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Gene Expression Pattern in Lethal Sepsis and Non-Fatal Sepsis

Hong Zhang[a], Tong Xue[b], Changzhan Guo[c], Qianqian Wang[d], Huazeng Yin[e], Wei Guo[f*]

Abstract

Sepsis is one of the oldest and most complex syndromes in medicine and a common disease with high mortality. Although the treatment of sepsis has attracted attention from people, it still has a high mortality rate. Recent research has focused on exploring the association of genes between lethal sepsis and nonfatal sepsis, while the association mechanism remains unclear. In this study, we explored different expression patterns of genes in lethal sepsis and non-fatal sepsis by analyzing gene expression data sets for lethal sepsis and non-fatal sepsis. As a result, genes up- and down-regulated representative expression pattern in both sepsis while genes and functional levels have opposite phenomena. In non-fatal sepsis, genes down-regulated in lethal sepsis are involved in Toll-like receptor signaling pathways, biologically related processes such as negative regulation of immune responses, and signaling pathways like protein processing in the endoplasmic reticulum. In non-fatal sepsis, genes up-regulated in lethal sepsis are involved in the regulation of the actin-based process, regulation of glucose import, biological processes like protein K48 linked to ubiquitination, and signal processing such as viral myocarditis as well as antigen processing and introduction. In conclusion, our results provide a framework for a comprehensive analysis of the expression patterns of lethal sepsis and non-fatal sepsis to determine effective molecular characteristics for clinical use.

Keywords: lethal sepsis, non-fatal sepsis, genes, biological processes, signaling pathways

Introduction

Sepsis is mainly caused by the body's inflammatory response to infection, with morbidity and mortality high in the world (Schlegel et al, 2017; Nunnally and ME,2016). The risk of death from sepsis is 30%, severe sepsis 50%, and septic shock 80%. The inflammatory response to the disease is divided into three phases: sepsis, severe sepsis, and septic shock. It ultimately leads to an increased risk of organ failure and death (Gustot et al, 2009). The main features of sepsis are fever or diarrhea, tachycardia, leukoplakia, leukocytosis or leukopenia (Sganga et al, 2015). The most common neonatal arrhythmia in patients with sepsis is atrial fibrillation (Keller et al, 2017). In addition to the above-mentioned main symptoms, sepsis can cause other complications, such as acute lung injury, acute kidney injury, inflammatory heart injury, and ARDS (Hatakeyama et al, 2014; Toner and McAuley,2015). Currently, the most common cause of sepsis is Gram-positive bacterial pathogens, and also may be other bacteria, fungi or viruses (Richter et al, 2017; Rello and Valenzuela-Sánchez,2017). In genetics, genome-wide joint studies have determined that mutations in the FER gene are associated with a reduced risk of sepsis death from pneumonia (Rautanen et al, 2015). Mitochondrial SNP may be involved in the pathogenesis of sepsis (Han et al, 2017). At the same time, the FPR 2/ALX gene rs11666254 polymorphism is a functional SNP with increased susceptibility to post-traumatic sepsis (Zhang et al, 2017) In addition, in the

[a]Department of Nursing, Shandong Qingdao West Coast New Area Traditional Chinese Medicine Hospital (Shandong Qingdao Huangdao District Traditional Chinese Medicine Hospital), Qingdao 266500, Shandong Province, China.
[b]Hemodialysis Room, Shandong Qingdao West Coast New Area Traditional Chinese Medicine Hospital (Shandong Qingdao Huangdao District Traditional Chinese Medicine Hospital), Qingdao 266500, Shandong Province, China.
[c]Shandong Qingdao West Coast New Area Disease Control and Prevention Center Office, Qingdao 266400, Shandong Province, China.
[d]Shandong Qingdao West Coast New Area Talent Market Health Subsector Office, Qingdao 266400, Shandong Province, China.
[e]Shandong Qingdao Huangdao District Market Supervision Authority, Comprehensive administrative law - enforcement group of nine squadrons of the market,China
[f]Department of Neurosurgery, Shandong Qingdao West Coast New Area Traditional Chinese Medicine Hospital (Shandong Qingdao Huangdao District Traditional Chinese Medicine Hospital), Qingdao 266500, Shandong Province, China.
**Corresponding Author: Wei Guo*
Email: guowei1876@163.com

patients confirmed by bacteriology, only the rs 2664349 genotype (MMP-16 gene) was significantly associated with increased risk, while rs 2569190 genotype (CD 14 gene) and rs 4073 genotype (IL 8 gene) were significantly associated with the risk of sepsis. The risk of rs 1800629 (lta gene) genotype and rs 1341023 (bpi gene) and Gram-negative increased significantly (Esposito et al, 2014). At present, researchers have studied the pathogenesis of genes in sepsis from various aspects with some progress. For example, in the study of neonatal sepsis, down-regulation of miRNA-26a promotes a significant up-regulation of IL-6 in blood mononuclear cells and serum, thereby regulating the immune response and pathogenesis of sepsis (Cheng et al, 2018). In addition, MALAT1 aggravates the heart inflammation and dysfunction of sepsis by activating p38MAPK / NFκB signaling pathway, which can be used as a diagnostic marker and therapeutic target for sepsis(Chen et al, 2018). Meanwhile, miR-155 up-regulates JNK-associated inflammatory signaling and Arrb2-mediated immunosuppression to improve survival in patients with advanced sepsis (Zhou et al, 2017). Besides, down-regulation of miR-375 inhibits the regulation of the JAK2-STAT3 pathway in advanced sepsis (Sheng et al, 2017). Although scientists study sepsis in all aspects, identifying, judging and treating it remains a challenge for clinicians (Sheng et al, 2017). The above research results deepen our understanding of sepsis and provide a theoretical basis for the study of genes in lethal sepsis and non-fatal sepsis.

In this study, we first determined the representative expression patterns involved in the development of nonfatal sepsis and fatal sepsis by analyzing the data set for sepsis. Further comprehensive analysis showed that in terms of gene and function, reverse pattern association exhibited during progression of nonfatal sepsis and fatal sepsis while negative regulation of immune response, and antigen processing and introduction signaling pathways contributed to the reverse non-fatal sepsis-fatal sepsis association, respectively. We further analyzed the biological characteristics of the corresponding genes in the non-fatal sepsis and lethal sepsis anti-expression patterns. In general, we studied the expression patterns of genes in non-fatal sepsis and lethal sepsis, and finally identified genes that were expressed in opposite directions, further obtaining the biological characteristics and signaling pathways. This provides a theoretical basis for the clinical study of non-fatal sepsis and the development of fatal sepsis.

Materials and Methods

Data resource

NCBI (National Center for Biotechnology Information) refers to the National Center for Biotechnology Information, and the GEO database (https://www.ncbi.nlm.nih.gov/geo/) is created and maintained by the National Center for Biotechnology Information NCBI (Barrett et al, 2013). The original intention of the design was to collect and sort out various expression chip data, but later added various chips such as methylation chips, lncRNA, miRNA, CNV chips, and even high-throughput sequencing data. Whole blood genetic data for fatal sepsis and non-fatal sepsis were first collected from the GEO database. The data set is numbered GSE54514(Parnell et al, 2013), comprising 31 non-fatal sepsis and 96 lethal sepsis. The data set was collected daily for 5 days from a sepsis patient in the intensive care unit. RNA was extracted from whole blood samples and detected with an Illumina HT-12 gene expression chip consisting of 48,804 probes.

Identification of gene clusters with consistent expression patterns

To further explore the pattern of gene expression during the progression of nonfatal sepsis and fatal sepsis, we placed the expression matrix of the gene in robust model gene selection, using self-organizing maps (SOM) for data preprocessing and linear regression. In learning algorithms, SOM simulates the dynamics of information processing between excitation, coordination and inhibition, and competition between biological neurons to guide the learning and working of the network, unlike the network of multi-layer neural networks (MLP)whose error is considered as a criterion for the algorithm. The basic idea of competing neural networks is that the neurons in the competition layer of the network compete for the opportunity to respond to the input mode. Finally, only one neuron becomes the winner of the competition, which represents the classification of the input pattern. Finally, gene clusters with highly similar expression patterns were identified to provide a comprehensive analysis of the pattern association between progression of nonfatal sepsis and nonfatal sepsis.

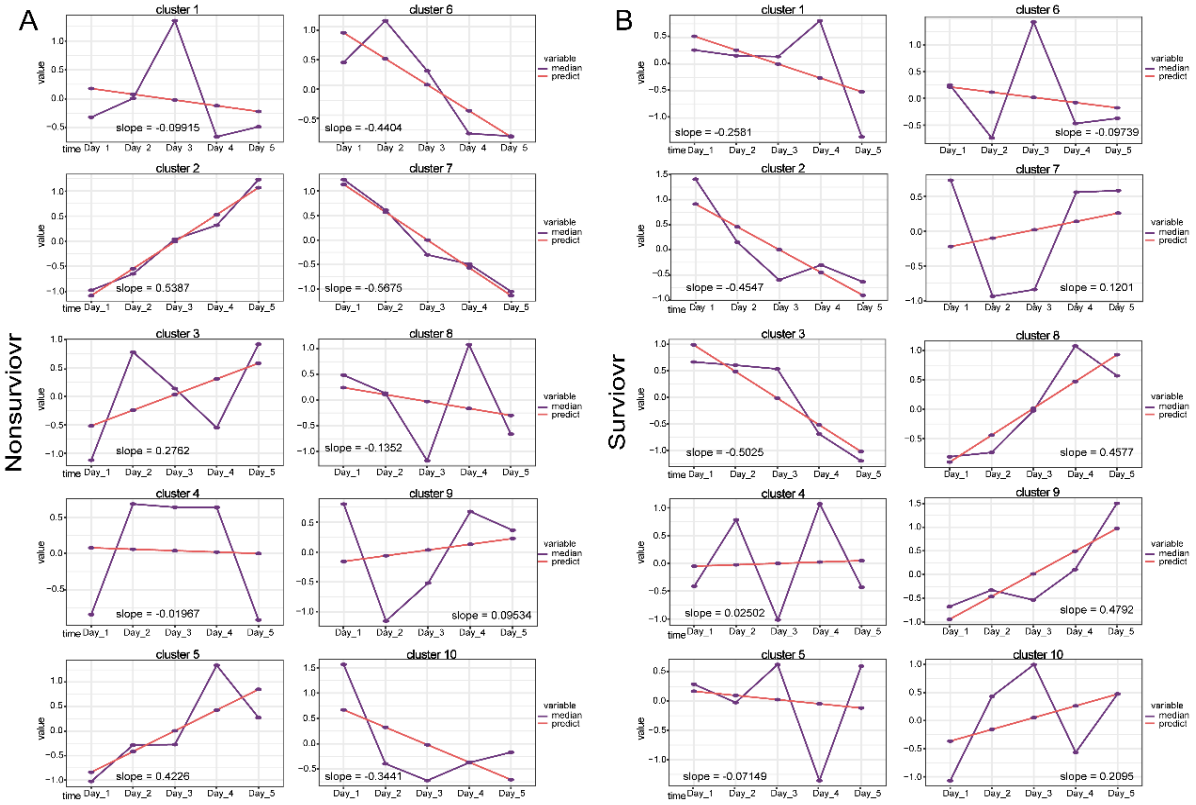
Enrichment analysis

Exploring the functions and signaling pathways involved in gene involvement often helps to study the molecular mechanisms of disease, and the

enrichment analysis of functions and pathways for genes that up-regulate expression is an effective means to explore the underlying mechanisms of sepsis. Therefore, we performed 250,000 and 2327 genes with different expressions using the R language Clusterprofiler package (Yu et al, 2012) for Go function and KEGG pathway enrichment analysis. ClusterProfiler is a Bioconductor software package that provides statistical analysis and visualization of functional clustering of gene sets or gene clusters.

Result

Gene expression in fatal sepsis and non-fatal sepsis was clustered using self-organizing neuron mapping by analyzing the data of fatal sepsis and non-fatal sepsis in human whole blood (see materials and methods), we explore the special expression patterns of genes in the pathogenesis of two phenotypes of sepsis, and performed the same procedure for the recognition of gene clusters with specific expression patterns. Whole-blood RNA expression profile data of patients with and without fatal sepsis and normal control samples were downloaded from GEO. Inconsistent expression in these genes may be responsible for the transition from nonfatal sepsis to fatal sepsis. To further analyze the expression patterns of genes in lethal sepsis and non-fatal sepsis, we used self-organizing neuron mapping and linear regression methods for feature selection according to genes for lethal sepsis and non-fatal sepsis. After self-organizing neuron mapping analysis, clustering analysis of 16070 genes from lethal sepsis and non-fatal sepsis resulted in 10 gene clusters (termed cluster1–cluster10) (Figure 1A-D). In addition, in terms of the onset of sepsis, it was observed that lethal sepsis and non-fatal sepsis have specific gene expression patterns (up- and down-regulation), respectively. Gene clusters 2, 3, 5, 9 of lethal sepsis are up-regulated, 1, 4, 6, 7, 8, 10 are down-regulated, while gene clusters 4, 7, 8, 9, 10 in non-fatal sepsis Up, 1, 2, 3, 5, 6 down. The median value of gene expression of the lethal sepsis gene clusters 1, 3, 4, 8, 9, 10 is significantly different from that predicted by linear regression, but in the gene cluster of non-lethal sepsis, 4, the median value of gene expression at 5, 6, 7, 10 differs greatly from that predicted by linear regression. Table I shows the number of distributions of 16670 genes in each gene cluster. Linear regression predicts the expression level of each gene cluster as shown in Table II. According to linear regression, the gene clusters 2, 3, 4, 5, 7, 8, 10 are predicted in fatal sepsis and non-fatal sepsis. It indicates that the genes of the same gene cluster are oppositely promoted or inhibited in lethal and non-fatal sepsis.



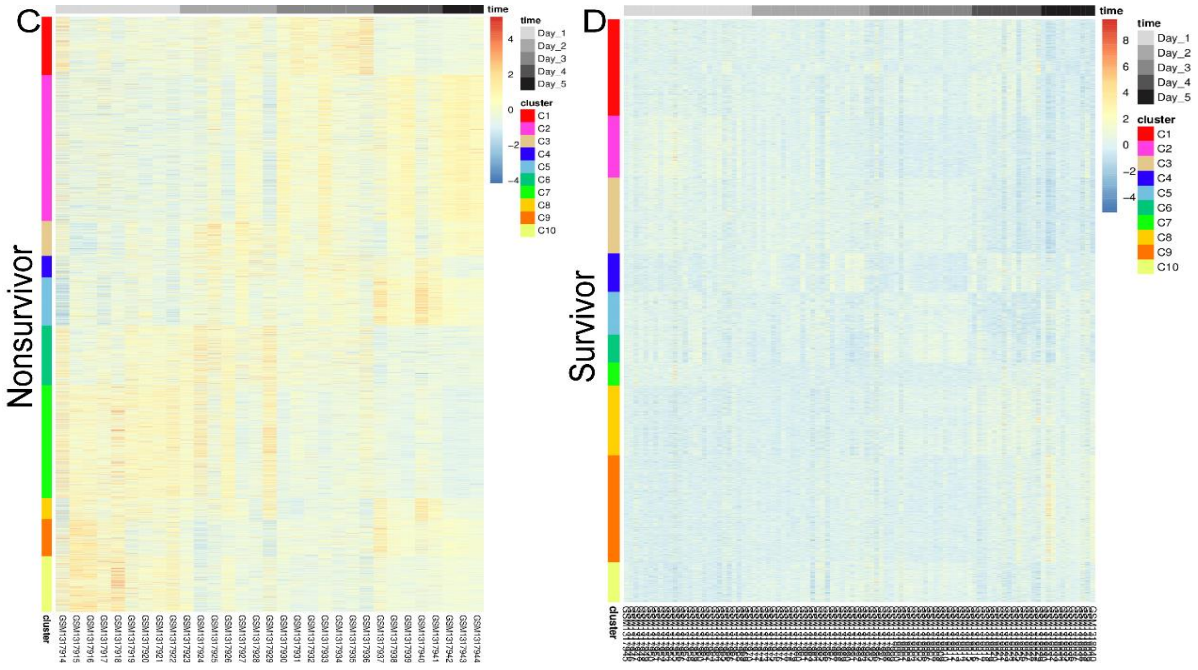


Figure 1. **Expression patterns of developmental processes in non-fatal sepsis and fatal sepsis.**

A.B. Gene clusters showing expression patterns on the timeline. The purple curve represents the median curve of gene expression values at five times, and the red curve represents the expression value of genes over time predicted by linear regression. C.D. Heat map of the magnitude of change in expression levels of each gene cluster. Each row represents the amount of expression of each gene in a different sample, and each column represents the amount of expression of all genes in the gene cluster. Each small square symbolizes each gene, and its color indicates the amount of expression of the gene. The larger the expression, the darker the color (red is up-regulated and blue is down-regulated).

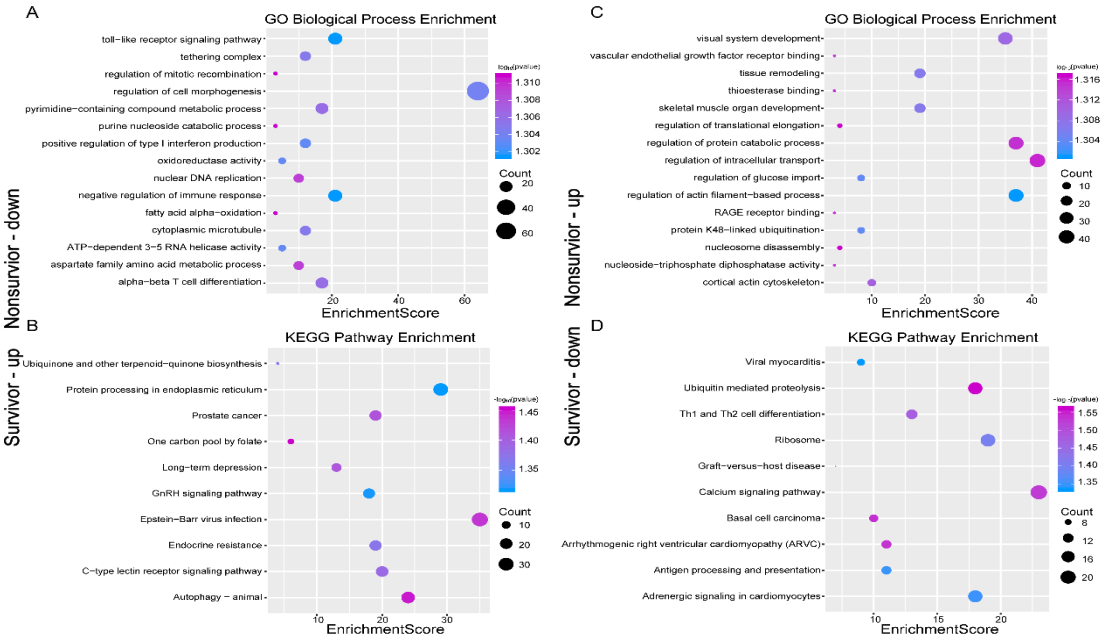


Figure 2. **Functional and pathway enrichment analysis excerpts of the reverse expression gene.**

A. C. Analysis excerpt of GO function enrichment in reverse expression genes from blue to purple, the enrichment increases significantly. The larger the circle, the greater the proportion of the module gene in GO function entry gene. A.

Analysis excerpt of KEGG pathway enrichment in reverse expression genes from blue to purple, the enrichment increases significantly. The larger the circle, the greater the proportion of the module gene in KEGG function entry gene.

Table 1. **Distribution of whole blood genes in gene clusters in lethal sepsis and nonfatal sepsis**

cluster	1	2	3	4	5	6	7	8	9	10
sepsis survivor	2652	1718	2087	1065	1174	769	632	1924	2954	1095
sepsis_nonsurvivor	1575	3942	947	576	1308	1608	3046	577	998	1493

Table 2 Linear regression predicts gene expression in gene clusters

cluster	sepsis survivor	sepsis_nonsurvivor
1	-0.2581	-0.09915
2	-0.4547	0.5387
3	-0.5025	0.2762
4	0.02502	-0.01967
5	-0.07149	0.4226
6	-0.09739	-0.4404
7	0.1201	-0.5675
8	0.4577	-0.1352
9	0.4792	0.09534
10	0.2095	-0.3441

Obtaining genes that express differences in lethal sepsis and non-fatal sepsis

Studies of differentially expressed genes in lethal sepsis and nonfatal sepsis can reveal the role of genes in expression between different phenotypes. Based on the above results, we obtained gene clusters that differed in the expression of lethal sepsis and non-fatal sepsis. Among them, gene clusters 1, 2, 3, 5, 6 were negatively correlated with non-fatal sepsis, and gene clusters 4, 7, 8, 9, 10 were positively associated with non-fatal sepsis, gene clusters 1, 4, and 6. 7,8,10 were negatively associated with lethal sepsis, and gene clusters 2, 3, 5, and 9 were positively associated with lethal sepsis. A positive correlation indicates a positive effect in the pathogenesis of the disease, and a negative correlation indicates an inhibitory effect in the disease. Through the threshold screening: |slope|>0.25, the gene clusters 8,9 of non-lethal sepsis were significantly up-regulated, and the gene clusters 1, 2, and 3 were significantly down-regulated. The gene clusters 2, 3, and 5 of the lethal sepsis were significantly up-regulated, and the gene clusters 6, 7, and 10 were significantly down-regulated. Statistical analysis found that there were 6197 up-regulated genes and 6147 down-regulated genes in the gene cluster of lethal sepsis; 4878 up-regulated genes and 6457 down-regulated genes in the non-lethal sepsis gene cluster. The intersection of genes that express different expression in lethal sepsis and non-fatal sepsis is up-regulated in non-lethal sepsis, and there are 2,805 genes down-regulated in lethal sepsis, called this inhibition gene. In the non-fatal sepsis, 2327 genes were up-regulated in lethal sepsis, which we call promotion genes

Functional annotation of genes with different expression

Function and pathway are important mediators of the physiological response of the disease. Exploring the functions and pathways involved in the dysfunctional module gene both helps determine the upstream and downstream relationship of gene in the same pathway of the module, but also contributes to construct a molecular bridge between the module and the disease in system biology, and deepen the understanding of the underlying molecular mechanism of the disease. We performed GO function and KEGG pathway enrichment analysis on 2805 inhibitory genes and 2327 promoter genes, respectively. The enrichment of the suppressor gene showed that these genes significantly participated in 1663 GO entries and 70 KEGG pathways (Table S3, Figure 2A, B). What's more, genes participate in biological related processes such as toll-like receptor signaling pathway, negative regulation of immune response (p value=0.049968435), and signaling pathways such as Protein processing in endoplasmic reticulum (p value=0.04823849) The results of promoting gene enrichment showed 816 GO entries and 22 KEGG pathways (Table S4, Figure 2C, D). Genes are significantly involved in biological processes such as regulation of actin filament-based process (pvalue=0.49996957), regulation of glucose import, protein K48-linked ubiquitination (pvalue=0.049648321), as well as signaling pathways like viral myocarditis (pvalue=0.046350075) and antigen processing and presentation (p value=0.044857546).

Discussion

Sepsis is a systemic inflammatory response syndrome secondary to infection, being severe when terminal organ dysfunction or tissue hypoperfusion occurs while chronic disease and immunosuppression are the most common risk factors (Sweis et al, 2016). Currently, sepsis and severe sepsis remain the most common causes of death in critically ill patients in the medical intensive care unit (Trivedi et al, 2015). Although, over the past half century, researchers have made progress in identifying as well as treating patients with sepsis and reducing mortality. However, the incidence of sepsis continues to increase, which is associated with the treatment of organ dysfunction. NCBI-GEO has included a number of studies related to sepsis, contributing to our following research. First, we collected whole blood RNA data from patients with fatal sepsis and non-fatal sepsis on the NCBI Gene Expression Omnibus database (GEO Dataset), analyzing the role of gene expression patterns in disease progression according to gene expression of lethal sepsis and nonfatal sepsis. Representative gene clusters were identified from gene expression profiles of lethal sepsis and non-fatal sepsis, and the association of inverse patterns was observed at the gene and functional levels. Concerning function, in non-fatal sepsis, genes down-regulated in lethal sepsis are involved in Toll-like receptor signaling pathways, biologically related processes such as negative regulation of immune responses, and signaling pathways like protein processing in the endoplasmic reticulum. In non-fatal sepsis, genes up-regulated in lethal sepsis are involved in the regulation of the actin-based process, regulation of glucose import, biological processes like protein K48 linked to ubiquitination, and signal processing such as viral myocarditis as well as antigen processing and introduction. In the study of Khakpour S, Toll-like receptors are mediated through NF-κB and MAP kinases to activate the inflammatory pathways in endothelial cells, which make difference to the health and pathological response to infection and sepsis (Khakpour et al, 2015). Meanwhile, the Toll-like receptor signaling pathway is central to initiation of an innate immune response, and its activation by bacterial endotoxin leads to sepsis, and thus Toll-like receptor signaling pathway regulators can serve as potential drugs for inflammation and sepsis (Kuzmich et al, 2017). Recent studies have shown that negative regulation of immune responses is a key to maintaining peripheral homeostasis and regulating immune responses, which brings new insights into immune homeostasis mechanisms and sepsis (Luan et al, 2012). The endoplasmic reticulum (ER) is involved in the folding and transport of proteins in eukaryotic cells, which can cause endoplasmic reticulum stress when misfolded proteins or accumulation of unfolded proteins occur (Wang et al, 2016). Incresing evidence suggest that ER stress is involved in the pathogenesis of sepsis (Khan et al, 2015). Erythrocyte actin filaments are not only a dynamic structural cytochrome, but their assembly and disassembly play an important role in erythrocyte membrane function (Gokhin et al, 2016). In addition, Arkadia-mediated K48-linked Nrf2 ubiquitination was found to positively regulate nuclear Nrf2 levels in response to oxidative stress (McIntosh et al, 2018). In the study with respect to dengue virus (DENV), it was found that the ubiquitination of the dengue virus NS1 protein may affect the replication of DENV (Giraldo et al, 2018). Dendritic cells are antigen-presenting cells that regulate innate and adaptive immunity and prolong life during the progression of sepsis (Wu et al, 2018). There are relatively few studies on regulating glucose import and viral myocarditis, and no correlation with sepsis is found. It is a key direction for our future research. However, the study concering the process of the regulation of actin filament and protein K48-linked ubiquitination didn't find the effect on sepsis, but our analysis showed that it regulates the process of lethal sepsis and non-fatal sepsis, which is the direction of further research.

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