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Original Article

The identification of the key genes and pathways in septic shock using an integrated bioinformatics analysis

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Abstract: Sepsis is a critical illness with a high mortality rate in intensive care units. Septic shock is a severe, dangerous type of sepsis; however, the molecular mechanisms involved in septic shock are largely unclear. The present study integrated three datasets with 210 septic shock and 68 control samples to identify the hub genes involved in septic shock progression. Datasets GSE9692, GSE26378, and GSE26440 were downloaded from the Gene Expression Omnibus (GEO). Using bioinformatics tools such as GEO2R, Gene Ontology (GO) analysis, Kyoto Encyclopedia of Genes, and Genomes (KEGG) pathway analysis, and a protein-protein interaction (PPI) network analysis, five clusters and ten hub genes were successfully identified. The hub genes, including ITGAM, TLR4, TLR8, TLR2, MMP9, C3AR1, CCL5, FPR2, MPO, and LCK, were mainly enriched in the immune signaling pathway and in the inflammatory response. In summary, the present study identified ten septic shock-related genes using a bioinformatics analysis. The results indicate that the candidate genes may be involved in the regulation of immunity and the inflammatory response in septic shock and may act as predictors or therapeutic targets for septic shock.

Keywords: Sepsis, gene expression omnibus, differentially expressed genes, immunity, inflammation

Introduction

Sepsis is defined as a life-threatening organ dysfunction, which is often induced by a dysregulated host response to infection; septic shock is a type of sepsis with serious circulatory, cellular, and metabolic dysregulation and is associated with high mortality [1]. Septic shock is particularly dangerous as it is often followed by organ function failure [2, 3]. Despite progress in clinical strategies, severe sepsis still one of the most common causes of death in intensive care units [4, 5].

The high mortality of severe sepsis is due to a dysregulated immune response and inflammation in the pathophysiological process, in which the expression levels of numerous molecules are significantly altered *in vivo*, contributing to the progression of the disease [6-8]. Gene microarray is a gene detection technique that is suitable for differentially expressed gene (DEG) screening, because it can easily detect gene expression levels at various time points [7].

The present study aimed to obtain gene targets contributing to the diagnosis or therapy of septic shock by screening key disease-related genes and integrating the analyzed microarray datasets. The study was approved by the Committee of the First Affiliated Hospital of Guangxi Medical University (approval no. 2019 KY-E-031).

Materials and methods

Microarray data source

Blood gene expression profiles GSE9692 (public since 2007 and last updated in 2019), GSE26378 (public since 2019) and GSE26440 (public since 2011 and last updated in 2019) were downloaded from the Gene Expression Omnibus (GEO) database (Internet site: http://www.ncbi.nlm.nih.gov/geo). Two groups of children with septic shock and one group of healthy children were included in all the datasets, and day 1 was the adopted timepoint. The microarray data of these trials were all based on

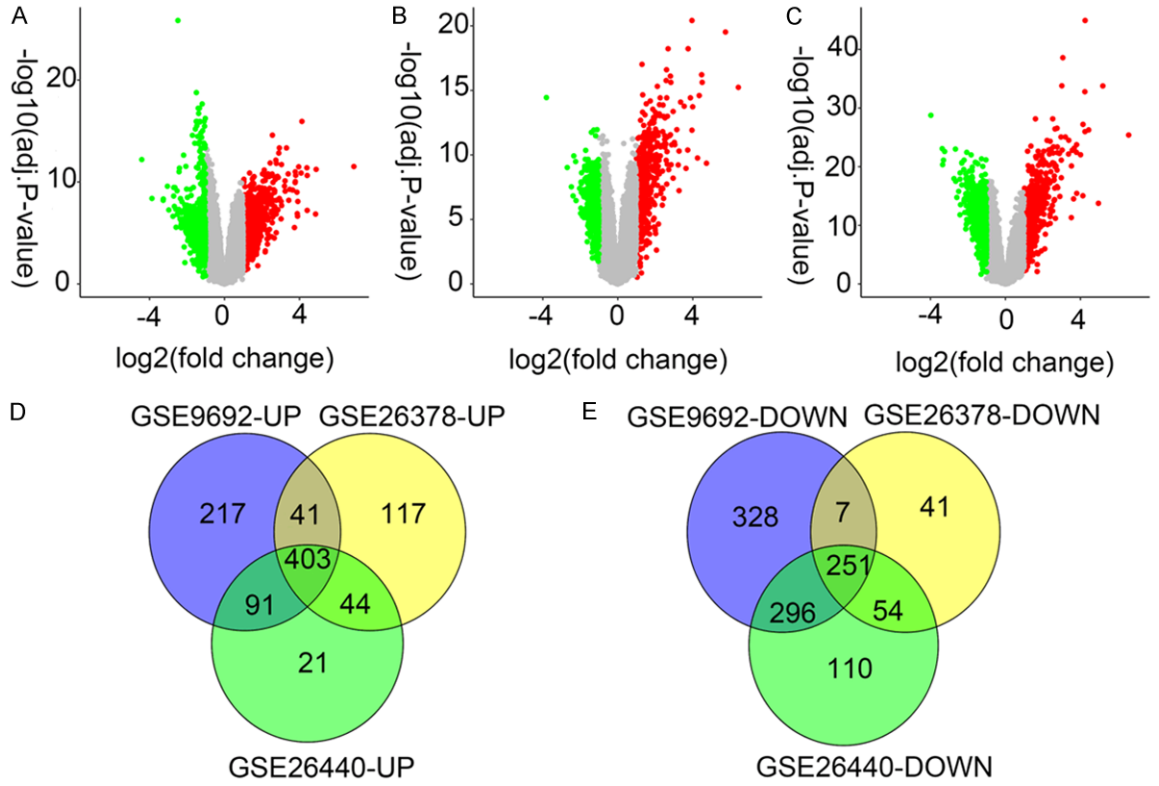

Figure 1. Volcano plots of three GEO datasets and Venn diagrams of the DEG screening. A. The volcano plot of the GSE9692 dataset. B. The volcano plot of the GSE26378 dataset. C. The volcano plot of the GSE26440 dataset. D. The overlapping upregulated DEGs in the three datasets. E. The overlapping downregulated DEGs in the three datasets. DEG, differentially expressed gene.

GPL570 Platforms (Affymetrix Human Genome U133 Plus 2.0 Array). The trials were conducted at Cincinnati Children's Hospital Medical Center (Cincinnati, OH, USA).

Data preprocessing and DEGs screening

In this work, we used GEO2R (Internet site: http://www.ncbi.nlm.nih.gov/geo/geo2r/) to screen DEGs. GEO2R is a web tool often used to screen DEGs in GEO datasets [9]. Following the data collection, GEO2R was applied to identify the DEGs between the septic shock samples and the control samples. The adjusted *P*-value <0.05 and |log2 [fold change (FC)]|>1 were set as the cut-off criteria.

Gene ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of the DEGs

The DEGs of the three datasets were grouped as upregulated and downregulated genes based on the direction of the change. VENNY 2.1.0 software (Internet site: http://bioinfogp.cnb.csic.es/tools/venny/index.html) was used to select the intersecting upregulated and downregulated genes in the three datasets.

The DAVID 6.8 database (Internet site: https://david.ncifcrf.gov) was used to perform the function annotation and pathway analysis. The interacting genes were classified according to the GO and KEGG pathways. Based on the enriched GO terms and significant KEGG pathways, the functions of the intersecting DEGs were explored. *P*-value <0.05 and count ≥2 were considered statistically significant.

DEGs protein-protein interaction (PPI) network and module analysis

The intersecting genes were imported into the STRING database 11.0 (Internet site: https://string-db.org) to construct a PPI network, which was subsequently imported into Cytoscape 3.6.0 to create a graphic of the network.

Based on the Plugin Molecular Complex Detection (MCODE) with the following screen-

Table 1. Top 30 enriched Gene Ontology terms of the differentially expressed genes

Category	Term	Count	*P*-value
Up-regulated			
BP	Innate immune response	37	1.73E-12
BP	Inflammatory response	33	2.55E-11
BP	Defense response to bacterium	15	2.39E-06
BP	Leukocyte migration	13	1.04E-05
BP	Immune response	24	3.18E-05
CC	Extracellular exosome	111	1.85E-13
CC	Extracellular space	61	1.90E-09
CC	Plasma membrane	130	5.17E-09
CC	Integral component of plasma membrane	52	1.91E-05
CC	Integral component of membrane	138	3.07E-05
MF	RAGE receptor binding	5	5.28E-05
MF	Interleukin-1 receptor activity	4	2.88E-04
MF	Catalytic activity	13	5.56E-04
MF	Glucose binding	4	0.00127778
MF	Non-membrane spanning protein tyrosine kinase activity	6	0.00250997
Down-regulated			
BP	T cell receptor signaling pathway	20	1.17E-14
BP	Regulation of immune response	19	3.86E-12
BP	Adaptive immune response	16	2.48E-10
BP	T cell costimulation	11	2.72E-08
BP	Cellular defense response	10	4.54E-08
CC	T cell receptor complex	8	6.52E-10
CC	Plasma membrane	80	3.68E-07
CC	Immunological synapse	7	2.12E-06
CC	Integral component of plasma membrane	37	4.30E-06
CC	Alpha-beta T cell receptor complex	4	1.44E-05
MF	Coreceptor activity	5	3.89E-04
MF	RNA polymerase II regulatory region sequence-specific DNA binding	10	7.68E-04
MF	Transmembrane signaling receptor activity	10	9.38E-04
MF	Core promoter sequence-specific DNA binding	5	0.001555
MF	T cell receptor binding	3	0.001971

BP: biological process; CC: cellular component; MF: molecular function.

ing parameters: degree cutoff ≥2; K-score ≥6; node score cutoff ≥0.2; and maximum depth = 100, the modules were picked out from the PPI network and then analyzed using DAVID 6.8 database.

Hub genes screening and function analysis

Among the nodes in the PPI network, the top 10 hub genes were identified using the degree algorithm of the CytoHubba plugin. The node degree was ranked by calculating the numbers of inter-connections in the PPI network. These hub genes were then imported into the DAVID 6.8 database to determine their function in septic shock.

Results

Identification of DEGs in septic shock

The gene expression levels of the three datasets were downloaded from the GEO database. Based on the GEO2R analysis, 22,185 DEGs were identified in septic shock compared with the healthy control samples. Based on the cut-off criteria of the adjusted *P*-value <0.05 and |log2(FC)|>1, 752 upregulated and 882 down-

Table 2. Top 20 enriched pathways of the differentially expressed genes

Category	Terms	Count	*P*-value
Up-regulated			
KEGG	Osteoclast differentiation	13	1.21E-04
KEGG	Legionellosis	8	4.09E-04
KEGG	Amoebiasis	10	0.001493
KEGG	Hematopoietic cell lineage	9	0.001636
KEGG	Leishmaniasis	8	0.002132
KEGG	Staphylococcus aureus infection	7	0.002402
KEGG	Complement and coagulation cascades	7	0.008141
KEGG	Pertussis	7	0.012066
KEGG	Tuberculosis	11	0.01507
KEGG	Toll-like receptor signaling pathway	8	0.018582
Down-regulated			
KEGG	T cell receptor signaling pathway	13	2.86E-09
KEGG	Hematopoietic cell lineage	11	1.00E-07
KEGG	HTLV-I infection	15	2.57E-06
KEGG	Graft-versus-host disease	6	4.89E-05
KEGG	Primary immunodeficiency	6	5.68E-05
KEGG	Viral myocarditis	7	6.98E-05
KEGG	Allograft rejection	6	8.64E-05
KEGG	Natural killer cell mediated cytotoxicity	9	1.30E-04
KEGG	Type I diabetes mellitus	6	1.61E-04
KEGG	Measles	9	2.36E-04

KEGG: Kyoto Encyclopedia of Genes and Genomes.

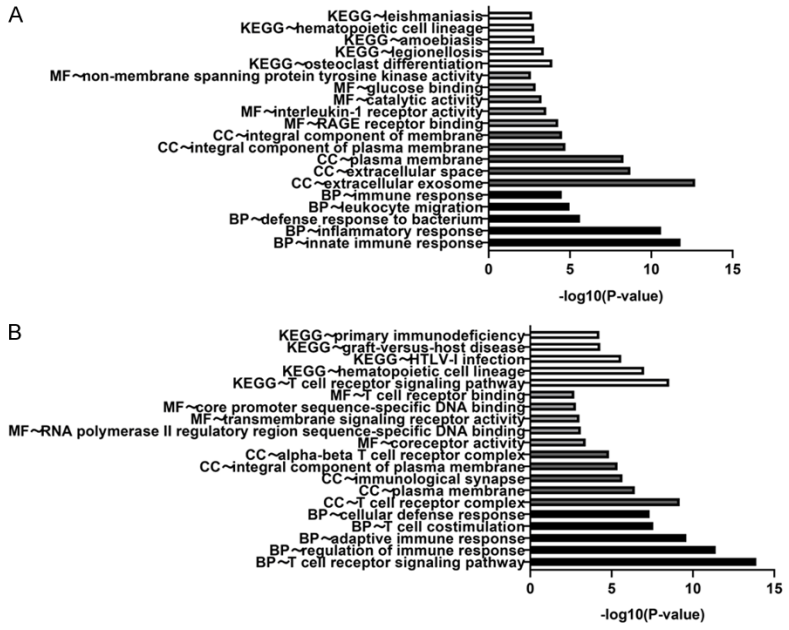

Figure 2. Top five GO enrichment analysis and KEGG pathways. A. GO terms and KEGG pathways of upregulated DEGs. B. GO terms and KEGG pathways of downregulated DEGs. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; DEGs, differentially expressed genes.

regulated genes were identified in GSE9692, 605 upregulated and 353 downregulated genes were identified in GSE26378, and 559 upregulated and 711 downregulated genes were identified in GSE26440 (**Figure 1A-C**). Using VENNY 2.1 software, 403 upregulated and 251 downregulated intersecting genes among the three datasets were selected (**Figure 1D**, **1E**).

GO ontology and KEGG pathway analysis of the DEGs in septic shock

The functional enrichment of the 403 upregulated and 251 downregulated candidate DEGs were analyzed using the DAVID 6.8 database. Biological processes, cellular components, molecular functions and KEGG pathways were obtained (**Tables 1**, **2**; **Figure 2A**, **2B**). The biological process results revealed that the upregulated DEGs were mainly enriched in an 'innate immune response', an 'inflammatory response' and a 'defense response to bacterium', but the downregulated DEGs were mainly enriched in the 'T cell receptor (TCR) signaling pathway', 'regulation of the immune response' and the 'adaptive immune response'. The cellular component results demonstrated that the upregulated DEGs were mainly enriched in 'extracellular exosomes', 'extracellular space', and 'plasma membrane', but the downregulated DEGs were mainly enriched in the 'T cell receptor complex', 'plasma membrane', and 'immunological syn-

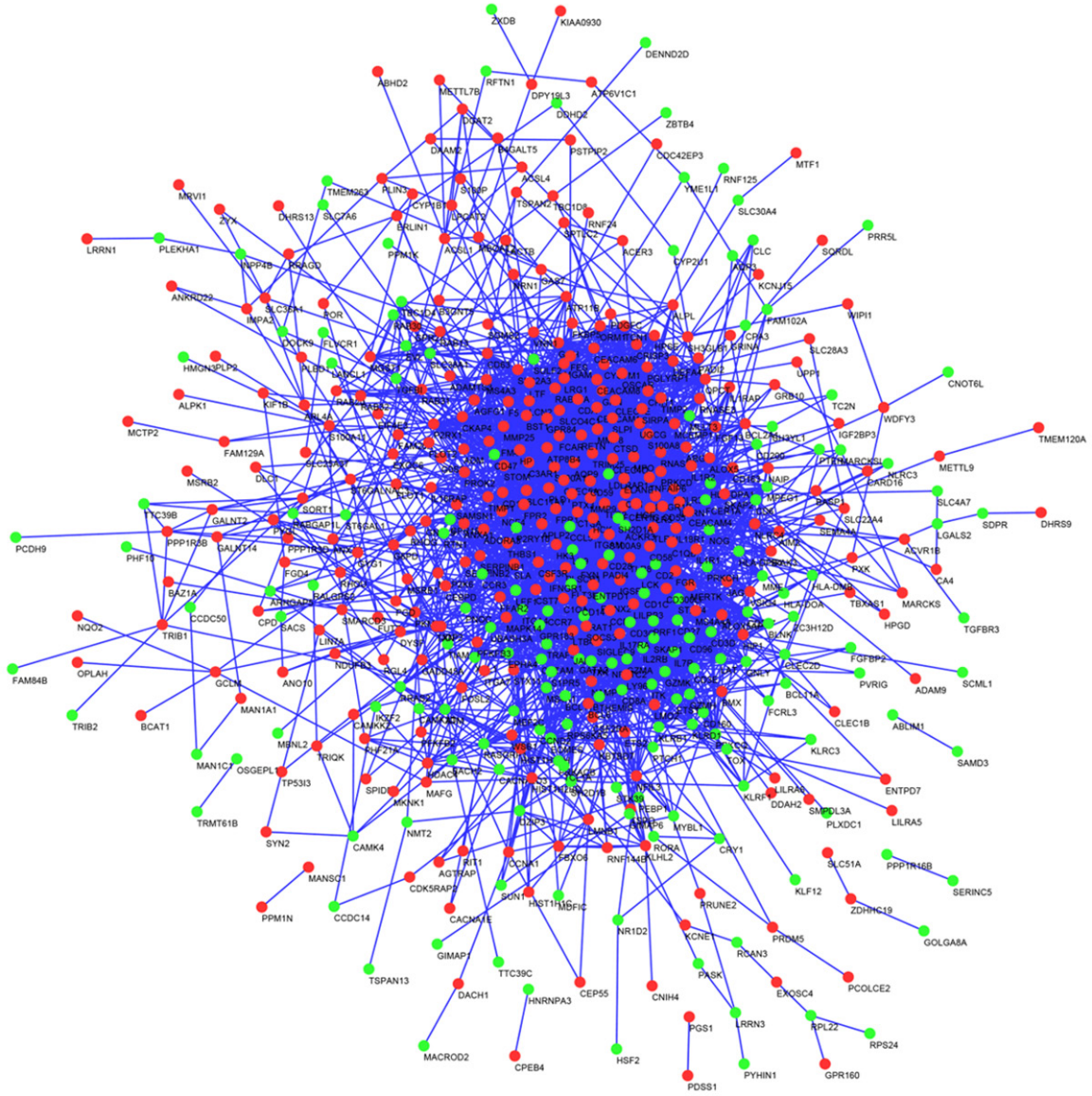

Figure 3. PPI network. Red nodes represent upregulated DEGs; green nodes represent downregulated DEGs. PPI, protein-protein interaction; DEGs, differentially expressed genes.

apse'. The molecular function analysis revealed that the upregulated DEGs were mainly enriched in 'RAGE receptor binding', 'interleukin-1 receptor activity', and 'catalytic activity', but the downregulated DEGs were mainly enriched in 'coreceptor activity'. 'RNA polymerase II regulatory region sequence-specific DNA binding', and 'transmembrane signaling receptor activity'. The KEGG pathway analysis results indicated that the upregulated DEGs were mainly enriched in 'osteoclast differentiation', 'legionellosis', and 'amoebiasis', but the downregulated DEGs were mainly enriched in the 'T cell receptor signaling pathways', 'hematopoietic cell lineage', and 'HTLV-1 infection'. These results demonstrated that the majority of the selected DEGs were significantly enriched in the immune and inflammatory responses.

PPI network construction and module analysis

The candidate DEGs (n = 654) were analyzed using the STRING 11.0 database and Cytoscape 3.6.0 software. A total of 511 nodes and 3,289 edges were included in the PPI network (**Figure 3**). Screened by MCODE, five clusters were obtained (**Figure 4A-E**). There were 54 nodes and 693 edges in cluster 1, 26 nodes

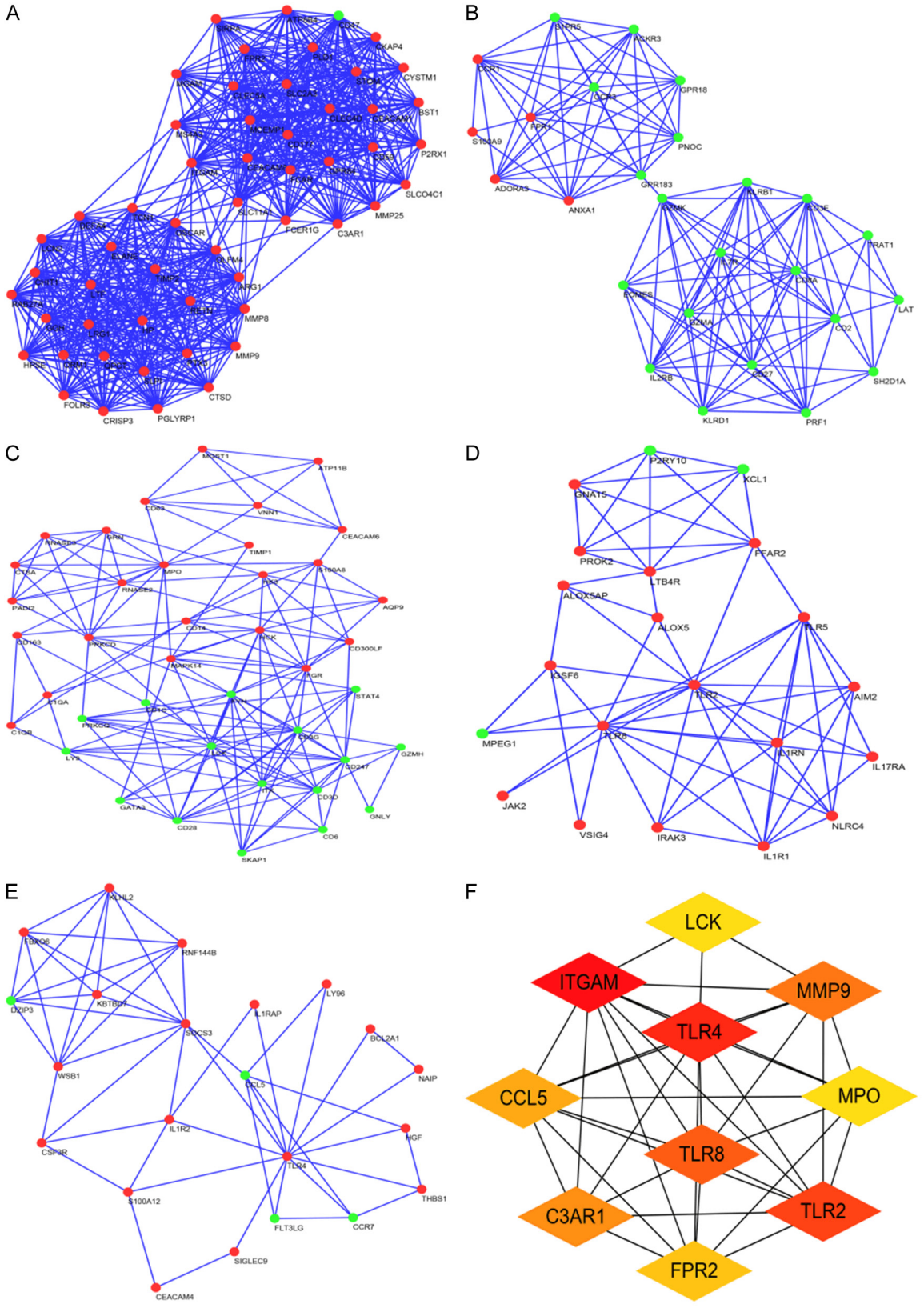

Figure 4. Modules and hub genes screened from the PPI network. A. Cluster 1. B. Cluster 2. C. Cluster 3. D. Cluster 4. E. Cluster 5. F. Top ten genes. Red nodes represent upregulated DEGs; green nodes represent downregulated DEGs. PPI, protein-protein interaction; DEGs, differentially expressed genes.

Table 3. Significantly enriched Gene Ontology terms of the module genes

Category	Term	Count	*P*-value
Module 1			
BP	Leukocyte migration	10	8.16E-11
BP	Positive regulation of phagocytosis	5	1.56E-06
BP	Innate immune response	8	2.65E-04
CC	Extracellular space	24	2.09E-13
CC	Extracellular exosome	31	1.55E-12
CC	Extracellular region	18	8.97E-07
MF	Serine-type endopeptidase activity	6	6.25E-04
MF	Protease binding	3	0.030928
MF	Metalloendopeptidase activity	3	0.03797
Module 2			
BP	Cell surface receptor signaling pathway	8	7.79E-08
BP	Adaptive immune response	6	1.85E-06
BP	Inflammatory response	7	1.21E-05
CC	Plasma membrane	21	4.77E-10
CC	External side of plasma membrane	7	2.68E-07
CC	Integral component of plasma membrane	11	5.50E-06
MF	Transmembrane signaling receptor activity	4	0.003341
MF	RAGE receptor binding	2	0.015533
MF	C-C chemokine receptor activity	2	0.016933
Module 3			
BP	T cell receptor signaling pathway	10	2.53E-11
BP	Innate immune response	11	2.05E-08
BP	Regulation of defense response to virus by virus	5	3.93E-07
CC	T cell receptor complex	5	4.31E-08
CC	Extrinsic component of cytoplasmic side of plasma membrane	5	1.07E-05
CC	Plasma membrane	21	3.17E-05
MF	Non-membrane spanning protein tyrosine kinase activity	6	3.15E-08
MF	ATP binding	10	0.002233
MF	Protein tyrosine kinase activity	4	0.002393
Module 4			
BP	Inflammatory response	7	2.69E-06
BP	MyD88-dependent toll-like receptor signaling pathway	4	6.56E-06
BP	Regulation of cytokine secretion	3	6.63E-05
CC	Integral component of plasma membrane	8	5.27E-04
CC	Membrane raft	3	0.021135
CC	Integral component of membrane	11	0.032883
MF	Transmembrane signaling receptor activity	4	0.001424
MF	Arachidonate 5-lipoxygenase activity	2	0.002132
MF	Interleukin-1 receptor binding	2	0.013778
Module 5			
BP	Inflammatory response	7	3.77E-06
BP	Protein ubiquitination	5	7.59E-04
BP	Protein polyubiquitination	4	0.001286
CC	Extracellular region	8	0.001145
CC	Extracellular space	5	0.055588
CC	Platelet alpha granule lumen	2	0.05869

MF	Ubiquitin-protein transferase activity	7	1.15E-06
MF	Interleukin-1 receptor activity	2	0.007854
MF	Protein binding	16	0.015119

BP: biological process; CC: cellular component; MF: molecular function.

Table 4. Significantly enriched pathways of the module genes

Category	Term	Count	*P*-value
Module 1			
KEGG	Staphylococcus aureus infection	4	6.34E-04
KEGG	Sphingolipid signaling pathway	3	0.055555
KEGG	Transcriptional misregulation in cancer	3	0.098635
Module 2			
KEGG	Cytokine-cytokine receptor interaction	5	0.001977
KEGG	Natural killer cell mediated cytotoxicity	4	0.002575
KEGG	Hematopoietic cell lineage	3	0.016913
Module 3			
KEGG	T cell receptor signaling pathway	9	1.89E-09
KEGG	Chagas disease (American trypanosomiasis)	5	5.71E-04
KEGG	Measles	5	0.001435
Module 4			
KEGG	Legionellosis	3	0.005182
KEGG	Toll-like receptor signaling pathway	3	0.018971
KEGG	Amoebiasis	3	0.018971
Module 5			
KEGG	Cytokine-cytokine receptor interaction	5	6.01E-04
KEGG	Hematopoietic cell lineage	3	0.009612
KEGG	Malaria	2	0.08227

KEGG: Kyoto Encyclopedia of Genes and Genomes.

Table 5. Top 10 genes ranked by degree

Gene name	Score	Rank	Category
ITGAM	111	1	Up-regulated
TLR4	84	2	Up-regulated
TLR2	75	3	Up-regulated
TLR8	71	4	Up-regulated
MMP9	69	5	Up-regulated
C3AR1	63	6	Up-regulated
CCL5	60	7	Down-regulated
FPR2	56	8	Up-regulated
MPO	54	9	Up-regulated
LCK	54	9	Down-regulated

and 126 edges in cluster 2, 40 nodes and 156 edges in cluster 3, 21 nodes and 63 edges in cluster 4 and 22 nodes and 52 edges in cluster 5. Gene ontology and KEGG pathways of the DEGs in the five clusters were analyzed; the results revealed that these genes were also mainly enriched in the immune signaling pathway and the inflammatory response (**Tables 3**, **4**).

Hub gene selection and enriched function analysis

Within the PPI network, the Cytohubba plugin was applied to screen for the hub genes. Based on the degree algorithm, the top ten hub genes were ITGAM, TLR4, TLR8, TLR2, MMP9, C3AR1, CCL5, FPR2, MPO, and LCK (**Table 5**; **Figure 4F**); among these genes, CCL5 and LCK were down-regulated, and the others were upregulated. Significantly the enriched GO terms and KEGG pathways of these hub genes were analyzed using the DAVID 6.8 database. The biological process results indicated that the top ten genes were mainly enriched in 'leukocyte migration', 'the inflammatory response', and 'regulation of cytokine secretion'. The cellular component results revealed that the top ten genes were mainly enriched in the 'intrinsic component of plasma membrane', 'extracellular space', and 'the integral component of the plasma membrane'. The molecular function analysis revealed that the top ten genes were mainly enriched in 'lipopolysaccharide receptor activity', 'receptor activity', and 'lipopolysaccharide binding'. The KEGG pathway analysis results indicated that the top ten genes were mainly enriched in 'the toll-like receptor signaling pathway', 'phagosome', and 'staphylococcus aureus infection'. (**Table 6**; **Figure 5**). These results indicated that the top ten genes may serve important roles in the immune and inflammation processes.

Discussion

Over the past several decades, studies have aimed to reveal the underlying mechanisms of

Table 6. Significantly enriched Gene Ontology terms and pathways of the top 10 genes

Category	Term	Count	*P*-value	Genes
BP	Leukocyte migration	5	3.25E-07	C3AR1, MMP9, LCK, FPR2, ITGAM
BP	Inflammatory response	6	6.67E-07	C3AR1, TLR2, TLR4, FPR2, CCL5, TLR8
BP	Regulation of cytokine secretion	3	1.40E-05	TLR2, TLR4, TLR8
CC	Intrinsic component of plasma membrane	2	0.013746	TLR2, TLR4
CC	Extracellular space	4	0.024141	MMP9, MPO, CCL5, ITGAM
CC	Integral component of plasma membrane	4	0.027505	C3AR1, TLR2, TLR4, FPR2
MF	Lipopolysaccharide receptor activity	2	0.002663	TLR2, TLR4
MF	Receptor activity	3	0.00558	TLR2, TLR4, TLR8
MF	Lipopolysaccharide binding	2	0.011671	TLR2, TLR4
KEGG	Toll-like receptor signaling pathway	4	2.79E-04	TLR2, TLR4, CCL5, TLR8
KEGG	Phagosome	4	7.75E-04	TLR2, MPO, TLR4, ITGAM
KEGG	Staphylococcus aureus infection	3	0.002102	C3AR1, FPR2, ITGAM

BP: biological process; CC: cellular component; MF: molecular function. KEGG: Kyoto Encyclopedia of Genes and Genomes.

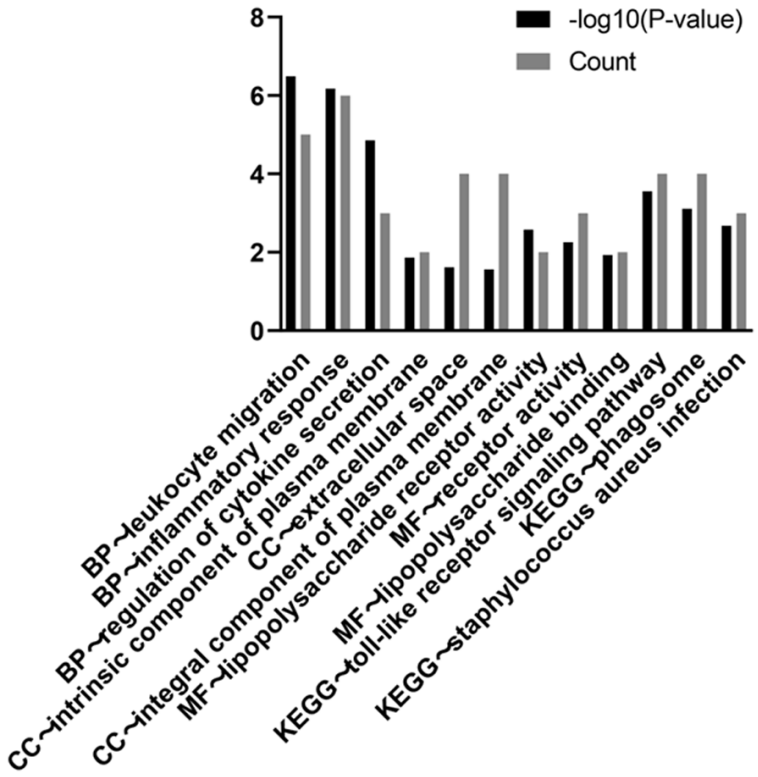

Figure 5. Significantly enriched GO terms and KEGG pathways of the top ten genes. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genome.

septic shock; however, reducing the mortality of sepsis is still difficult [4, 10]. The majority of studies indicated that the high mortality of septic shock was associated with immune dysfunction, particularly due to T cell dysfunction [11, 12]. In addition, excessive inflammation is an important factor that contributes to the mortality of septic shock [13]. However, the exact molecular changes in the immune and inflammatory pathways and how they interact with each other during sepsis are still unclear. The present study integrated three datasets to analyze data using bioinformatics methods. Through DEG screening, GO terms, the KEGG pathway and PPI network analysis, and the application of CytoHubba, ten disease-related hub genes, including ITGAM, TLR4, TLR8, TLR2, MMP9, C3AR1, CCL5, FPR2, MPO, and LCK, were identified, among which CCL5 and LCK were downregulated, but the others were upregulated.

In the present study, the timepoint of sample collection was day 1, which is the early stage of sepsis progress. According to the results of the GO and KEGG analysis, ten hub genes may serve important roles in innate immunity and in the inflammatory response. These findings are consistent with previous studies. For example, Pop-Began et al. [14] demonstrated that the toll-like receptor (TLR) family is an important upstream sensor and effector sys-

tem of innate immunity. Chong et al. [15] indicated that TLRs linking to pattern recognition receptors form a key step in initiating pro-inflammatory signaling pathways, which contribute to the further production of pro-inflammatory cytokines. The matrix metalloproteinase (MMP) family are a series of proteases that can mediate immunological and neoplastic processes [16]. MMP-9 is one member of the MMP family and often significantly upregulated in sepsis, which is associated with disease severity [17]. ATGAM is a gene that encodes CD11b, which serves an anti-inflammatory role in leukocytes by negatively regulating the TLR signaling pathways and B cell autoreactivity [18, 19]. CCL5 is a key modulator of host response that can trigger the upregulation of pro-inflammatory cytokines *in vivo*, leading to an increase of mortality in sepsis [20]. Targeting CCL5 can decrease inflammatory responses, which may become a novel therapeutic method for inflammatory disease [21].

A limited number of previous studies involved key gene screening in septic shock. Yang et al. screened DEGs from the GSE26440 dataset and identified 10 hub genes including GAPDH, TNF, EGF, MAPK3, IL-1β, IL-10, TLR2, TLR4, PIK3CB, and MAPK14 [22]. The hub genes obtained in their study were partially different from the ones obtained in the present study; however, the majority of the hub genes identified in the previous study were mainly enriched in inflammatory pathways, which was consistent with the results of the present study. Liu et al. [23] also used the GSE26440 dataset for a bioinformatics analysis. The top five genes they obtained were KDM6B, HDAC2, MYC, HSP90AB1, and PABPC1. Although their results differed from the present study, the functions of the genes were also mainly enriched in immunity and inflammation. The above authors all used a single dataset for analysis; the present study integrated three datasets from GEO and screened the intersecting genes, so the findings may be more reliable due to a larger sample size analyzed using the same experimental design.

Following the accomplishment of the Human Genome Project, genome analysis has contributed to the understanding of the molecular mechanisms that may influence therapy and disease evaluation and lead to precision medicine, which includes determining the molecular characteristics of each patient, the selection of the best therapeutic method, and the reduction of adverse reactions [24]. Precision medicine is recommended for various conditions, including sepsis. The application of precision medicine requires a clear understanding of the molecular basis of disease progression. Precision medicine may serve an important role in subtype classification, risk assessment, and the selection of suitable patients for new therapies [25]. Microarray, high-throughput technologies and other tools have contributed to the insight in the molecular level of disease progression, which may be an important factor in precision medicine.

In summary, using microarray datasets and bioinformatical analysis, ten sepsis-related genes were identified, genes which are involved in the immune signaling pathway and the inflammatory response. These findings may improve the understanding of the underlying molecular events in septic shock, and the candidate genes may be diagnostic or therapeutic targets for septic shock.

Conclusion

Using GEO datasets and a bioinformatics analysis, ten hub genes were identified to be involved in septic shock. These hub genes are involved in the regulation of immunity and the inflammatory response, which suggests that they may be predictors or therapeutic targets for septic shock.

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Disclosure of conflict of interest

None.

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