brown yellow module.

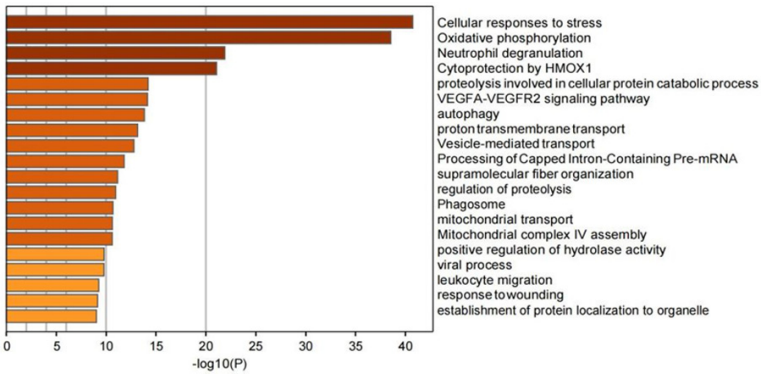

Figure S9. GO/KEGG enrichment analysis of the Blue module.

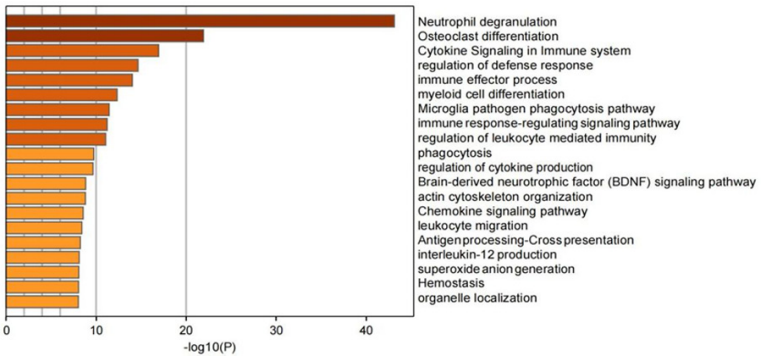

Figure S10. GO/KEGG enrichment analysis of the Black module.