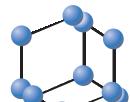
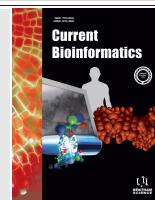


RESEARCH ARTICLE

BENTHAM
SCIENCE**Identification of Mitophagy-Related Genes in Sepsis**

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Abstract: **Background:** Numerous studies have shown that mitochondrial damage induces inflammation and activates inflammatory cells, leading to sepsis, while sepsis, a systemic inflammatory response syndrome, also exacerbates mitochondrial damage and hyperactivation. Mitochondrial autophagy eliminates aged, abnormal or damaged mitochondria to reduce intracellular mitochondrial stress and the release of mitochondria-associated molecules, thereby reducing the inflammatory response and cellular damage caused by sepsis. In addition, mitochondrial autophagy may also influence the onset and progression of sepsis, but the exact mechanisms are unclear.

Methods: In this study, we mined the available publicly available microarray data in the GEO database (Home - GEO - NCBI (nih.gov)) with the aim of identifying key genes associated with mitochondrial autophagy in sepsis.

Results: We identified four mitophagy-related genes in sepsis, TOMM20, TOMM22, TOMM40, and MFN1.

Conclusion: This study provides preliminary evidence for the treatment of sepsis and may provide a solid foundation for subsequent biological studies.

Keywords: sepsis, mitochondrial autophagy, robust rank aggregation, protein-protein interaction (PPI) network analysis, hub genes.

1. INTRODUCTION

Sepsis is a critical systemic infection, a syndrome of the severe inflammatory response of the organism to various pathogenic microorganisms. When the organism is infected, the immune system releases inflammatory mediators, such as cytokines and white blood cells, to attack and destroy the invading pathogens. However, in some cases, the body's defense system may go out of control, leading to a massive release of these mediators into the whole body, resulting in increased vascular permeability of multiple organ tissues, edema formation, and rupture causing phenomena such as tissue necrosis and organ failure [1-5]. According to statistics, about 3 million people worldwide suffer from sepsis every year, with a mortality rate of 25% to 30% or more, among which the proportion is higher in developing countries. Meanwhile, the incidence of sepsis has shown a trend

of increasing year by year in recent years [6]. The clinical manifestations of sepsis are diverse. In the early stage, there may be only some uncomfortable symptoms such as fever and rapid heart rate, and as the condition worsens, alternating high fever and low temperature, decreased blood pressure, respiratory distress, confusion, dysfunction of vital organs, etc. Complications include traumatic infection, pneumonia, urinary tract infection, gastrointestinal bleeding, etc. Therefore, it is of great importance to find the therapeutic target of sepsis.

Mitochondrial autophagy is a specific process of cellular autophagy which removes damaged or aged mitochondria. Normal mitochondria have important metabolic functions, but under the influence of multiple mixed factors such as oxidative stress and DNA damage, a series of dysfunctions and oxidative stress may occur, accelerating the aging and pathogenic process. At this point, mitochondrial autophagy becomes an important rescue pathway [7-11]. Mitochondrial autophagy consists of different steps, such as initiation, localization and pull-out. Parkin and Pink1 are the most important initiation proteins, which act on membrane structures relying on electrochemical transfer and ubiquitination modifications to initiate mitochondrial autophagy. In addition, during the pre-autophagic phase, the body also concentrates around mitochondria through specific membrane proteins

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LC3-II. It binds to their membrane surface, pointing markers such as NIX or FUNDC1 for specific mechanisms such as mitochondrial localization, wrapping and gradual pull-out [12, 13]. In the course of sepsis, the presence of bacterial infection or other exogenous damaging factors in the organism leads to the activation of the immune system, initiating the release of multiple inflammatory mediators and the associated effects of blood coagulation and peripheral fibrinolysis, of which abnormal mitochondrial function and dysregulation of the autophagic process are considered to be an important part [14]. In the onset of sepsis, immune cells produce large amounts of oxygen radicals, which increase permanent DNA damage in the mitochondria [15]. These degenerative alterations lead to mitochondria exhibiting multiple problems, such as structural disorders, alienation of metabolic capacity, and dysregulation of oxidative stress and Ca²⁺ homeostasis, increasing the likelihood that mitochondria will be subject to autonomic or induced autophagic activation [16, 17]. At the tissue-organ level, sepsis activates a series of nuclear receptors and transcription factors. It regulates mitochondrial function, security, and autophagic pathways through various factors that influence cell fate decisions. Correspondingly, abnormal mitochondrial autophagy predisposes to various pathological underlying processes and end-organ damage, and there is a degree of crosstalk effect and mutual positive feedback mechanism between these organs, which further exacerbates the severity of sepsis [18-20].

In this study, we used a bioinformatics approach to integrate multiple microarray data to screen for mitochondrial autophagy-related hub genes associated with sepsis onset and progression in a more scientific and systematic manner. This study provides a preliminary exploration of the mechanisms underlying sepsis development and lays the foundation for future biological experimental validation.

2. MATERIAL AND METHODS

2.1. Data Access

The Gene Expression Omnibus (GEO) database, maintained by the National Center for Biotechnology Information (NCBI) in the United States, serves as a comprehensive repository for gene expression data contributed by research institutions globally [21]. For our study, we employed the following inclusion criteria: (1) the sequencing specimens comprised human peripheral blood, (2) each dataset included both sepsis cases and healthy individuals as controls, and (3) a minimum of 20 total samples were encompassed. Finally, we identified five eligible microarray datasets: GSE137342, GSE69063, GSE64457, GSE570065, and GSE167914.

2.2. Data Pre-Processing

We began by downloading the gene expression series matrix, platform information, and clinical data of the four datasets from the GEO database. Using the corresponding platform information, we converted probe IDs in the expres-

sion series matrix into gene symbols. This resulted in an internationally standardized expression matrix with gene symbols as row names and sample names as column names. We then divided the matrix into two groups based on clinical information: control and sepsis groups. The expression series matrix was normalized using quartiles, and subsequent analyses were performed. DEGs (differentially expressed genes) were calculated using the "limma" R package for the above four datasets, with a $|\log_2 \text{fold change} (\text{FC})| > 0.585$ and a p -value < 0.05 as the cutoff criteria.

2.3. RRA Analysis

Robust rank aggregation (RRA) is a powerful algorithm for integrating gene expression data generated from multiple independent sources [22]. The algorithm is designed with four primary features: (1) noise resistance, thereby enabling robustness even in the presence of noise; (2) the ability to handle incomplete ranking, which results from genes that may not be measured or recognized by all platforms under consideration; (3) high computational efficiency, which ensures that large datasets can be processed quickly and reliably; (4) allocation of significant scores for each element in the resulting ranking. This technique has the potential to minimize inconsistencies arising from sequencing platform variability and individual differences across samples, among other factors. By making use of gene rankings based on an aggregate metric, RRA can be used to extract reliable and reproducible biological signals, thereby aiding the identification of numerous differential gene expressions that are common and biologically significant between different datasets. All genes from the above five datasets were integrated using the "Robust Rank Aggregation" R package, and genes with p -values < 0.05 and $|\log_2 \text{fold change} (\text{FC})| > 0.585$ were considered as DEGs.

2.4. Gene ontology (GO) functional enrichment analysis

The Gene Ontology (GO) functional enrichment analysis contains three components: Molecular Function (MF), Biological Process (BP), and Cellular Component(CC). All terms of the Gene Ontology (GO) functional enrichment analysis were performed by using the "enrichGO" R package.

2.5. Protein-Protein Interaction (PPI) Network Analysis

The database on the STRING website (string-db.org) currently includes 14,000 proteins from diverse organisms and its interaction network is based on various sources, including high-throughput sequencing data, computer genome prediction, automated text mining, and other databases. Consequently, it is one of the most extensive protein interaction databases in terms of species coverage and information content [23]. We uploaded the top 100 DEGs lists obtained from the RRA method analysis to the STRING network to capture protein interactions and visualized the results using Cytoscape software. We used the Betweenness (BC) method in "cytoNCA" to quantify the connectivity of each node.

2.6. Ethical Declaration

All of the data used in this study were obtained from public databases. This study does not contain any studies associated with animals or humans.

3. RESULT

3.2. Data

In this study, a total of five datasets are included, and their details are shown in Table 1.

Table 1 Details of the included datasets.

GSE ID	Participants	Tissues	Analysis Type	Year
GSE137342	55cases and 12 control	Peripheral blood	Array	2022
GSE69063	57cases and 33 control	Peripheral blood	Array	2021
GSE64457	15 cases and 8 control	Peripheral blood	Array	2015
GSE57065	82cases and 25 control	Peripheral blood	Array	2014
GSE167914	29cases and 10 control	Peripheral blood	Array	2021

Table 2. Details of the MRGs.

ATG5	ATG12	CSNK2A1	CSNK2A2	CSNK2B
MAP1LC3A	FUNDC1	MAP1LC3B	MFN1	MFN2
PGAM5	MTERF3	PINK1	PARK2	RPS27A
SRC	SQSTM1	TOMM20	TOMM22	TOMMM40
TOMM6	TOMM5	TOMM7	TOMM70A	UBA52
UBC	UBB	ULK1	VDAC1	

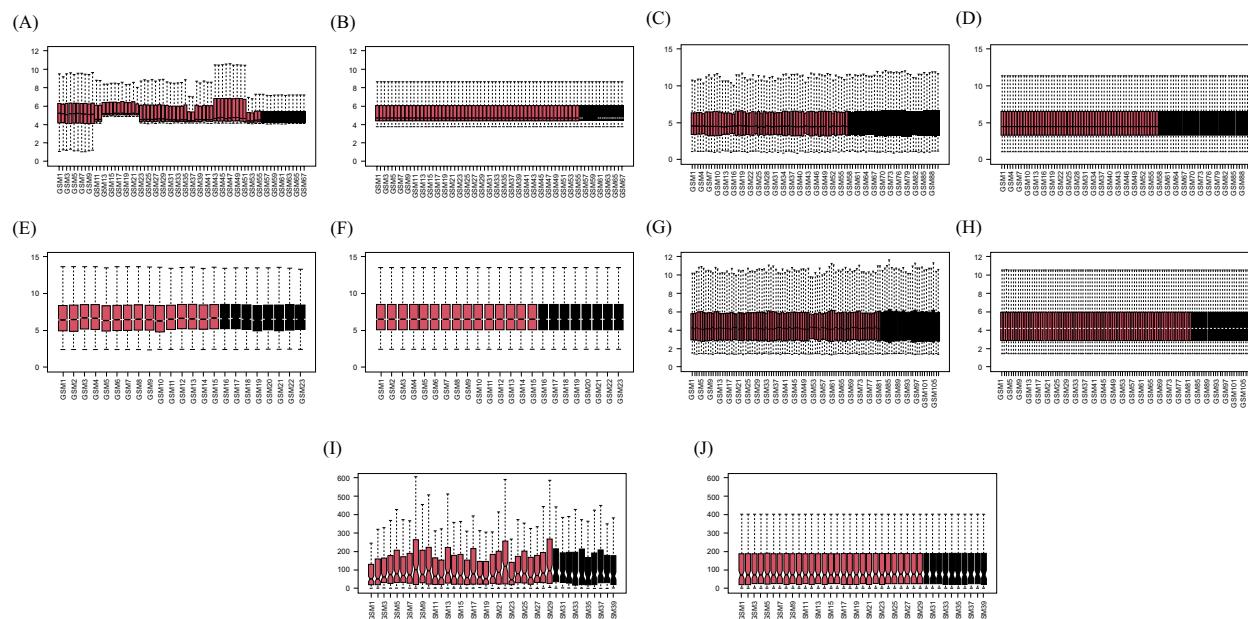


Fig. (1). Normalization of gene expression. (A-B) Normalization of the GSE137342 data set. (C-D) Normalization of the GSE69063 data set. (E-F) Normalization of the GSE64457 data set. (G-H) Normalization of the GSE57065 data set. (I-J) Normalization of the GSE167914 data set. Left represents data before normalization, and right represents data after normalization. (A higher resolution/colour version of this figure is available in the electronic copy of the article).

We obtained mitochondrial autophagy-related genes (MRGs) in the Reactome Pathway Database (<https://reactome.org>), details of which are given in Table 2.

3.3. Data pre-Processing

To minimize batch effects, all five microarray datasets described above were first normalized by the quantiles method for normalization. The results are shown in Fig. (1). We obtained their differential expression matrices using the "limma" R package and sorted them according to log2 fold change (FC). Volcano plots for the 5 microarrays are shown in Fig. (2).

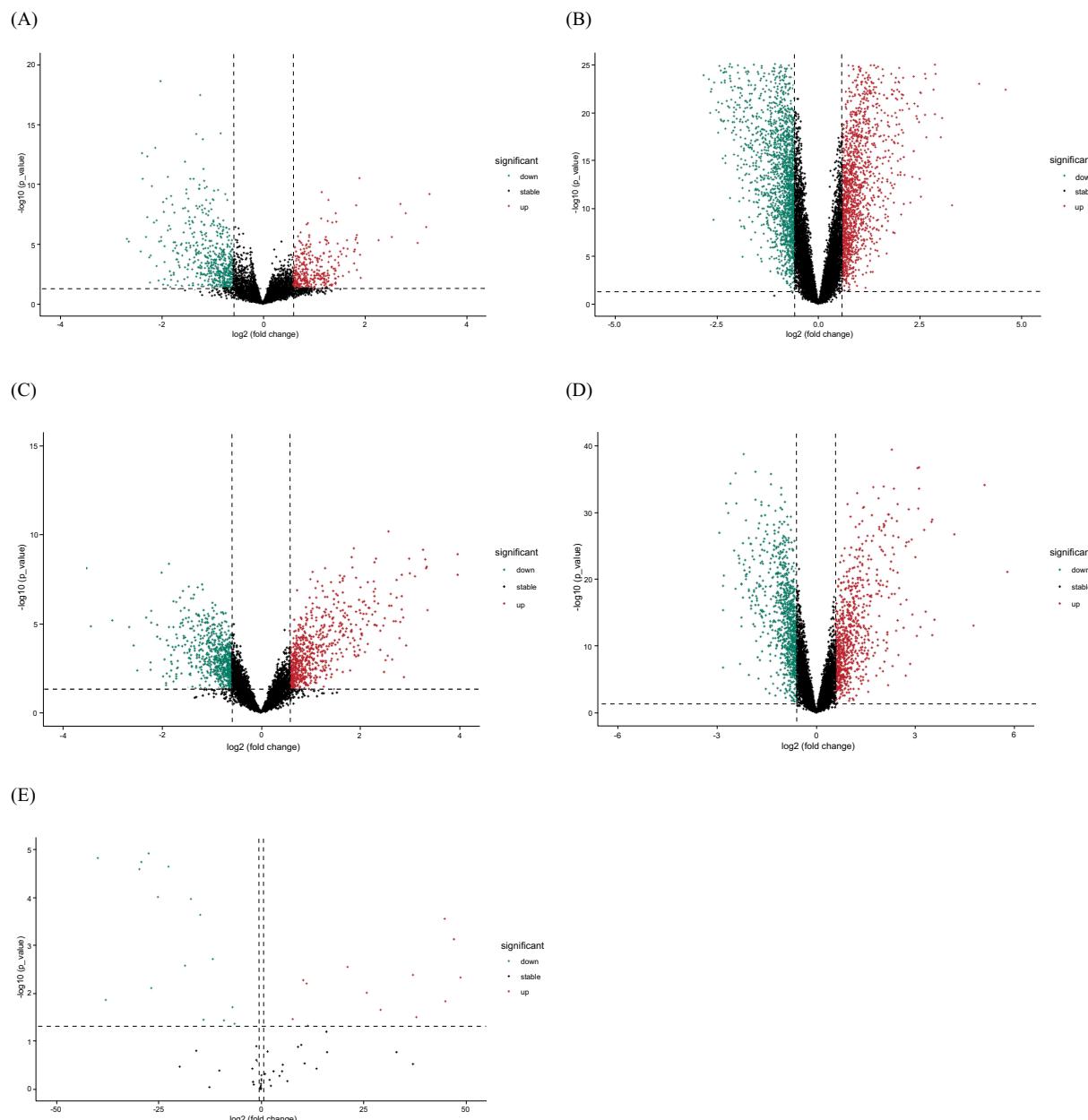


Fig. (2). Differentially expressed genes between the two groups of samples in each dataset. (A) GSE137342, (B) GSE69063, (C) GSE64457, (D) GSE57065, (E) GSE167914. The red dots represent the upregulated genes based on an $P < 0.05$ and $|\log_2 \text{fold change (FC)}| > 0.585$; the green dots represent the downregulated genes based on an $P < 0.05$ and $|\log_2 \text{fold change (FC)}| > 0.585$; the black spots represent genes with no significant difference in expression. (A higher resolution/colour version of this figure is available in the electronic copy of the article).

4. RESULTS IN THE RRA INTEGRATED ANALYSIS

We present the top 100 genes from RRA analysis results by heat map in Fig. (3). The results show that the top 20 up-regulated genes obtained by RRA analysis method were SLC25A37SH3GLB1, RPLP0, UCP2, SLC25A3, TSPO, RHOT1, SLC25A5MFN1, UXT, TOMM22, TAZ, TOMM20SLC25A24, STARD3, TIMM10BTIMM8B, TP53, TOMM40L, TIMM17A. The top 20 down-regulated genes were ADAM21AACSP, AMTN, ABCA8AADAT, A2M, L1, ANGPT1, ACMSD, ACOT4, ANGPTL1, ACSBG2,

AARS1, ACSS3, AMER3, CCDC65, ADH6, ACCSL, ABCA4, ADAM2AMIGO2, where TOMM22 and TOMM20 were present in both mitochondrial autophagy-related genes.

4.1. Gene Ontology (GO) Functional Annotation

We performed the Gene Ontology (GO) functional annotation (including biological process, cellular component, and molecular function) analysis of the 140 DEGs. It turned out that mitochondrial transport (GO: 0006839) was credited with the most significantly enriched biological process, fol-

lowed by the establishment of protein localization to the mitochondrion (GO: 0072655) and so on. It turned out that the mitochondrial inner membrane (GO: 0005743) was credited with the most significantly enriched cellular composition, followed by the mitochondrial protein complex (GO: 0098798) and so on. It turned out that active transmembrane

transporter activity (GO: 0022804) was credited with the most significantly enriched molecular function, followed by primary active transmembrane transporter activity (GO:0015399) and so on. The results are shown in Fig. (4). The raw analysis result data are provided in Supplementary Tables 1-3.

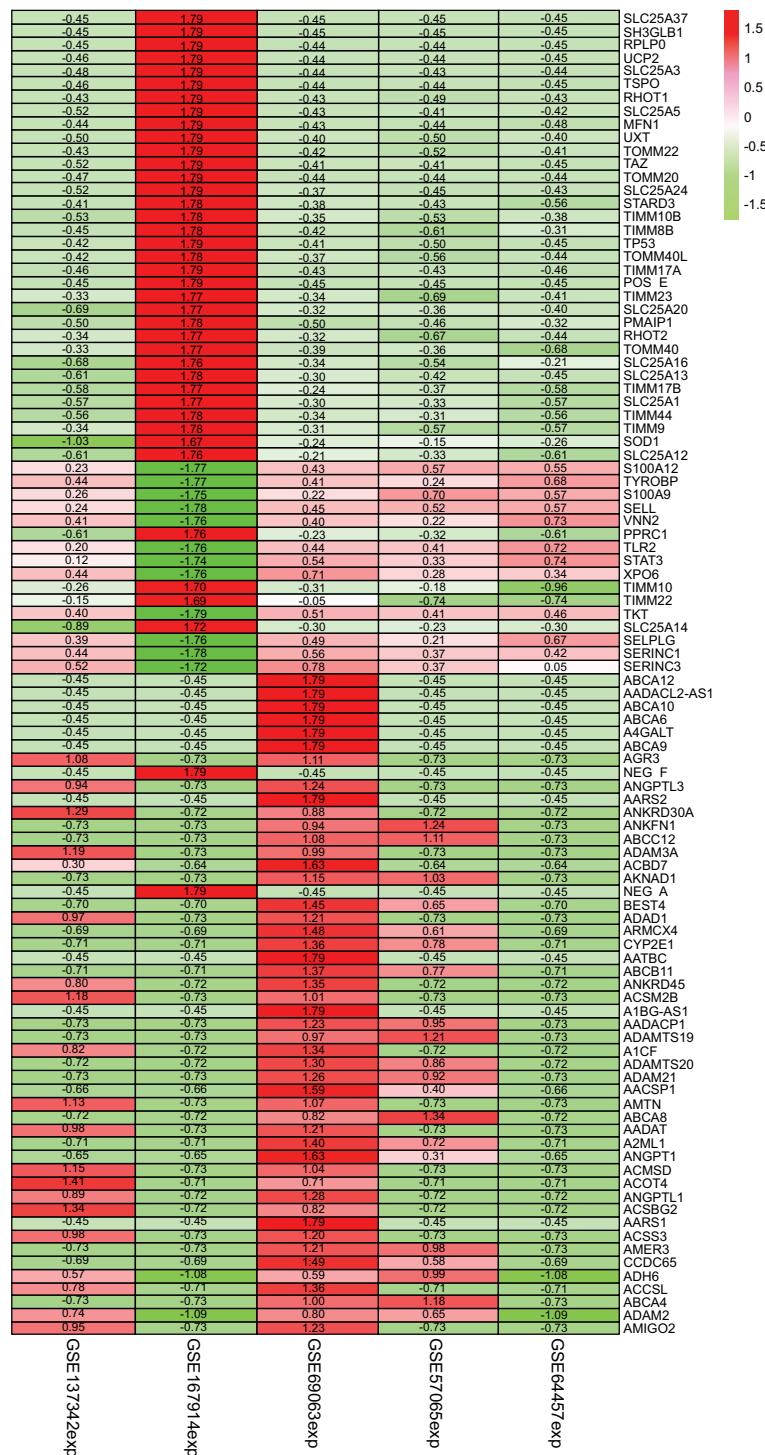


Fig. (3). Log2 FC heatmap of each expression microarray. The abscissa represents the GEO IDs, the ordinate represents the gene name, the red represents log2FC > 0, the green represents log2 FC < 0 and the value in the box represents the log2 FC value. (A higher resolution/colour version of this figure is available in the electronic copy of the article).

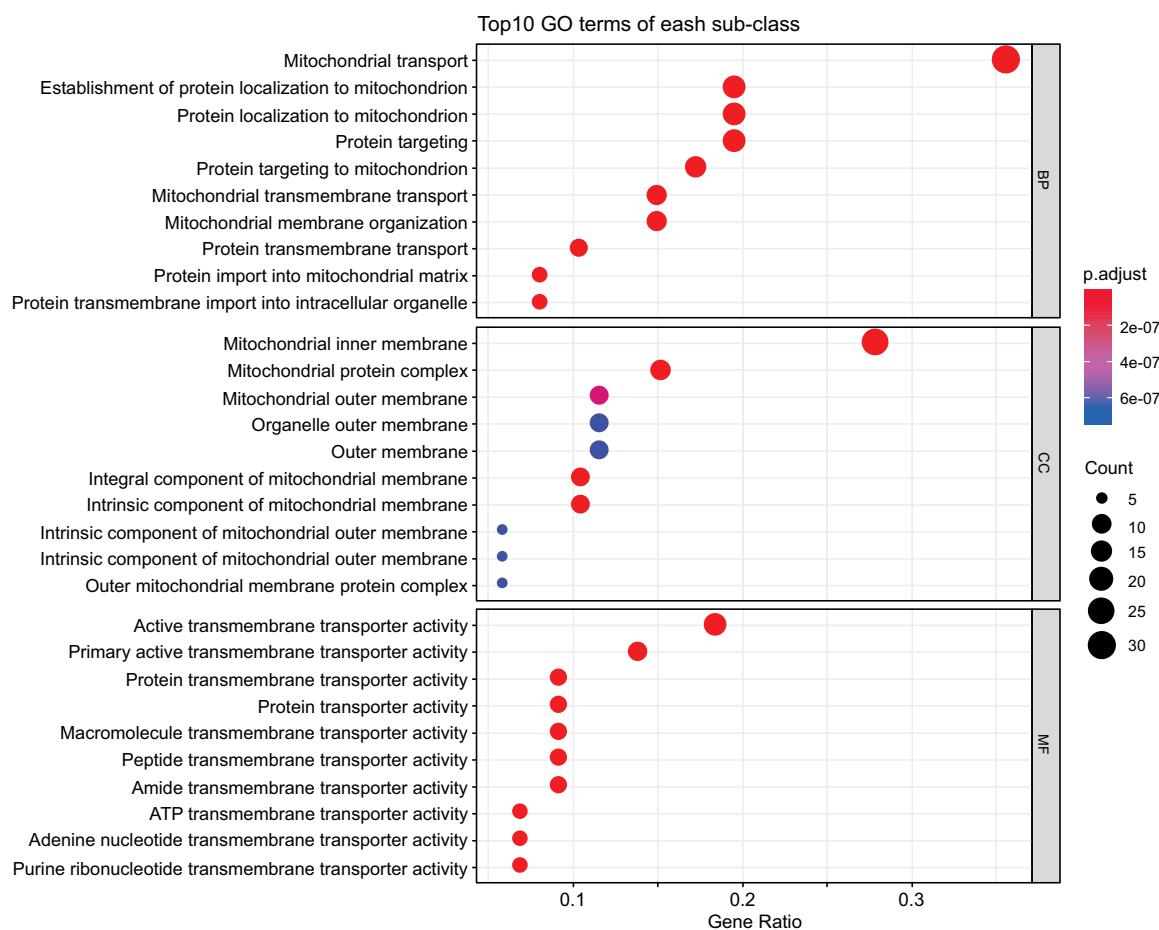


Fig. (4). The enriched biological process (BP), cellular component (CC), and molecular function (MF) terms in GO analysis. (A higher resolution/colour version of this figure is available in the electronic copy of the article).

4.2. Protein-Protein Interaction (PPI) Network Analysis

We uploaded 100 DEGs to the STRING online database and visualized the obtained results using Cytoscape software. The results are shown in Fig. (5). The top 20 genes in PPI were TOMM20, TOMM40, SOD1, TP53, MFN1, STAT3, TIMM10, TLR2, TIMM23, CYP2E1, SLC25A12, SLC25A3, TIMM8B, SLC25A5, TSPO, SH3GLB1, ACSM2B, SELL, TIMM9, TOMM22, where TOMM22, TOMM20, TOMM40, MFN1 are also mitochondrial autophagy-related genes.

Combined with the results of RRA analysis, we finally identified TOMM20, TOMM22, TOMM40, and MFN1 as key genes associated with mitochondrial autophagy in sepsis.

5. DISCUSSION

Sepsis is a systemic inflammatory response syndrome caused by bacterial or viral invasion of the circulatory system infection, which can lead to shock and tissue and organ failure or even death. It has become a public health problem worldwide. The management of patients with sepsis remains a challenge in healthcare and requires more precise and targeted strategies for effective treatment [24-29]. Numerous studies have shown that mitochondrial autophagy is dysregu-

lated during the development of sepsis, which could provide clinicians with better molecular targets. Stopping the development of excessive autophagy early may prevent prolonged mitochondrial overconsumption, cellular fatigue, and damage to the cellular infrastructure [18, 30-33]. First, during the onset of sepsis, immune cells produce large amounts of oxygen radicals, which increase permanent DNA damage in mitochondria and reduce ATP levels by promoting mitochondrial glycolytic channels through PARP-1 activation [34]. These degenerative alterations lead to mitochondria exhibiting multiple problems, such as structural disorders, alienation of metabolic capacity, and dysregulation of oxidative stress and Ca²⁺ homeostasis, increasing the likelihood that mitochondria will be subject to autonomic or induced autophagic activation [20, 35]. Second, immune cells, including lymphocytes and monocytes, still initiate the process of cellular autophagy in sepsis in response to altered levels of signal induction or phagocytosis [36]. However, when the boundary between cellular autophagy and mitochondrial autophagy is not clarified, such excessive autophagy may trigger problems with mitochondrial reproduction and division and generate more accumulation of harmful metabolic waste and ROS molecules, ultimately increasing the risk factors for the immune system to cope with the septic shock state [30].

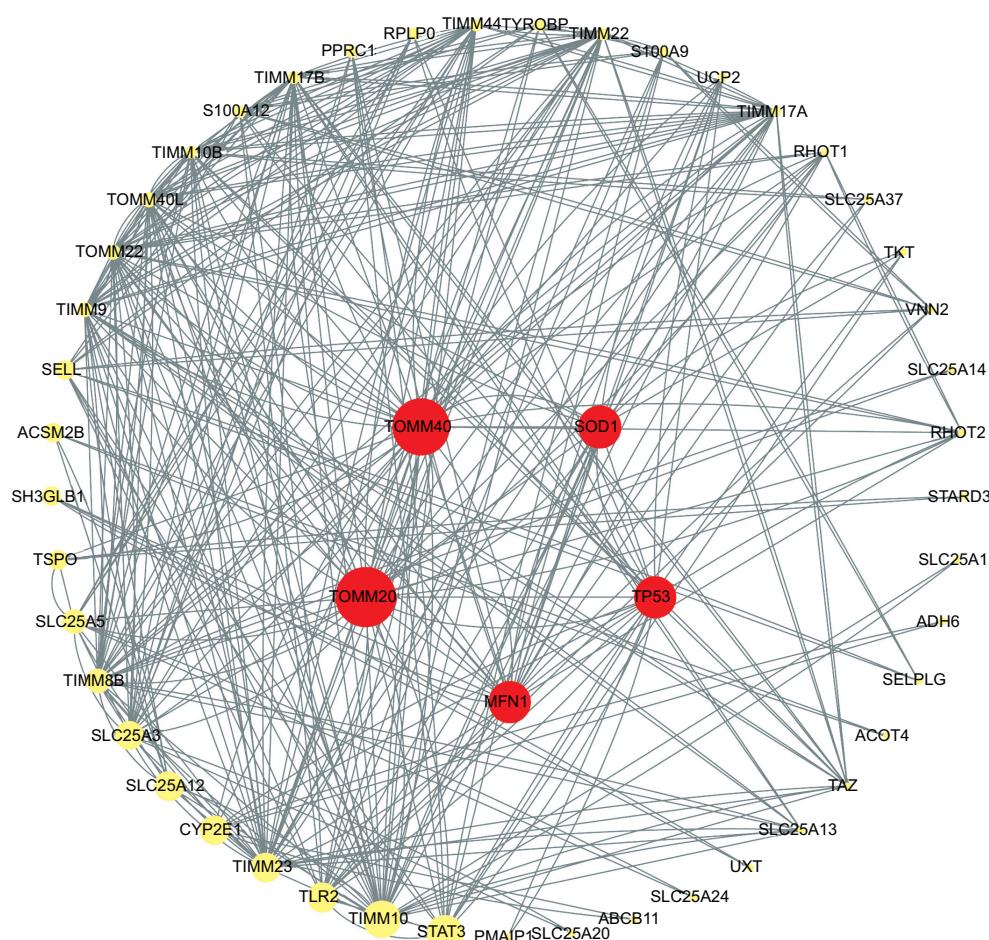


Fig. (5). The PPI network of DEGs in NPP (Cytoscape). (A higher resolution/colour version of this figure is available in the electronic copy of the article).

The above evidence suggests that dysregulated mitochondrial autophagy plays an important role in the development of sepsis, but the exact mechanism remains unclear. In this study, we used a bioinformatics approach RRA to integrate 5 microarray datasets with the aim of preliminarily identifying central genes associated with mitochondrial autophagy in the development of sepsis and providing new potential targets for sepsis treatment. Meanwhile, we performed GO analysis on 100 DEGs to identify the pathways enriched by this gene list. In addition, we constructed a PPI network combined with the RRA analysis method to finally identify 4 key genes, namely TOMM20, TOMM22, TOMM40, and MFN1.

TOMM20, one of the components of the outer mitochondrial membrane channel protein complex, is widely present in eukaryotic cells and is involved in mitochondrial protein transport. The main biological functions of TOMM20 are to recognize and direct mitochondrial presequences into the mitochondrial membrane, to facilitate the delivery and transport of mitochondrial precursor proteins in the inner mitochondrial lumen, and to maintain the level of mitochondrial fibrosis [37, 38]. Recent studies have shown that mitochondrial dysfunction plays a crucial role in the development and progression of sepsis and that TOMM20, as one of the components of the outer mitochondrial membrane channel

protein complex, plays an important role in sepsis. It has been shown that TOMM20 is involved in mitochondrial activation and endoplasmic reticulum membrane-mediated stress response of immune cells. When the organism is infected, immune cells release various hormones and cytokines that stimulate a rapid mitochondrial response and initiate a mitochondrial inflammatory response. TOMM20 is able to recruit other mitochondrial transport channel proteins, enhance mitochondrial water channel assembly as well as regulate mitochondrial membrane potential and calcium ion concentration, and improve the ability of mitochondria to adapt to the metabolic load in stressful situations such as antibacterial and antiviral situations [39, 40]. It has also been shown that TOMM20 can maintain the homeostasis of body metabolism by regulating the activity of the mitochondrial respiratory chain. The mitochondrial respiratory chain is the main pathway that regulates energy metabolism and ATP production. Deficiency or abnormal expression of TOMM20 affects changes in mitochondrial membrane potential, calcium ion concentration and adenylate levels, leading to impaired mitochondrial function [41]. It has been reported that TOMM20 is closely related to the inflammatory response and plays an important role in the inflammatory process. When the organism is exposed to infection or other forms of injury, immune cells release a series of cytokines, inflamma-

tory mediators and other substances that cause a systemic inflammatory response. TOMM20 influences the progression of the inflammatory response by participating in the regulation of multiple inflammatory signaling pathways and regulating processes such as apoptosis and secretion of inflammatory factors. In some cases, TOMM20 upregulation may promote the onset and maintenance of the inflammatory response [42].

TOMM22 is a mitochondrial membrane channel protein located in the outer mitochondrial membrane. As part of the central mitochondrial machinery, TOMM22 facilitates protein transport within the mitochondria by interacting with other mitochondrial proteins. It is involved in the transport of glycogen synthase, α -methylacetyl coenzyme A carboxylase, and other protein complexes. It plays a key role in energy metabolism as well as organic matter catabolism within the mitochondria [43, 44]. It has been demonstrated that TOMM22 is involved in biological processes such as the regulation of redox homeostasis within mitochondria and the control of cell death [43, 45]. In addition, the TOMM mechanism is a key molecular switch in the mitochondrial clearance program controlled by the PINK1-PARK2 pathway, and the deficiency of TOMM22 leads to the attenuation of PARK2/PARKIN mitochondrial clearance, which brings new ideas for the treatment of sepsis [46].

TOMM40 is a mitochondrial membrane channel protein that is a key component of the outer mitochondrial membrane transport complex and a member of the TOMM family that performs a variety of biological functions by participating in the maintenance of a normal chemical environment within the mitochondria and metabolic homeostasis throughout the cell. TOMM40 plays an important role in mitochondrial protein transport. It contributes to the regulation of the internal mitochondrial organic matter transport process, the stability of the electron transport chain, and photosynthesis. Deletion or malfunction of TOMM40 may lead to the production of damaged and mutated mitochondrial DNA, thus interfering to some extent with redox reactions and ATP synthesis, with implications for essential life processes such as cell survival metabolism and growth and reproduction [47, 48]. TOMM40 is involved in the sepsis-induced oxidative stress response. The oxidative stress process is one of the early events of mitochondrial damage. In sepsis conditions, this process induces undesirable consequences such as dynamic changes and depletion of mitochondria and apoptosis. In contrast, dysregulation of TOMM40 may weaken mitochondrial channel function, disrupt redox homeostasis, accelerate the development of intracellular interlayer permeability, and increase drastic environmental changes inside and outside the mitochondria. Further aggravating the situation to develop to atrophy and regression, especially when the function of vital organs such as heart, lung, liver and kidney is lost, TOMM40 may also cause multi-factor-induced apoptosis of immune cells [49, 50].

MFN1 is a member of the mitochondrial fusion protein gene family, which mainly encodes for interactions with other fusion proteins and regulatory factors responsible for the initiation of transmembrane fusion events during internal

mitochondrial fusion. It also plays an important role in the maintenance of mitochondrial function, redox homeostasis, and apoptosis [51, 52]. MFN1 is involved in the sepsis-induced oxidative stress response. The oxidative stress process is one of the early events in many diseases and has a key role in the development of sepsis. Dysregulation of MFN1, in turn, may reduce mitochondrial function, leading to the production of free radical damage, such as huge amounts of ROS and RNS in cells, inducing the release of inflammatory mediators and changes in muscle dynamics and apoptosis, thereby increasing the risk of adverse outcomes in organ-level ecosystems and MODS [53, 54].

CONCLUSION

In this study, we used a bioinformatics analysis method, RRA, to integrate five gene microarray datasets to identify pivotal genes associated with mitochondrial autophagy in sepsis. Gene ontology (GO) functional annotation results show that these hub genes are mainly enriched in mitochondrial transport and establishment of protein localization to the mitochondrion. Finally, we constructed the PPI network with the top 100 genes obtained from the RRA method analysis. Based on the RRA results, the PPI results and the mitochondrial autophagy-related genes we found in the Reactome Pathway Database, we finally identified four key genes as TOMM20, TOMM22, TOMM40, and MFN1, respectively.

This study integrates bioinformatics data to provide a preliminary exploration of the identification of mitochondrial autophagy-related genes in sepsis and to enrich the pathogenesis of sepsis. This study provides potential targets and preliminary evidence for the treatment of sepsis, but further biological experiments are needed to confirm the results of this study.

LIST OF ABBREVIATIONS

BP	=	Biological Process
CC	=	Cellular Component
GEO	=	Gene Expression Omnibus
GO	=	Gene Ontology
MF	=	Molecular Function
NCBI	=	National Center for Biotechnology Information
PPI	=	Protein-protein Interaction
RRA	=	Robust Rank Aggregation

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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