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Decoding Sepsis Shock Genetics: Immune Pathway Disruption and Target Discovery

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Abstract: Recent advancements in understanding the pathogenesis and therapeutic approaches for septic shock have been made; however, research elucidating genetic-level mechanisms remains limited. This study aims to explore genetic contributors to septic shock pathogenesis and evaluate differentially expressed genes as potential diagnostic targets. Utilizing the GSE95233 dataset from the GEO database, we compared blood samples from 51 septic shock patients and 22 healthy controls via R language and GEO2R tools. We identified 38 differentially expressed genes (21 upregulated, 17 downregulated). GO functional enrichment analysis of differential genes was carried out using the Cluster Profiler package in R language, and the results showed that most of the differential genes were distributed in T cells, which were related to the development, differentiation, recognition, and clearance of T cells, and the regulation of inflammatory cytokines, which directly affected immune signaling and immune killing pathways. We also analyzed the interaction network between differentially expressed proteins with the help of string online website and MCODE plug-in in Cytoscape 3.8.2, and identified 9 core genes, including *BCL11B* and *TBX21* genes related to immune cell development and differentiation, *CD247, CD3G, CD8A* and *S1PR5* genes related to T cell signaling, *PRF1* and *GNLY* genes related to immune cell killing activity. Through the evaluation of gene function and the prediction of the mechanism of action, we determined that *BCL11B, TBX21, S1PR5, CD247, PRF1* and other differential genes can be used as new targets for research to prevent the exacerbation of sepsis and treat septic shock.

Keywords: Sepsis shock, R language, GEO database, Differential genes, Bioinformatics

1. Introduction

1.1. Definition

Sepsis is defined by the Third International Consensus as life-threatening organ dysfunction caused by a dysregulated host response to infection, which is a syndrome of physiological, pathological, and biochemical abnormalities caused by infection and an important public health problem. Sepsis shock (also known as septic shock) is a subtype of late-stage sepsis that causes severe circulatory, cellular, and metabolic abnormalities and a high risk of mortality [1].

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1.2. Epidemiological features

Global sepsis incidence declined by 18.8% between 1997–2017, yet it caused approximately 11 million deaths in 2017, reflecting a 52.8% reduction in mortality compared to previous decades. Despite declining morbidity and mortality, sepsis remains one of the biggest health problems worldwide, particularly in sub-Saharan South Africa [2]. It is worth noting that in China, in 2017, there were about 3 million sepsis patients and about 710,000 related deaths, with a mortality rate of 32%; Normalized, the incidence rate was approximately 214 per 100,000 and the mortality rate was approximately 43.3 per 100,000 [3]. These statistics highlight the significant burden sepsis places on society and the urgent need for more effective diagnostic approaches.

In terms of distribution, the incidence of sepsis varies significantly from country to region, and is affected by a variety of factors. According to a survey, the incidence of sepsis is characterized by the following characteristics: it is higher in developing countries, about 66/100,000~300/100,000; The incidence is higher in older people and children than in other age groups; The incidence is higher in females than in males. The mortality rate of sepsis is also affected by a variety of factors, including the age of the patient, the underlying disease, the type of infectious agent, the treatment strategy, etc., and the global mortality rate in 2017 ranged from 27%~36%, accounting for 19.7% of the total number of deaths in the world.

When sepsis progresses to septic shock, the case fatality rate increases dramatically, and despite many new advances in the treatment of septic shock in recent years, the case fatality rate is still higher than 40 percent [2]. It can be seen that early diagnosis of septic shock have an important impact on the survival of patients.

1.3. Pathogenesis

Previous studies have shown that the pathogenesis of sepsis involves many aspects, including imbalance of inflammatory response, immune dysfunction, macrophage autophagy and other pathological processes.

An imbalance in the inflammatory response is key to the onset and exacerbation of sepsis. In the early stages of sepsis, pro-inflammatory cytokines are released in large quantities, and although this is beneficial for the elimination of pathogens, the resulting inflammatory factor storm can cause a series of damages; In the later stage of sepsis, a large number of anti-inflammatory cytokines are released to reduce the damage of inflammatory response to the body, but excessive anti-inflammatory factors will lead to the depletion of pro-inflammatory factors, the patient's resistance will be reduced, and the patient will be susceptible to infection, and eventually multiple organ dysfunction syndrome [4, 5].

Immune dysfunction, particularly Th1/Th2 polarization, plays a critical role in sepsis progression. Early hyperinflammation driven by Th1 cells transitions to immunosuppression mediated by Th2 responses, increasing susceptibility to secondary infections [6-9]. In addition, the maturation and activation of macrophages also play an important role in the development of sepsis, and the M1 subtype of macrophages can release inflammatory factors to cause inflammatory responses, which are more active in the early stage of sepsis. The M2 subtype releases anti-inflammatory factors and participates in the immunosuppression of sepsis in the later stages of sepsis to cause secondary infections [10, 11].

It is worth noting that at the genetic level, there are few studies on how sepsis develops into septic shock, so this paper hopes to predict the potential pathogenesis of septic shock at the genetic level with the help of bioinformatics data, so as to provide new ideas for the timely detection of septic shock.

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In summary, sepsis is a major public health problem that brings a great burden to patients, families and society. Preventing the onset of septic shock is of great significance to the survival of patients. In recent years, with the development of bioinformatics, we have been able to analyze the occurrence and development of diseases at the genetic and molecular levels. However, the pathogenesis of septic shock at the genetic level has not been clearly studied, so this paper analyzes the bioinformatics of relevant samples in the GEO database to predict the potential pathogenesis of septic shock at the genetic level, hoping to provide new ideas for the subsequent research on the diagnosis of septic shock.

2. Methods

2.1. Sources and selection of genetic data

In this paper, the GEP microarrays provided by the dataset numbered GSE95233 in the GEO database are selected using the GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array. The study samples consisted of admitted blood samples from 51 patients with septic shock and 22 healthy volunteers.

2.2. Extraction and analysis of differential genes

Differential genes were screened using R language and GEO2R with thresholds of $log_2FC > 3.5$ (P <0.05) for upregulation and $log_2FC < -2.5$ (P <0.05) for downregulation. Through the above conditions, the differential genes in the blood of healthy people and patients with septic shock were screened, and the ggplot2 package [12] in R language was used to plot these data into more intuitive volcano maps and heat maps.

2.3. Functional enrichment analysis and pathway annotation of differential genes

The Cluster Profiler package [13-16] in R language was used to analyze the GO function and KEGG pathway of differentially differentiated genes. In terms of GO function, molecular function (MF), biological pathway (BP), and cellular component (CC) were analyzed. The filter conditions of each pathway were set as: P. adjust less than 0.1 (MF), P. adjust less than 0.05 (BP), P. adjust less than 0.05 (CC), and then the analysis results were filtered and plotted using the ggplot2 package in R language. In terms of KEGG pathway analysis, the KEGG signaling pathway analysis of key differential genes was carried out in this paper, and the interaction relationship between the proteins of each gene expression product was obtained. Under the condition of P. adjust less than 1, the first 10 KEGG pathways were screened and plotted using the ggplot2 package.

2.4. Construct the protein interaction network of differential genes and screen the cor genes:

The interaction between differential genes was analyzed with the help of the STRING database (https://string-bd.org/), and the PPI network was generated online. In addition, the MCODE plug-in in Cytoscape 3.8.2 was used to analyze and screen the differentially interacting genes. By traversing outward from the densely connected regions in the PPI, the density of each local neighborhood was calculated to isolate the dense areas and remove the poorly connected nodes, so as to find out the core genes associated with septic shock.

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3. Results

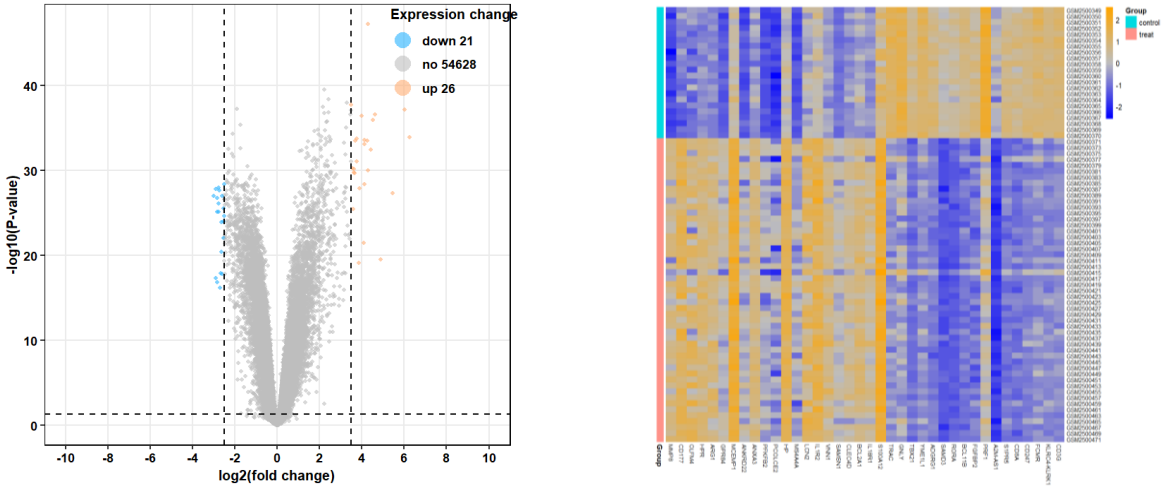
3.1. Genes expressed in blood samples from patients with septic shock that are significantly different from those of healthy people

Analysis via GEO2R and R language identified 38 DEGs in septic shock patients versus controls, including 21 upregulated genes (e.g., *S100A12*, *IL18R1*) and 17 downregulated genes (e.g., *CD3G*, *PRF1*). The differential genes are shown in Table 1.

Table 1: Differential genes in blood samples from patients with septic shock and healthy individuals

Gene Types	Filter Conditions	Genes
Upregulated	$log_2FC > 3.5, P\_value < 0.05$	*S100A12*、*IL18R1*、*BCL2A1*、*CLEC4D*、*SAMSN1*、*VNN1*、*IL1R2*、*LCN2*、*MS4A4A*、*HP*、*PCOLCE2*、*PFKFB2*、*ANXA3*、*ANKRD22*、*MCEMP1*、*GPR84*、*ARG1*、*HPR*、*OLFM4*、*CD177*、*MMP8*
Downregulation	$log_2FC < -2.5, P\_value < 0.05$	*CD3G*、*KLRC4-KLRK1*、*FCMR*、*CD247*、*CD8A*、*S1PR5*、*A2M-AS1*、*PRF1*、*FGFBP2*、*BCL11B*、*RORA*、*SAMD3*、*ADGRG1*、*YME1L1*、*TBX21*、*GNLY*、*TRAC*

In addition, the above differential genes were plotted into volcano maps (Figure 1-a. The data used in this figure is the expression amount corresponding to the ID of the microarray platform, considering that some gene names have multiple IDs or some IDs do not have corresponding gene names, so the number of IDs corresponding to the differential genes displayed in the volcano diagram is more than the number of differential genes) and heat maps (Figure 1-b) using the ggplot2 package in the R language.



(a) (b)

Figure 1: (a)Volcano diagram of differential genes, where the orange dots represent the up-regulated genes, and the blue dots indicate the down-regulated genes. (b) Differential gene heat map, in which the blue-green band on the left is for healthy people (control group), and the red-pink band on the left is for patients with septic shock (treat group), and the expression level of single gene increases from blue to yellow.

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3.2. Functional enrichment analysis and pathway annotation of differential genes

With the help of the Cluster Profiler package in R language, we performed GO functional enrichment analysis of differential genes from three aspects: MF, CC, and BP. Then, the first ten entries of MF, CC, BP were taken and the barplot function in the ggplot2 package in R language was used to plot the bar chart (Figs. 2-a, 2-b, and 2-c). We found that in MF, differential genes were mainly associated with: Immune receptor activity, Calcium-dependent protein binding, MHC class Ⅰ protein binding, Serine-type endopeptidase/peptidase activity, etc.; In CC, differential genes were mainly associated with: Specific/tertiary granule, α-β T cell receptor complex, etc.; In BP, differential genes were mainly associated with: α-β T cell activation, Lymphocyte/T cell differentiation, Leukocyte/Lymphocyte/T cell mediated immunity, Lymphocyte differentiation, Cell surface receptor, etc.

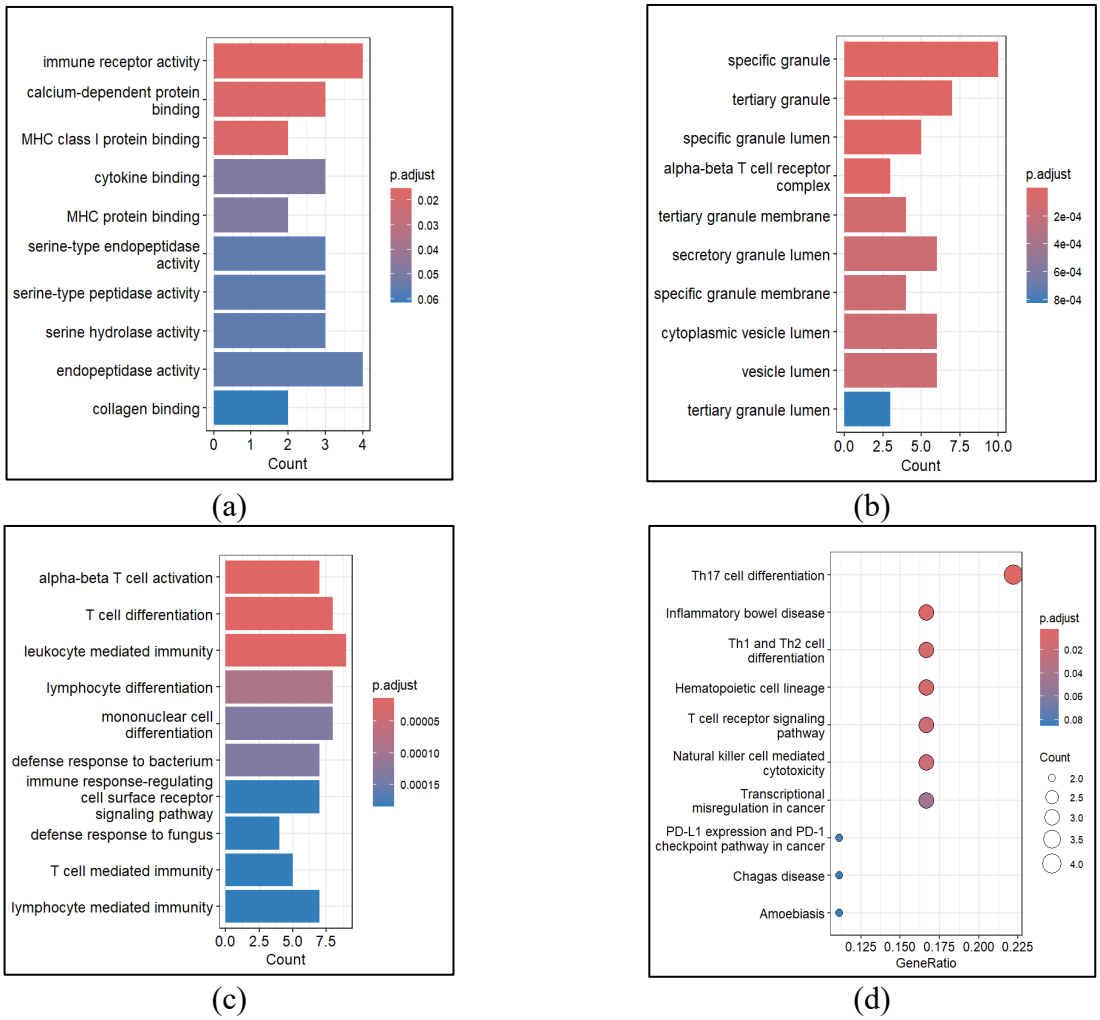

Figure 2: (a) MF enrichment analysis of differential genes. (b) CC enrichment analysis of differential genes. (c) BP enrichment analysis of differential genes. (d) KEGG pathway analysis of differential genes.

In addition, we analyzed the KEGG pathways of the differential genes and plotted the first ten pathways into a bubble plot using the dotplot function (Fig. 2-d), and we found that the KEGG pathways associated with the differentially genetically related are Th 1/2/17 cell differentiation, T cell receptor signaling pathway, natural killer cell mediated cytotoxicity, etc.

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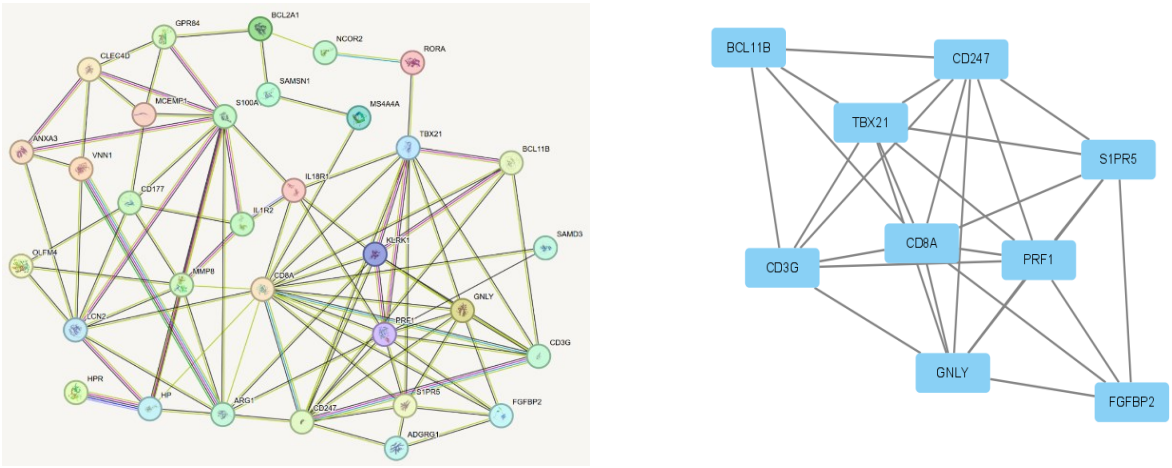
3.3. Protein interaction networks and screening of core genes

After analyzing and constructing the PPI network online with the help of the STRING website, and eliminating isolated nodes, we obtained 32 interacting differential genes (Figure 3-a).

With the help of the MCODE plug-in in Cytoscape 3.8.2, we analyzed and screened the above differential genes, and we obtained nine interacting core genes (Figure 3-b), which are *BCL11B, PRF1, S1PR5, CD247, CD3G, CD8A, TBX21, GNLY* and *FGFBP2*, all of which are down-regulated genes.



(a) (b)

Figure 3: (a) Protein Interaction Network (PPI). (b) Core Genes.

4. Discussion

In this study, we screened 38 differentially GSE95233 genes associated with septic shock through bioinformatics analysis of datasets. Then, we further analyzed the signal enrichment pathways and gene annotation of these differential genes, and the results showed that the differentially related genes associated with sepsis are involved in inflammatory responses such as T cell maturation and differentiation, immune cell-to-cell signaling, granulocyte and natural killer cell-mediated immunity, lymphocyte-mediated immune regulation, and the body's defense against fungi and bacteria. Existing studies have shown that sepsis is caused by the disorder of the release of pro-inflammatory factors and anti-inflammatory factors, which is manifested in the early stage by the release of a large number of pro-inflammatory factors, the overactivation of the immune system, and the killing of healthy cells. Late stages, including septic shock, are characterized by massive release of anti-inflammatory factors, weakened immune defenses, and inability to fight foreign pathogen invasion, ultimately leading to cross-infection and multi-organ failure and death [17].

Considering that the occurrence of septic shock is the result of multi-gene interaction, we screened 9 core differential genes by PPI analysis, including *BCL11B, TBX21, S1PR5, CD247, CD3G, CD8A, PRF1, GNLY, and FGFBP2*.

BCL11B, encoding a C2H2 zinc finger transcription factor, regulates T cell development and identity maintenance. Its dysregulation is implicated in pathologies ranging from malignancies to sepsis. Studies have shown [18] that pre-T cell apoptosis in the thymus of mice with *BCL11B* knockout eventually develops into T cell malignancy due to hindered T cell maturation. Studies by V. Le Douce et al. [19] have shown that dysregulated expression of *BCL11B* is associated with a variety of pathologies such as cancer, myocardial hypertrophy, AIDS, and sepsis. In a study of

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neonatal sepsis [20], L.H. et al. found that has-miR-150 targeted inhibition of *BCL11B* had an effect on the development of sepsis.

TBX21 protein is a Th1 cell-specific transcription factor, which promotes Th precursor cells to initiate Th1 lineage development and inhibits Th precursor cells to initiate Th2 and Th17 genetic programs [21, 22], and Bartsch, P et al. [23] showed that mice with abnormal *TBX21* defects will lose their ability to resist bacteria such as Staphylococcus aureus, which in turn leads to bacterial sepsis, which is related to the production of septic shock; At the same time, this protein activates the transcription of genes related to Th1 cell function, including the iconic Th1 cytokine interferon-γ (IFNG) gene and the chemokine receptor CXCR3 gene [24]. Almansa, R et al. [25] showed that *TBX21* affects the development of sepsis by participating in T-cell immunity. In addition, the *TBX21* gene is also involved in the developmental and immune processes of natural killer cells (NK) and has been linked to the occurrence of sepsis [25, 26].

S1PR5, a sphingosine-1-phosphate receptor, modulates cellular processes such as proliferation and apoptosis. Its downregulation in septic shock may impair lymphocyte trafficking and immune coordination. Upregulation of *S1PR5* gene expression promotes T cell differentiation and has a significant impact on the transport of lymphocytes and hematopoietic cells [27]. In a study of chronic obstructive pulmonary disease [28], the researchers found that the expression of *S1PR5* was significantly related to the phagocytosis of macrophages, which can be used as a targeted therapeutic strategy for chronic inflammatory diseases and may also be helpful in the study of septic shock. The results of Tian Y. et al. [29] showed that the upregulation of *S1PR5* expression increased the survival rate of sepsis patients, while the results of this study showed that the expression of *S1PR5* in the blood of patients with septic shock was down-regulated, and the conclusions of the two were consistent, which can confirm that *S1PR5* has a certain relationship with the occurrence of sepsis shock.

CD247, *CD3G*, and *CD8A* receptor protein genes are used to encode T cell surface receptor proteins, which are involved in antigen recognition and cell signaling. Among them, the *CD3G* gene encodes the γ chain in CD3, and the *CD247* gene encodes the ζ chain in CD3, which together with CD3-δ and T cell receptor α/β and γ/δ heterodimers form the TCR-CD3 complex, and the cytoplasmic domains of all CD3 chains contain Immunoreceptor Tyrosine-based Activation Motifs (ITAM) and TCR Upon binding, these motifs are phosphorylated by the *Src* family of proteins tyrosine kinases LCK and FYN, leading to the activation of downstream signaling pathways for antigen recognition and cell signaling [30-33]. A series of studies [34-37] have shown that *CD247* is involved in the occurrence of a variety of autoimmune diseases, such as systemic lupus erythematosus, rheumatoid joints, systemic sclerosis, etc., so *CD247* is closely related to the occurrence of autoimmune diseases. In addition, *CD3G* plays an important role in the dynamic regulation of TCR expression [38], and *CD247* plays an important role in thymic T cell differentiation. The protein encoded by the *CD8A* gene is present on most cytotoxic T cells, is involved in the recognition of MHC I. antigen-presenting antigen-presenting antigens, recruits the Src kinase LCK near the TCR-CD3 complex, and opens different intracellular signaling pathways by phosphorylating different substrates, affecting lymphofactor production and cytotoxic T cell activation [39]. Zeng X. and Jiang Y. et al. [40, 41] also found that *CD247, CD3G* and *CD8A* genes were the core genes of septic shock and their expression was down-regulated, which was consistent with the results of this study.

The granzyme encoded by *PRF1* and *GNLY* granzyme family genes exists in the cytotoxic granules of cytotoxic T cells and natural killer cells, and is one of the main means for cytotoxic T cells and natural killer cells to exert their functions. The *SAPLIP* protein encoded by *GNLY* has a killing effect on Mycobacterium tuberculosis and other microorganisms, and existing studies have determined that *GNLY* is closely related to the antibacterial ability of the body [42, 43], and the abnormality of *GLNY* also leads to the occurrence of a variety of pathological conditions, mainly including infection and cancer [44]. *PRF1*-encoded perforin is inserted into the target cell membrane by binding to Ca2+,

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oligomerizing to form membrane pores, killing tumor cells and virus-infected cells, and this gene plays an important role in recognizing non-self cells, which can cause immune rejection and autoimmune diseases in organ transplantation [45-49]. The *PRF1* gene has been identified as a causative factor in cellular lymphohistiocytosis (HLH) [50]. A study by Ozan, ZK et al. on neonatal sepsis [51] showed that mutations in *PRF1* occur in some patients with sepsis that lead to sepsis.

In general, at the level of cell development, the down-regulation of *BCL11B* gene expression in patients with septic shock will lead to the inability of immature T cells to develop and differentiate normally, and the T cell-related immune pathways will be blocked. The down-regulation of *TBX21* gene expression will lead to the development of T cells in the direction of Th2 and Th17, the release of pro-inflammatory factors will decrease, the release of anti-inflammatory factors will increase, and the body's immune system will be further weakened. In addition, down-regulation of the expression of *CD247, CD3G, CD8A* and *S1PR5* receptor protein expression genes on the surface of T cells will weaken the migration, infiltration, recognition and signal transmission functions of mature T cells, resulting in a decrease in immune response efficiency. In particular, the *CD8A* gene, which expresses a receptor protein that is involved in the recognition of MHC I. antigen-presenting antigens by cytotoxic T cells, greatly weakens the activation and killing function of cytotoxic T cells. In terms of killing pathogens, in addition to the *CD8A* gene, the granzyme encoded by *PRF1* and *GNLY* genes is one of the main means for cytotoxic T cells and natural killer cells to exert their functions.

However, there are some limitations in this study: individual differences such as age and gender were not considered in the selection of samples in this study, and in fact, there are some differences in the mechanism of sepsis shock among different age groups; Moreover, this study has not been experimentally verified, and the specific mechanism of differential genes needs to be further clarified through experiments.

5. Conclusion

This study utilized bioinformatics approaches to explore the genetic underpinnings of septic shock, identifying 38 differentially expressed genes (DEGs) and highlighting nine core genes (*BCL11B, TBX21, S1PR5, CD247, CD3G, CD8A, PRF1, GNLY*, and *FGFBP2*) through protein interaction network analysis. The downregulation of *BCL11B* and *TBX21* disrupts T cell lineage commitment and Th1/Th2 balance, impairing pathogen clearance and exacerbating immunosuppression. Similarly, reduced expression of *CD247, CD3G*, and *CD8A* compromises antigen recognition and T cell receptor signaling, while diminished *S1PR5* levels hinder lymphocyte trafficking. The downregulation of cytotoxic effector genes *PRF1* and *GNLY* further weakens immune cell-mediated pathogen elimination. Collectively, these findings suggest that septic shock progression is driven by a collapse in immune coordination, marked by impaired T cell functionality and diminished cytotoxic activity. These genes offer critical insights into the immune dysregulation characteristic of septic shock and highlight their potential as therapeutic targets.

References

[1] *Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801-10.*

[2] *Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study Rudd, Kristina E et al. The Lancet, Volume 395, Issue 10219, 200 – 211.*

[3] *Liu YC, Yao Y, Yu MM, Gao YL, Qi AL, Jiang TY, Chen ZS, Shou ST, Chai YF. Frequency and mortality of sepsis and septic shock in China: a systematic review and meta-analysis. BMC Infect Dis. 2022 Jun 21;22(1):564.*

[4] *van der Poll T,Shankar-Hari M,Wiersinga WJ.The immunology of sepsis[J]. Immunity, 2021,54(11):2450-2464.*

DOI: 10.54254/2753-8818/94/2025.21887

[5] Hotchkiss RS,Monneret G,Payen D.Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy[J]. Nat Rev Immunol, 2013,13(12):862-874.
[6] Shang Q, Yu X, Sun Q, Li H, Sun C, Liu L. Polysaccharides regulate Th1/Th2 balance: A new strategy for tumor immunotherapy. Biomed Pharmacother. 2024 Jan;170:115976.
[7] Wang J, Wu Y, Chen J, Zhang Q, Liu Y, Long H, Yu J, Wu Q, Feng L. Th1/Th2 Imbalance in Peripheral Blood Echoes Microglia State Dynamics in CNS During TLE Progression. Adv Sci (Weinh). 2024 Oct;11(39):e2405346.
[8] Xue M, Xie J, Liu L, Huang Y, Guo F, Xu J, Yang Y, Qiu H. Early and dynamic alterations of Th2/Th1 in previously immunocompetent patients with community-acquired severe sepsis: a prospective observational study. J Transl Med. 2019 Feb 27;17(1):57.
[9] Martin MD, Badovinac VP, Griffith TS. CD4 T Cell Responses and the Sepsis-Induced Immunoparalysis State. Front Immunol. 2020 Jul 7;11:1364.
[10] Qiu Y,Tu GW,Ju MJ,et al.The immune system regulation in sepsis:from innate to adaptive[J]. Curr Protein Pept Sci, 2019,20(8):799-816.
[11] Chen X, Liu Y, Gao Y, Shou S, Chai Y. The roles of macrophage polarization in the host immune response to sepsis.Int Immunopharmacol. 2021 Jul;96:107791.
[12] H. Wickham. ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag New York, 2016.
[13] G Yu. Thirteen years of clusterProfiler. The Innovation. 2024, 5(6):100722
[14] S Xu, E Hu, Y Cai, Z Xie, X Luo, L Zhan, W Tang, Q Wang, B Liu, R Wang, W Xie, T Wu, L Xie, G Yu. Using clusterProfiler to characterize multiomics data. Nature Protocols. 2024, 19(11):3292-3320
[15] T Wu, E Hu, S Xu, M Chen, P Guo, Z Dai, T Feng, L Zhou, W Tang, L Zhan, X Fu, S Liu, X Bo, and G Yu. clusterProfiler 4.0: A universal enrichment tool for interpreting omics data. The Innovation. 2021, 2(3):100141
[16] Guangchuang Yu, Li-Gen Wang, Yanyan Han and Qing-Yu He. clusterProfiler: an R package for comparing biological themes among gene clusters. OMICS: A Journal of Integrative Biology 2012, 16(5):284-287
[17] Qiu P, Liu Y, Zhang J. Review: the Role and Mechanisms of Macrophage Autophagy in Sepsis. Inflammation. 2019 Feb;42(1):6-19.
[18] Ehrlich LA, Yang-Iott K, Bassing CH. Tcrδ translocations that delete the Bcl11b haploinsufficient tumor suppressor gene promote atm-deficient T cell acute lymphoblastic leukemia. Cell Cycle. 2014;13:3076–82.
[19] V. Le Douce, T. Cherrier, R. Riclet, O. Rohr, C. Schwartz. CTIP2, a multifunctional protein: cellular physiopathology and therapeutic implications. M S-Med Sci, 30 (2014), pp. 797-802
[20] Huang, L., Qiao, L., Zhu, H. et al. Genomics of neonatal sepsis: has-miR-150 targeting BCL11B functions in disease progression. Ital J Pediatr 44, 145 (2018).
[21] Szabo SJ, Kim ST, Costa GL, Zhang X, Fathman CG, Glimcher LH. A novel transcription factor, T-bet, directs Th1 lineage commitment. Cell. 2000 Mar 17;100(6):655-69.
[22] Hertweck A, Evans CM, Eskandarpour M, Lau JC, Oleinika K, Jackson I, Kelly A, Ambrose J, Adamson P, Cousins DJ, Lavender P, Calder VL, Lord GM, Jenner RG. T-bet Activates Th1 Genes through Mediator and the Super Elongation Complex. Cell Rep. 2016 Jun 21;15(12):2756-70.
[23] Bartsch, P., Kilian, C., Hellmig, M., Paust, H., Borchers, A., Sivayoganathan, A., . . . Th17 cell plasticity towards a T-bet-dependent Th1 phenotype is required for bacterial control in staphylococcus aureus infection. PLoS Pathogens, 18(4). https://orcid.org/0000-0003-2739-5578, C. F. K. (2022).
[24] Yang R, Mele F, Worley L, Langlais D, Rosain J, Benhsaien I, Elarabi H, Croft CA, Doisne JM, Zhang P, Weisshaar M, Jarrossay D, Latorre D, Shen Y, Han J, Ogishi M, Gruber C, Markle J, Al Ali F, Rahman M, Khan T, Seeleuthner Y, Kerner G, Husquin LT, Maclsaac JL, Jeljeli M, Errami A, Ailal F, Kobor MS, Oleaga-Quintas C, Roynard M, Bourgey M, El Baghdadi J, Boisson-Dupuis S, Puel A, Batteux F, Rozenberg F, Marr N, Pan-Hammarström Q, Bogunovic D, Quintana-Murci L, Carroll T, Ma CS, Abel L, Bousfiha A, Di Santo JP, Glimcher LH, Gros P, Tangye SG, Sallusto F, Bustamante J, Casanova JL. Human T-bet Governs Innate and Innate-like Adaptive IFN-γ Immunity against Mycobacteria. Cell. 2020 Dec 23;183(7):1826-1847.e31.
[25] Raquel Almansa, María Heredia-Rodríguez, Esther Gomez-Sanchez, David Andaluz-Ojeda, Verónica Iglesias, Lucia Rico, Alicia Ortega, Estefanía Gomez-Pesquera, Pilar Liu, Marta Aragón, Jose Maria Eiros, Maria Ángeles Jiménez-Sousa, Salvador Resino, Ignacio Gómez-Herreras, Jesús F. Bermejo-Martín, Eduardo Tamayo. Transcriptomic correlates of organ failure extent in sepsis, Journal of Infection, Volume 70, Issue 5, 2015, Pages 445-456, ISSN 0163-4453.
[26] Yang R, Mele F, Worley L, Langlais D, Rosain J, Benhsaien I, Elarabi H, Croft CA, Doisne JM, Zhang P, Weisshaar M, Jarrossay D, Latorre D, Shen Y, Han J, Ogishi M, Gruber C, Markle J, Al Ali F, Rahman M, Khan T, Seeleuthner Y, Kerner G, Husquin LT, Maclsaac JL, Jeljeli M, Errami A, Ailal F, Kobor MS, Oleaga-Quintas C, Roynard M, Bourgey M, El Baghdadi J, Boisson-Dupuis S, Puel A, Batteux F, Rozenberg F, Marr N, Pan-Hammarström Q, Bogunovic D, Quintana-Murci L, Carroll T, Ma CS, Abel L, Bousfiha A, Di Santo JP, Glimcher LH, Gros P, Tangye SG, Sallusto F, Bustamante J, Casanova JL. Human T-bet Governs Innate and Innate-like Adaptive IFN-γ Immunity against Mycobacteria. Cell. 2020 Dec 23;183(7):1826-1847.e31.

DOI: 10.54254/2753-8818/94/2025.21887

[27] Evrard M, Wynne-Jones E, Peng C, Kato Y, Christo SN, Fonseca R, Park SL, Burn TN, Osman M, Devi S, Chun J, Mueller SN, Kannourakis G, Berzins SP, Pellicci DG, Heath WR, Jameson SC, Mackay LK. Sphingosine 1-phosphate receptor 5 (S1PR5) regulates the peripheral retention of tissue-resident lymphocytes. J Exp Med. 2022 Jan 3;219(1):e20210116.

[28] Barnawi J, Tran H, Jersmann H, et al. Potential link between the sphingosine-1-phosphate (S1P) system and defective alveolar macrophage phagocytic function in chronic obstructive pulmonary disease (COPD). PloS One . 2015;10(10): e0122771.

[29] Tian, Y. , Wang, L. , Chen, W. , Zhong, W. & Hu, Y. (2023). Screening of Potential Core Genes in the Peripheral Blood of Adult Patients with Sepsis Based on immunoregulation and Signal Transduction Functions. Shock, 59 (5), 708-715.

[30] Barber EK, Dasgupta JD, Schlossman SF, Trevillyan JM, Rudd CE. The CD4 and CD8 antigens are coupled to a protein-tyrosine kinase (p56lck) that phosphorylates the CD3 complex. Proc Natl Acad Sci U S A. 1989 May;86(9):3277-81.

[31] Osman N, Ley SC, Crumpton MJ. Evidence for an association between the T cell receptor/CD3 antigen complex and the CD5 antigen in human T lymphocytes. Eur J Immunol. 1992 Nov;22(11):2995-3000.

[32] Burgess KE, Yamamoto M, Prasad KV, Rudd CE. CD5 acts as a tyrosine kinase substrate within a receptor complex comprising T-cell receptor zeta chain/CD3 and protein-tyrosine kinases p56lck and p59fyn. Proc Natl Acad Sci U S A. 1992 Oct 1;89(19):9311-5.

[33] Iwashima M, Irving BA, van Oers NS, Chan AC, Weiss A. Sequential interactions of the TCR with two distinct cytoplasmic tyrosine kinases. Science. 1994 Feb 25;263(5150):1136-9.

[34] Gorman C. L., Russell A. I., Zhang Z., Cunninghame Graham D., Cope A. P., and Vyse T. J., Polymorphisms in the CD3Z gene influence TCRζ expression in systemic lupus erythematosus patients and healthy controls, The Journal of Immunology. (2008) 180, no. 2, 1060–1070.

[35] Takeuchi T. and Suzuki K., CD247 variants and single-nucleotide polymorphisms observed in systemic lupus erythematosus patients, Rheumatology. (2013) 52, no. 9, 1551–1555.

[36] Zhou S., Lu H., and Xiong M., Identifying immune cell infiltration and effective diagnostic biomarkers in rheumatoid arthritis by bioinformatics analysis, Frontiers in Immunology. (2021) 12, 726747.

[37] Radstake T. R., Gorlova O., Rueda B., Martin J. E., Alizadeh B. Z., Palomino-Morales R., Coenen M. J., Vonk M. C., Voskuyl A. E., Schuerwegh A. J., Broen J. C, van Riel P. L., van 't Slot R., Italiaander A., Ophoff R. A., Riemekasten G., Hunzelmann N., Simeon C. P., Ortego-Centeno N., González-Gay M. A., González-Escribano M. F., Airo P., van Laar J., Herrick A., Worthington J., Hesselstrand R., Smith V., de Keyser F., Houssiau F., Chee M. M., Madhok R., Shiels P., Westhovens R., Kreuter A., Kiener H., de Baere E., Witte T., Padykov L., Klareskog L., Beretta L., Scorza R., Lie B. A., Hoffmann-Vold A. M., Carreira P., Varga J., Hinchcliff M., Gregersen P. K., Lee A. T., Ying J., Han Y., Weng S. F., Amos C. I., Wigley F. M., Hummers L., Nelson J. L., Agarwal S. K., Assassi S., Gourh P., Tan F. K., Koeleman B. P., Arnett F. C., Martin J., and Mayes M. D., Genome-wide association study of systemic sclerosis identifies CD247 as a new susceptibility locus, Nature Genetics. (2010) 42, no. 5, 426–429.

[38] Dietrich J, Hou X, Wegener AM, Geisler C. CD3 gamma contains a phosphoserine-dependent di-leucine motif involved in down-regulation of the T cell receptor. EMBO J. 1994 May 1;13(9):2156-66.

[39] Snow PM, Terhorst C. The T8 antigen is a multimeric complex of two distinct subunits on human thymocytes but consists of homomultimeric forms on peripheral blood T lymphocytes. J Biol Chem. 1983 Dec 10;258(23):14675-81.

[40] Zeng X., Feng J., Yang Y., Zhao R., Yu Q., Qin H., Wei L., Ji P., Li H., Wu Z., and Zhang J., Screening of key genes of sepsis and septic shock using bioinformatics analysis, Journal of Inflammation Research. (2021) 14, 829–841.

[41] Jiang Y., Miao Q., Hu L., Zhou T., Hu Y., and Tian Y., FYN and CD247: key genes for septic shock based on bioinformatics and meta-analysis, Combinatorial Chemistry & High Throughput Screening. (2021) 24, 1–9.

[42] Ermis E, Celik SK, Solak N, Genc GC, Dursun A. The role of GNLY gene polymorphisms in psoriasis pathogenesis. An Bras Dermatol. 2019;94(2):198–203.

[43] Khalid HN, Elghobashy YAE, Elsayed AN. GNLY gene polymorphism: A potential role in understanding psoriasis pathogenesis. J Cosmet Dermatol. 2022;21(10):4805–9.

[44] Lettau M, Dietz M, Dohmen K, Leippe M, Kabelitz D, Janssen O. Granulysin species segregate to different lysosome-related effector vesicles (LREV) and get mobilized by either classical or non-classical degranulation. Mol Immunol. 2019;107:44–53.

[45] Praper T, Sonnen A, Viero G, Kladnik A, Froelich CJ, Anderluh G, Dalla Serra M, Gilbert RJ. Human perforin employs different avenues to damage membranes. J Biol Chem. 2011 Jan 28;286(4):2946-55.

[46] Law RH, Lukoyanova N, Voskoboinik I, Caradoc-Davies TT, Baran K, Dunstone MA, D'Angelo ME, Orlova EV, Coulibaly F, Verschoor S, Browne KA, Ciccone A, Kuiper MJ, Bird PI, Trapani JA, Saibil HR, Whisstock JC. The structural basis for membrane binding and pore formation by lymphocyte perforin. Nature. 2010 Nov 18;468(7322):447-51.

DOI: 10.54254/2753-8818/94/2025.21887

[47] Stewart SE, Kondos SC, Matthews AY, D'Angelo ME, Dunstone MA, Whisstock JC, Trapani JA, Bird PI. The perforin pore facilitates the delivery of cationic cargos. J Biol Chem. 2014 Mar 28;289(13):9172-81.

[48] Vergelli M, Hemmer B, Muraro PA, Tranquill L, Biddison WE, Sarin A, McFarland HF, Martin R. Human autoreactive CD4+ T cell clones use perforin- or Fas/Fas ligand-mediated pathways for target cell lysis. J Immunol. 1997 Mar 15;158(6):2756-61.

[49] Ando K, Hiroishi K, Kaneko T, Moriyama T, Muto Y, Kayagaki N, Yagita H, Okumura K, Imawari M. Perforin, Fas/Fas ligand, and TNF-alpha pathways as specific and bystander killing mechanisms of hepatitis C virus-specific human CTL. J Immunol. 1997 Jun 1;158(11):5283-91.

[50] Zhu GH, Zhang LP, Li ZG, Wei A, Yang Y, Tian Y, Ma HH, Wang D, Zhao XX, Zhao YZ, et al. Associations between PRF1 Ala91Val polymorphism and risk of hemophagocytic lymphohistiocytosis: a meta-analysis based on 1366 subjects. World J Pediatr. 2020;16(6):598–606.

[51] Kadi Ozan, Z. , Erduran, E. , Ceylaner, S. , Aslan, Y. , Bahadir, A. , Reis, G. & Mutlu, M. (2024). Familial Hemophagocytic Lymphohistiocytosis Screening in Neonatal Sepsis. Journal of Pediatric Hematology/Oncology, 46 (6), e393-e401.