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Screening and identification of key gene in sepsis development

Evidence from bioinformatics analysis

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Abstract

Sepsis is one of the leading causes of mortality in intensive care units (ICU). The growing incidence rate of sepsis and its high mortality rate result are very important sociosanitary problems. Sepsis is a result of infection which can cause systemic inflammatory and organ failure. But the pathogenesis and the molecular mechanisms of sepsis is still not well understood. The aim of the present study was to identify the candidate key genes in the progression of sepsis.

Microarray datasets GSE28750, GSE64457, and GSE95233 were downloaded from Gene Expression Omnibus (GEO) database. The differentially expressed genes (DEGs) were identified, and function enrichment analyses were performed. The protein–protein interaction network (PPI) was constructed and the module analysis was performed using STRING and Cytoscape. Furthermore, to verify the results of the bioinformatics analyses, the expression levels of selected DEGs were quantified by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) in libobolysaccharide (LPS)-induced Human Umbilical Vein Endothelial Cells (HUVECs) to support the result of bioinformatics analysis.

Thirteen hub genes were identified and biological process analysis revealed that these genes were mainly enriched in apoptotic process, inflammatory response, innate immune response. Hub genes with high degrees, including MAPK14, SLC2A3, STOM, and MMP8, were demonstrated to have an association with sepsis. Furthermore, RT-PCR results showed that SLC2A3 and MAPK14 were significantly upregulated in the HUVECs induced by LPS compared with controls.

In conclusion, DEGs and hub genes identified in the present study help us understand the molecular mechanisms of sepsis, and provide candidate targets for diagnosis and treatment of sepsis.

Abbreviations: DEGs = differentially expressed genes, GEO = Gene Expression Omnibus, GO = Gene Ontology, HUVECs = Human Umbilical Vein Endothelial Cells, ICU = intensive care units, KEGG = Kyoto Encyclopedia of Genes and Genomes, LPS = libobolysaccharide, PPI = protein–protein interaction network, RT-PCR = Reverse Transcription-Polymerase Chain Reaction, STRING = Search Tool for the Retrieval of Interacting Genes.

Keywords: microarray, protein–protein interaction, sepsis

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Sepsis, a syndrome of physiologic, pathologic, and biochemical abnormalities induced by infection, is one of the most common critical illnesses with a rise in new cases worldwide each year.[1] It is also the leading cause of death in intensive care units (ICU) even if the method of medical treatment is better than before.[2] Every year, there are more than 1.8 million cases of severe sepsis in the world.[3] The development of sepsis involves various factors such as inflammation and immune response. The immune dysfunction of sepsis is the key link in its development.[4] Studying the process of its occurrence and development has great scientific and social significance for further improving the success rate of critical illness treatment.

The specific molecular mechanism of sepsis remains unclear. Therefore, in order to develop effective diagnostic and therapeutic strategies, it is crucial to understand the precise molecular mechanisms of sepsis. With the development and application of gene chip technology in the last decades, microarray technology and bioinformatic analysis have been widely used to screen genetic alterations at the gene level.[5] Bioinformatics technology can help researchers quickly find hub-gene clusters. A comprehensive analysis of sepsis can build gene networks and screen for potential key molecular targets. These molecular targets may provide new insights into pathogenesis of

sepsis, and may be used for early diagnosis of sepsis and provide new ideas for clinical treatment of sepsis.

In the present, we aimed to identify differentially expressed (DEGs) in sepsis by the method of bioinformatics technology. Three mRNA microarray datasets from Gene Expression Omnibus (GEO) were downloaded and analyzed to obtain DEGs between sepsis and normal. Subsequently, Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis, and protein–protein interaction (PPI) network analyses were performed to help us understand the molecular mechanisms underlying sepsis. Furthermore, reverse transcription polymerase chain reaction (RT-PCR) was performed to analyze the expression of candidate DEGs in HUVECs induced by libobolysaccharide (LPS). The DEGs in the present study may have potential diagnositic biomarkers.

2. Materials and methods

2.1. Gene expression profiles

This study was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine. GEO (http://www.ncbi.nlm.nih.gov/geo)[6] is a public functional genomics data repository of high throughout gene expression data, chips, and microarrays. Three gene expression datasets [GSE (28750),[7] GSE (64457),[8] and GSE (95233)[9]] were downloaded from GEO. The GSE 28750 dataset contained 10 sepsis tissue samples and 20 normal samples. GSE 64457 contained sepsis samples and normal samples. GSE 95233 contained sepsis samples and normal samples.

2.2. Identification of DEGs

The differential expression genes between sepsis and healthy controls were screened using GEO2R (http://www.ncbi.nlm.nih.gov/geo/geo2r). GEO2R is an excellent web tool that can identify DEGs between sepsis and healthy controls across experimental conditions. The adjusted *P*-values (adj. P) and Benjamini and Hochberg false discovery rate were applied to provide a balance between discovery of statistically significant genes. LogFC (fold change) >1.5 and adj. *P*-value $<.05$ were considered statistically significant.

2.3. Functional and pathway enrichment analyses of DEGs

In order to obtain the biological function and signaling pathways of DEGs, DAVID (http://david.ncifcrf.gov)[10] was used to GO annotation and KEGG pathways enrichment of DEGs. $P<.05$ was considered statistically significant. Top 200 genes of DEGs were used to gene set enrichment analysis. DAVID is a web-based gene function enrichment analysis software. It can provide a comprehensive set of functional annotation information of genes and proteins. GO annotation is a main bioinformatics tool to annotate genes and analyze biological process of DEGS.[11] KEGG is a database resource for understanding high-level functions and biological systems from large-scale molecular datasets generated by high-through put experimental technologies.[12]

2.4. PPI network construction

In order to gain the interaction between DEGs, the STRING (Search Tool for the Retrieval of Interacting Genes http://string-db.org) online database used to obtain the predicted interactions (version 10.0).[13] In our study, PPI network of DEGs was constructed by STRING database, and the interaction with a combined score >0.7 was considered statistically significant. The visualization of PPI network was used by Cytoscape software. The software of Cytoscape (version 3.6.1) which can display molecular interaction networks is an open source bioinformatics software platform.[14] The APP of MCODE (Molecular Complex Detection) in Cytoscape is used to obtain densely connected regions from a network analyzed by STRING. The figures of PPI networks were drawn by Cytoscape and the most significant module in the PPI networks was identified by the software of MCODE.

2.5. RT-PCR validation

HUVECs were obtained from the Cell Resource Center of Shanghai institute of Life Science (Shanghai, China). The cells were cultured in endothelial cell medium (ECM) (ScienCell, San Diego, CA). HUVECs were incubated at 37°C in 5% CO_2 and maintained using standard cell culture. After reaching a confluence of 80%, HUVECs were detached using 0.25% trypsin-EDTA. Total RNA was isolated from cells using the TRIzol reagent (Invitrogen, Carlsbad, CA) according to the manufacturer's instructions. The real-time PCR was performed using SYBR Green PCR Master Mix (Bio-Rad Laboratories) on a MyiQ Single Color Real-time PCR Detection System (Bio-Rad Laboratories). The sequence-specific primers for the indicated genes were synthesized by Sangon Biothech (Shanghai, China). The sequences of reverse and forward primers for all of the genes analyzed were as follows: SLC2A3 forward (F), GGTCGCTTGGTTATTGGC and reverse (R), ACCGCTGGAGGATCTGCT; MMP8 F, ACCAATACTGGGCTCTGAGTGGCTAT and R, ACAGCCACATTTGATTTTGCTTCAG; STOM F, AGAGCTCCTGGTCCTCAA, and R, TCTGTCCATCCAGCCAATG; MAPK14 F, TATGCGTCTGACAGGAACAC, and R, GATCGGCCACTGGTTCATCA.

3. Result

3.1. Identification of DEGs in sepsis

After standardization of the microarray results, DEGs (5595 in GSE28750, 2257 in GSE64457, and 7221 in GSE95233) were identified. The DEGs of these 3 datasets showed in Volcano diagram (Fig. 1). The overlap among the 3 datasets contained 619 genes as shown in the Venn diagram (Fig. 1), consisting of 253 downregulated genes and 366 upregulated genes between sepsis and normal control.

3.2. Enrichment analyses of DEGs

The DEGs were analyzed by GO term and KEGG pathway enrichment by DAVID (Tables 1 and 2). Gene Ontology functional enrichment analysis results showed that changes in biological processes (Fig. 2) of DEGs were significantly enriched in apoptotic process, inflammatory response, innate immune response, protein phosphorylation, protein ubiquitination, and negative regulation of apoptotic process. Changes in cell component (Fig. 3) were mainly enriched in the cytoplasm, integral component of membrane, cytosol, extracellular exosome, nucleoplasm, membrane, and endoplasmic reticulum. Changes in molecular function (MF) were mainly enriched in the protein binding, ATP binding, poly(A) RNA binding, threonine

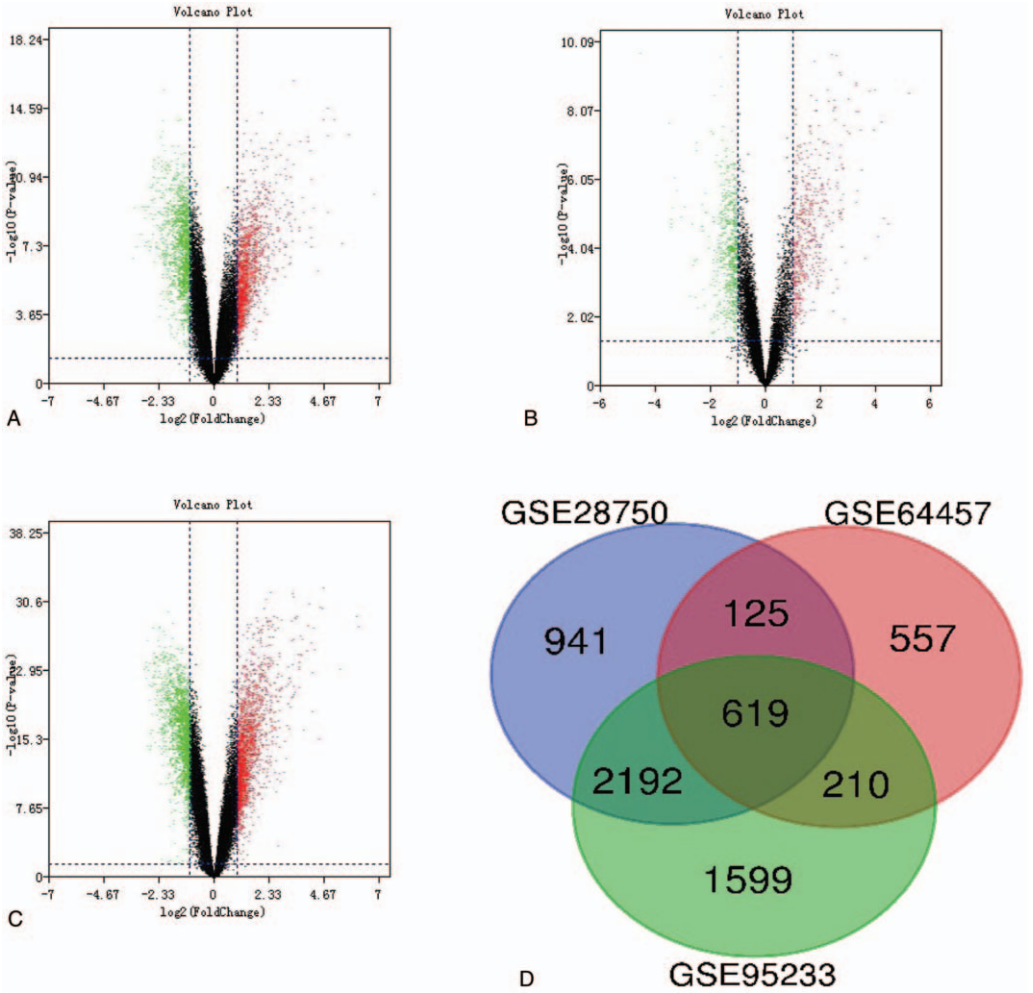

Figure 1. Venn diagram and volcano diagram of DEGs. (A) Volacano diagram of GSE 28750. (B) Volacano diagram of GSE 64457. (C) Volacano diagram of GSE 95233. (D) DEGs were selected with a LogFC (fold change) >1.5 and adj. *P*-value < .05 among above three mRNA expression profiling sets datasets. The 3 datasets showed an overlap of 619 genes. DEGs = differentially expressed genes; GEO = Gene Expression Omnibus.

kinase activity, nucleotide binding, ubiquitin protein ligase binding, and magnesium ion binding(Fig. 4). MAPK signaling pathway and TNF signaling pathway were associated with sepsis development among the significantly enriched KEGG pathways (Fig. 5).

3.3. PPI network analysis and hub-gene selection

The most significant module of PPI network was obtained and visualized using Cytoscape. (Fig. 6) The hub genes were selected with degrees >15. A total of 13 genes were identified as hub genes. The names, abbreviations, and functions for these hub genes are shown in Table 3.

3.4. RT-PCR validation

A total of 4 DEGs with higher degree including MAPK14, SLC2A3, STOM, and MMP8 were selected as candidate according to the bioinformatics analyses. HUVECs were administrated with different concentrations of LPS (5, 10, or 20 ng/mL). After 24 and 48 hours, mRNA were extracted from the specimens collected separately. Then we measured the expression level of MAPK14, SLC2A3, STOM, and MMP8 by RT-PCR. SLC2A3 and MAPK14 were significantly upregulated in the HUVECs induced by LPS compared with controls (Fig. 7). No significant difference was identified between the MMP8 and STOM mRNA expression in HUVECs induced by LPS with controls.

4. Discussion

Although there are numerous studies on sepsis have been conducted, the mortality of sepsis is still high. This may be due to the lack of effective biomarkers for detection of early stage sepsis and of effective treatment for sepsis. Therefore, molecular mechanisms of sepsis are necessary for scientists to find the treat and diagnosis method of sepsis. Because of the rapid development of microarray technology, it is more convenient to find out the genetic alterations of progression of diseases. Microarray technology enables us to explore the gene, the genetic change in sepsis, which had been proved to be a better approach to identify new biomarkers in other diseases.

In the present study, we observed whether there were more valuable genes which could be a better biomarker for the

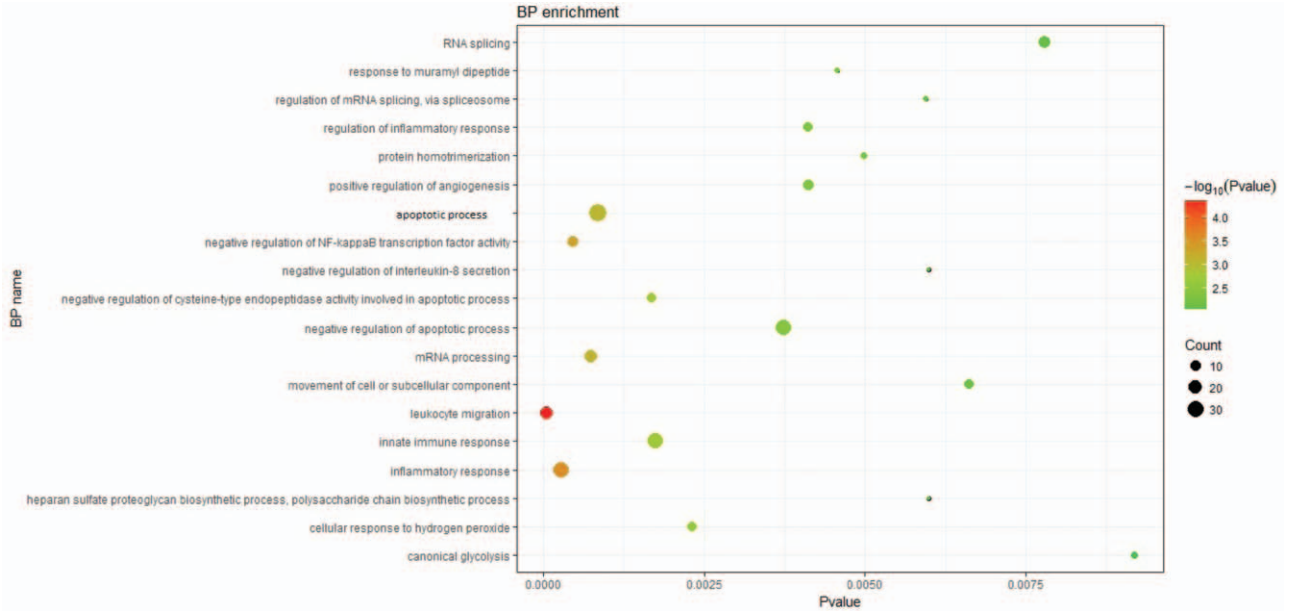

Figure 2. Top 19 significant BP terms that differentially expressed genes within 3 datasets (GSE 28750, GSE 64457, and GSE 95233) were enriched in. BP = biological process; FDR = false discovery rate; GO = gene ontology.

diagnosis for sepsis. In order to find out the significant gene of sepsis, we analyzed the sepsis gene expression array of GSE 28750, GSE 95233, and GSE 64457 in GEO2R, where a total number of 619 DEGs were obtained between sepsis and normal samples of peripheral blood, comprising 253 downregulated genes and 366 upregulated genes. The GO, KEGG, and STRING analyses were used to further understand the potential biological functions of DEGs. GO term analysis indicated that the DEGs were mainly enriched in apoptotic process, negative regulation of apoptotic process, TNF signaling pathway, and MAPK signaling pathway. Previous study showed that apoptosis play a central role in the process of sepsis by affecting immune response at various levels.[15] This is consistent with our study. According to KEGG pathway enrichment analysis, DEGs were enriched in TNF signaling pathway and MAPK signaling pathway. TNF signaling pathway is a major contributor to the development of sepsis. In the study of Huang, it is also reported that TNF signaling pathway play an important role in the progression of

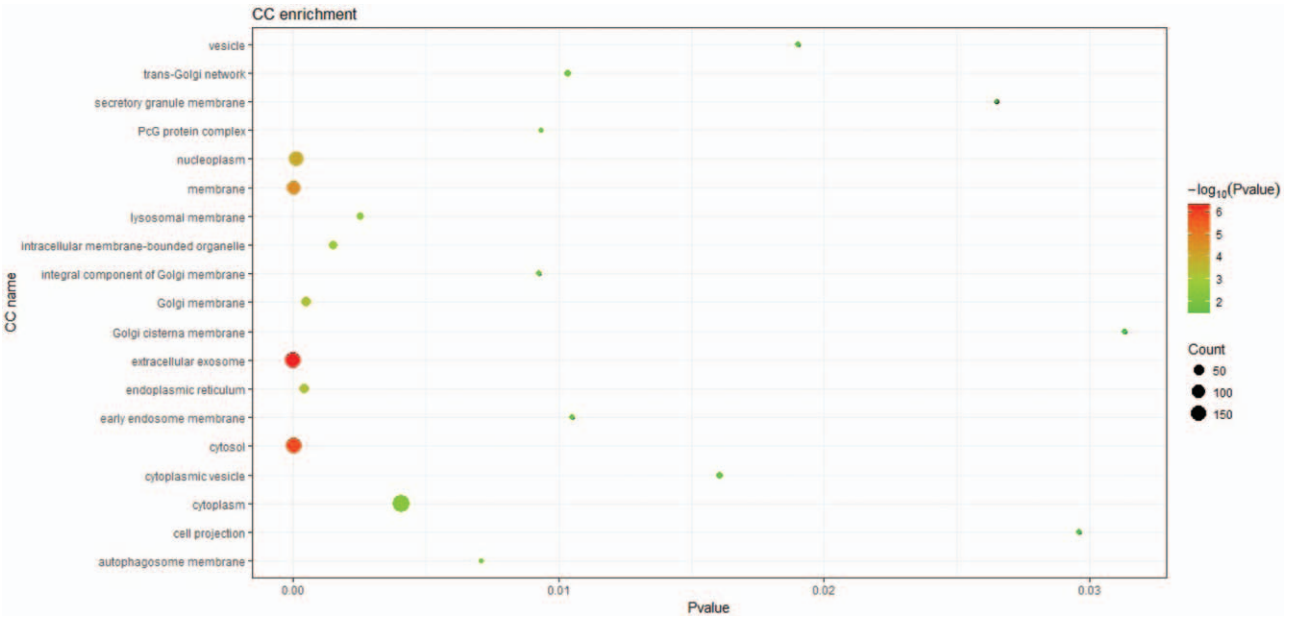

Figure 3. Top 19 significant CC terms that differentially expressed genes within 3 datasets (GSE 28750, GSE 64457, and GSE 95233) were enriched in. CC = cellular component; FDR = false discovery rate; GO = gene ontology.

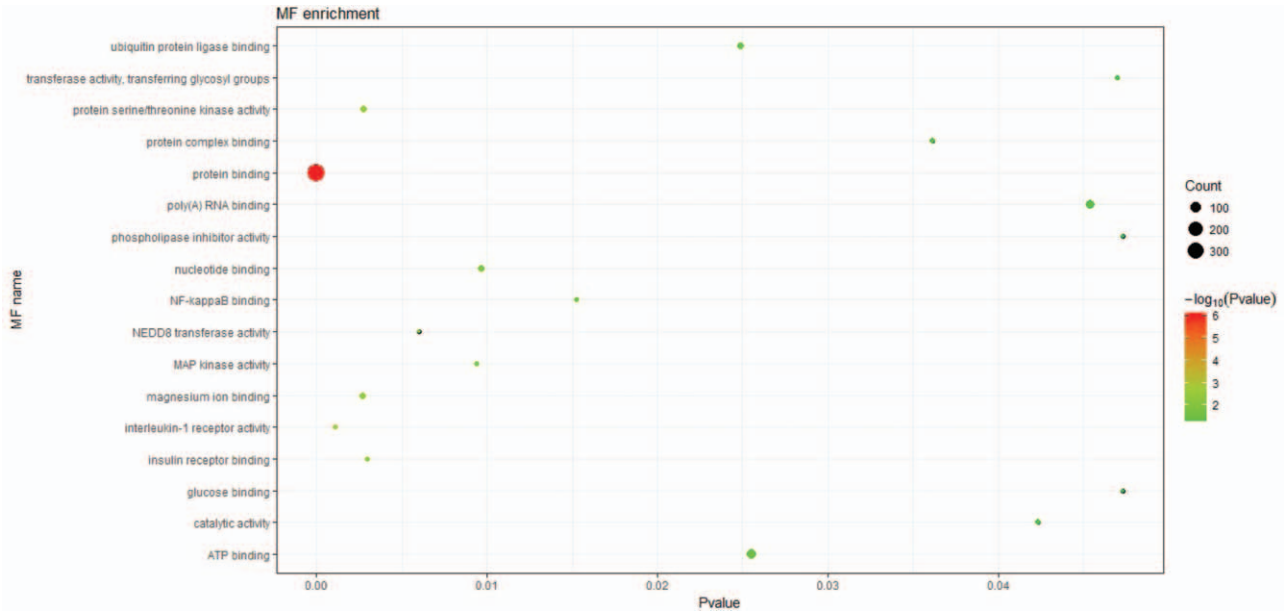

Figure 4. Top 19 significant MF terms that differentially expressed genes within 3 datasets (GSE 28750, GSE 64457, and GSE 95233) were enriched in. FDR = false discovery rate; GO = gene ontology; MF = molecular function.

sepsis. Our study also demonstrated that TNF signaling pathway may regulate the development of sepsis. This is consistent with previous studies.

In addition, some recent studies also found the hub-gene from microarray technology. Lu et al[16] identified 5 hub genes (IRAK3, ADM, ALOX5, MMP9, and S100A8) related to sepsis from 2 GEO datasets by developing an integrated method including DEG screen, pathway analysis, gene annotations, PPI networks. Wang et al[17] identified candidate biomarkers (Icam1 and Socs3) for sepsis from one GEO datasets by performing DEG, gene functional enrichment, and PPI network analyses, and validated their results with RT-qPCR. Huang et al[18] identified hub genes (MAPK14, ZAP70, and TSPO) and miRNA related to sepsis progression from 1 dataset of E-MTAB-4765 by developing an integrated method including DEG screen, pathway analysis, gene annotations, PPI networks, and regulatory network construction. These studies also identified some hub-genes of sepsis. Some hub-genes in these studies are consistent

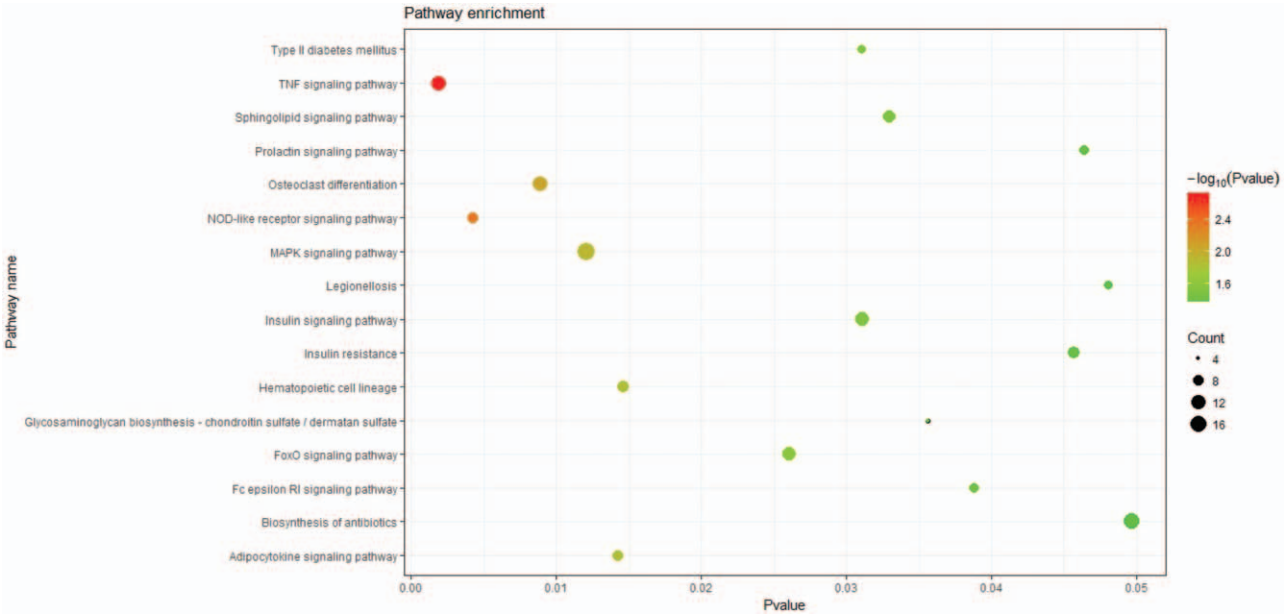

Figure 5. Top 19 significant KEGG pathway terms that differentially expressed genes within 3 datasets (GSE 28750, GSE 64457, and GSE 95233) were enriched in. FDR = false discovery rate; KEGG = Kyoto Encyclopedia of Genes and Genomes; GO = gene ontology.

Table 1

GO and KEGG pathway enrichment analysis of DEGs.

Term	Description	Count in gene set	*P*-value
Downregulated			
GO:0006397	mRNA processing	10	5.79E–05
GO:0045892	Negative regulation of transcription, DNA-templated	16	9.33E–05
GO:0005654	Nucleoplasm	60	3.36E–10
GO:0005634	Nucleus	80	3.61E–06
GO:0044822	poly(A) RNA binding	31	6.93E–07
GO:0000166	Nucleotide binding	15	1.03E–05
GO:0005515	Protein binding	111	2.74E–04
hsa04010	MAPK signaling pathway	7	0.040575
hsa03040	Spliceosome	5	0.044008
hsa00514	Other types of O-glycan biosynthesis	3	0.020127
Upregulated			
GO:0009617	Response to bacterium	30	8.70E–07
GO:0009605	Response to external stimulus	70	3.74E–06
GO:0006952	Defense response	56	3.95E–06
GO:0044710	Single-organism metabolic process	113	1.71E–05
GO:0006950	Response to stress	107	4.34E–06
GO:0070062	Extracellular exosome	86	2.26E–06
GO:0016021	Integral component of membrane	129	9.52E–05
GO:0019788	NEDD8 transferase activity	3	0.002057
GO:0005158	Insulin receptor binding	5	0.002573
hsa05134	Legionellosis	6	0.006892
hsa01130	Biosynthesis of antibiotics	12	0.007806
hsa04668	TNF signaling pathway	8	0.009902

DEGs = differentially expressed genes, GO = Gene Ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes.

Table 2

GO and KEGG pathway enrichment analysis of DEGs in the most significant module.

Pathway ID	Pathway description	Count in gene set	*P*-value
GO:0050900	Leukocyte migration	5	8.15E–05
GO:0002430	Complement receptor mediated signaling pathway	2	0.018899
GO:0045766	Positive regulation of angiogenesis	3	0.020173
GO:0006954	Inflammatory response	4	0.034897
GO:0070062	Extracellular exosome	21	8.43E–09
GO:0005615	Extracellular space	12	2.02E–05
GO:0005576	Extracellular region	11	5.11E–04
GO:0042470	Melanosome	4	8.73E–04
GO:0031012	Extracellular matrix	4	0.017506
GO:0005886	Plasma membrane	14	0.029049
GO:0072562	Blood microparticle	3	0.03257
GO:0005887	Integral component of plasma membrane	7	0.044649
hsa05150	*Staphylococcus aureus* infection	4	1.24E–04

DEGs = differentially expressed genes, GO = Gene Ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes.

with our results. There are also some hub-genes different from our results. Therefore, some further research are needed to identified the function of these hub-genes in sepsis.

We identified 13 major hub genes in the PPI network. TMEM30A, STOM, RBX1, SLC2A3, C3AR1, CTSD, MAPK14, PGLYRP1, ORM1, MMP8, CHI3L1, CLEC4D, TCN1, and coincidentally all of them were up-regulated genes in sepsis. Therefore, we use the RT-PCR to verify the result of bioinformatics analyses. According to the result of RT-PCR,

Table 3

Functional roles of 13 hub genes with degree ≥15.

No.	Gene symbol	Full name	Function
1	TMEM30A	Transmembrane protein 30A	Diseases associated with TMEM30A include intrahepatic cholestasis Of pregnancy. Among its related pathways are innate immune system.
2	STOM	Stomatin	The encoded protein localizes to the cell membrane of red blood cells and other cell types, where it may regulate ion channels and transporters.
3	RBX1	Ring-box 1	This locus encodes a RING finger-like domain-containing protein. The encoded protein interacts with cullin proteins and likely plays a role in ubiquitination processes necessary for cell cycle progression.
4	SLC2A3	Solute carrier family 2 member 3	Gene Ontology (GO) annotations related to this gene include transmembrane transporter activity and glucose transmembrane transporter activity.
5	C3AR1	Complement component 3a receptor 1	C3a is an anaphylatoxin released during activation of the complement system. Binding of C3a by the encoded receptor activates chemotaxis, granule enzyme release, superoxide anion production, and bacterial opsonization.
6	CTSD	Cathepsin D	Mutations in this gene play a causal role in neuronal ceroid lipofuscinosis-10 and may be involved in the pathogenesis of several other diseases, including breast cancer and possibly Alzheimer's disease.
7	MAPK14	Mitogen-activated protein kinase 14	MAP kinases act as an integration point for multiple biochemical signals, and are involved in a wide variety of cellular processes such as proliferation, differentiation, transcription regulation and development.
8	PGLYRP1	Peptidoglycan recognition protein 1	Pattern receptor that binds to murein peptidoglycans (PGN) of Gram-positive bacteria. Plays a role in innate immunity.
9	ORM1	ORM1	The specific function of this protein has not yet been determined; however, it may be involved in aspects of immunosuppression.
10	MMP8	Matrix metallopeptidase 8	MMP8 is a protein coding gene. Diseases associated with MMP8 include preterm premature rupture of the membranes and gingivitis
11	CHI3L1	Chitinase 3 like 1	The protein of this gene is thought to play a role in the process of inflammation and tissue remodeling
12	CLEC4D	C-type lectin domain family 4 member D	Members of this gene family share a common protein fold and have diverse functions, such as cell adhesion, cell–cell signaling, glycoprotein turnover, and roles in inflammation and immune response.
13	TCN1	Transcobalamin 1	The protein of this gene is a major constituent of secondary granules in neutrophils and facilitates the transport of cobalamin into cells.

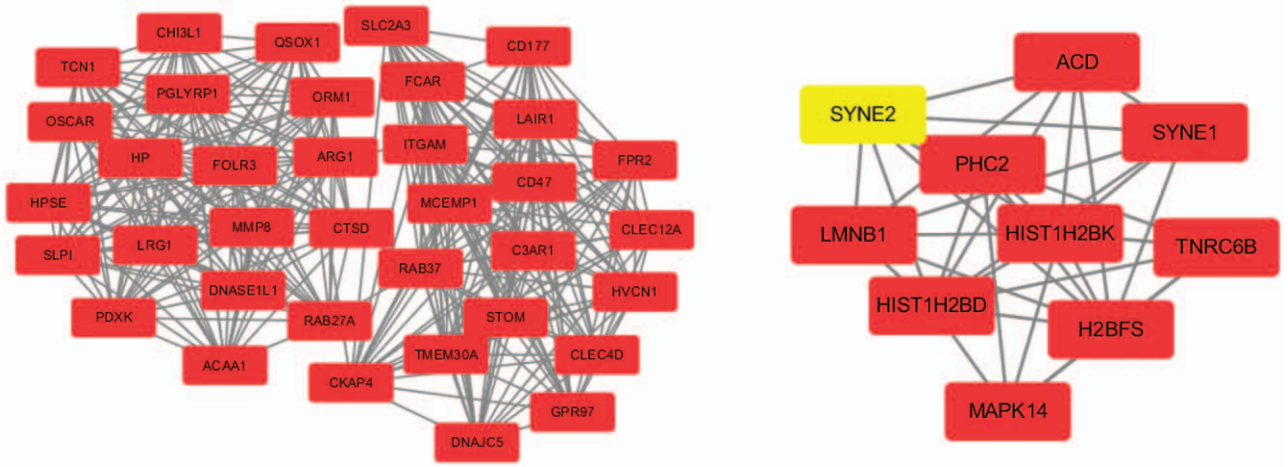

Figure 6. Protein–protein interaction networks of the upregulated DEGs within GSE 28750, GSE 64457, and GSE 95233 datasets. The most significant module was obtained from PPI network using Cytoscape. DEG = differentially expressed gene.

MAPK14 and SLC2A3 may have diagnostic value in sepsis. MAPK14 is one of the 4 p38 MAPKs which play an important role in the cascades of cellular responses evoked by extracellular stimuli such as proinflammatory cytokines or physical stress leading to direct activation of transcription factors. MAPK14 has been previously reported as hub-gene of sepsis in several studies, which are consistent with our study.[19,20] But there are rare studies demonstrated that its expression levels have been investigated as prognostic biomarkers of sepsis. In the present study, RT-PCR demonstrated that the expression of MAPK14 was significantly upregulated in the HUVECs induced by LPS compared with controls, which was concordant with the bioinformatics analysis results. This result indicated vital roles of MAPK14 in the progression of sepsis. Therefore, further study of MAPK14 about function in the pathophysiology of sepsis is needed to confirm our hypothesis.

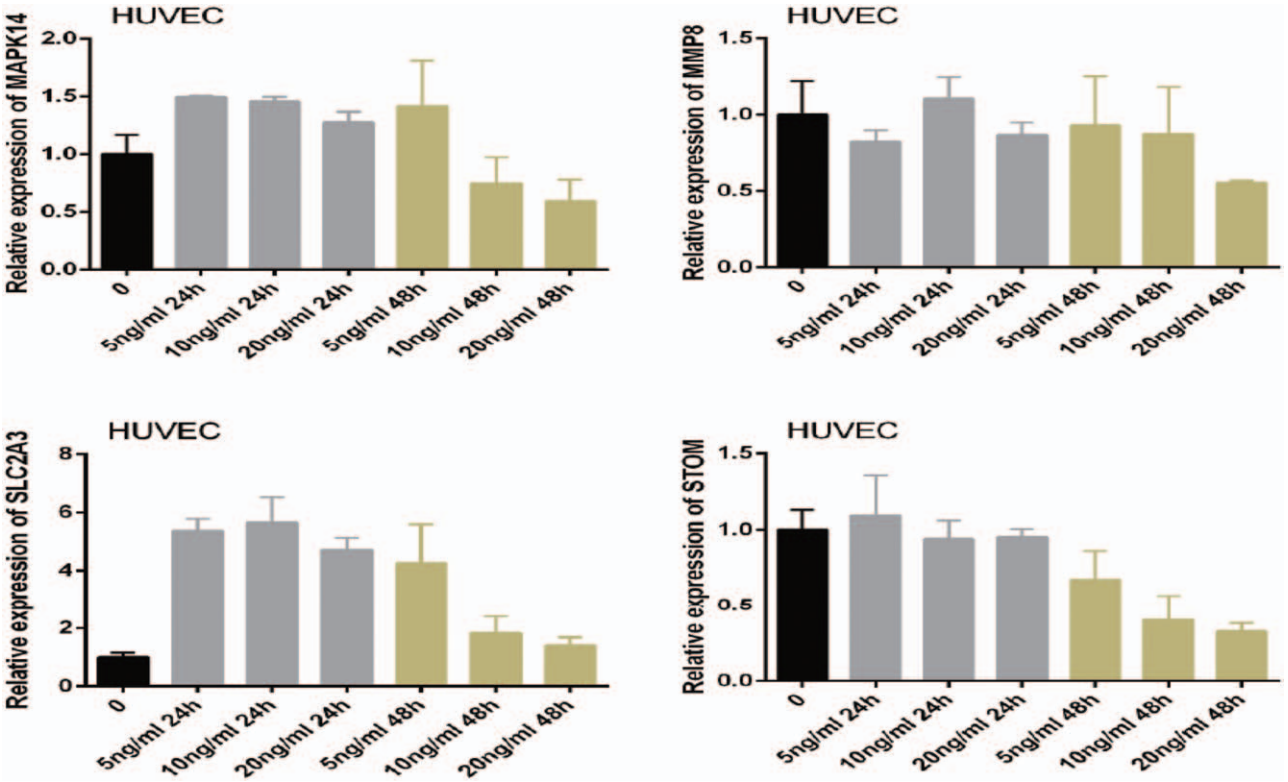

Figure 7. The expression of MAPK14, STOM, MMP8, and SLC2A3 in HUVECs induced by LPS. SLC2A3 and MAPK14 were significantly upregulated in the HUVECs induced by LPS compared with controls. No significant difference was identified between the MMP8 and STOM mRNA expression in HUVECs induced by LPS with controls. HUVECs = human umbilical vein endothelial cells, LPS = libobolysaccharide.

SLC2A3 is a member of the SLC2A3 gene family and is located on the chromosome 12p13.31. SLC2A3 is low or no expression in many normal organs and tissues.[21] SLC2A3 has a high expression in many types of cancer cell including non-small cell lung cancer,[22] glioblastoma, laryngeal squamous carcinoma,[23] endometrial carcinoma, and breast carcinoma.[24] A previous study showed that highly expressed SLC2A3 played an important role in human cancer.[25] But there are rare studies reported that SLC2A3 had an significant role in sepsis and infection. Only Wang et al[26] reported that the expression of mammalian cell glucose transporter proteins 1 (GLUT1) and glucose transporter proteins 3 (GLUT3) were up-regulated during chlamydial infection. In our study, RT-PCR demonstrated that the expression of SLC2A3 was significantly upregulated in the HUVECs induced by LPS compared with controls, which was concordant with the bioinformatics analysis results. Currently, the role of SLC2A3 and MAPK14 in sepsis has not been studied clearly yet.

There are several limitations in the present study. Firstly, the expression of MAPK14 and SLC2A3 were significantly upregulated. Therefore, future in vitro and in vivo experiments are required to investigate the function and pathway of these genes in sepsis pathology. Secondly, studies with larger cohorts of patients with sepsis are required to confirm the diagnostic and therapeutic value of the identified genes.

In conclusion, in the present study, we have performed a bioinformatics analysis to identify DEGs that may be involved in the progression of sepsis. Additionally, our study showed that sepsis causes dysregulation of genes in the apoptotic process, negative regulation of apoptotic process, and innate immune response. In the present study, there are 13 differentially expressed hub genes in responses to sepsis. These genes were significantly upregulated in sepsis compared with controls. These findings can be used to carrying on further study to identify the biological function, appropriate treatment targets, and biomarkers in different stages of sepsis.

Author contributions

Ting-bo Liang contributed to the conception of the study;
Wenqiao Yu and Enjiang Chen performed the experiment;
Shaoyang Zhang contributed significantly to analysis and manuscript preparation;
Qinghui Fu performed the data analyses and wrote the manuscript;
Shuiqiao Fu helped perform the analysis with constructive discussions.

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