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Differential genes and pathogenesis of sepsis-induced lung injury data analysis

Jiao Long[1], Lei Zheng[1]

[1]*Surgical Anesthesia Center, Seventh Affiliated Hospital of Sun Yat-sen University, Shenzhen, Guangdong, 518107, China*

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Abstract: To explore the related differentially expressed genes (differentially expressed gene, DEG) and signal transduction pathways of sepsis-associated lung injury, based on the genomic data of the blood tissue of patients with sepsis-induced lung injury from the Gene Expression Omnibus (GEO) database, gene ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis, as well as protein-protein interaction network (PPI) analysis were used to determine the DEG of sepsis-induced lung injury.DEG was significantly enriched in Ribosome, Leishmaniasis, Natural killer cell mediated cytotoxicity and so on. Ten hub genes were screened by PPI analysis, including RPL21, RPL23A, RPL6, RPS18, RPL5, RPL14, RPL23, RPS15A, RPL26, RPL7.Through bioinformatics methods, 10 hub genes related to sepsis-induced lung injury were excavated, which were related to the RPL family and the RPs family.

1. Introduction

Sepsis is one of the common critical diseases in clinic. Its incidence has been increasing in recent years, and the mortality rate is high. Acute lung injury is an acute progressive hypoxic respiratory failure caused by many factors, which is characterized by refractory hypoxemia and respiratory distress. Lung is the most vulnerable target organ of sepsis. Therefore, patients with sepsis are prone to acute lung injury, and the prognosis is usually poor.Acute lung injury is one of the most common complications of sepsis, 25 % ~ 50 % of patients can be complicated with sepsis-induced acute lung injury [1], and the mortality of sepsis-induced acute lung injury is significantly higher than that of non-sepsis-induced acute lung injury, the 60-day mortality of the two is 38.2 % and 22.6 %, respectively [2]. The mortality rate of acute lung injury is also affected by many factors such as age, severity of disease and physical condition.Gene expression omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/)) is an international public database that stores a large number of high-throughput gene expression data and other genome data sets. In this study, through the analysis of GEO data, combined with bioinformatics microarray data analysis, the differential genes of patients with sepsis-induced lung injury were excavated, in order to explore the gene changes and related pathways in the process of disease progression, and to understand the occurrence and development mechanism of sepsis-induced lung injury.

2. Materials and methods

2.1 Data sources

The GEO of the US Biotechnology Information Center is a public sample data repository, which contains gene expression data for sepsis-induced lung injury. The gene data set of sepsis-induced lung injury (GSE32707) was screened from GEO. RNA samples were extracted from blood tissue samples of sepsis patients with lung injury and non-sepsis patients, and the data were obtained after transcriptome analysis and sequencing.

2.2 Chip data processing

The most commonly used GEO2R was used to obtain differentially expressed genes (DEGs), in which fold change (FC) and P value (| log2FC | ≥ 1 and $P < 0.05$) were used as criteria to filter DEGs.

2.3 Gene ontology (GO) enrichment analysis and kyoto encyclopedia of genes and genomes (KEGG) enrichment analysis.

GO enrichment analysis and KEGG enrichment analysis were performed on DEGs, and Database for Annotation Visualization and Integrated Discovery (DAVID) online network platform was used for analysis, including biological processes, cell composition and molecular functions. $P < 0.05$ was considered statistically significant.

2.4 Protein-protein interaction (PPI) network analysis.

The signal transduction, energy and material metabolism of human cells are achieved through the interaction between proteins. The functional network system formed between proteins is called PPI. In PPI, hub nodes interact with most proteins and may play a more important role in the occurrence and development of diseases. The STRING website is an interactive gene search tool. The website is used to construct a PPI using differential genes, and then the Cytohubb plug-in is used to screen the first 10 genes in the Cytoscape software to obtain the hub genes affecting sepsis-induced lung injury.

3. Result

3.1 DEG screening

GEO2R was used to screen the DEGs of blood tissues of patients with sepsis-induced lung injury and non-sepsis patients in the GSE32707 dataset, and a total of 713 DEGs (| log2FC | ≥ 1, $P < 0.05$) were obtained, of which 388 were significantly up-regulated and 315 were significantly down-regulated.

3.2 GO enrichment analysis and KEGG enrichment analysis.

The results of GO enrichment analysis showed that DEG was involved in biological processes such as neutrophil detoxication, translation, and antibacterial humoral response ($P < 0.05$). The cell components mainly included extracellular exosome, cytosolic large ribosomal subunit, and specific granule lumen ($P<0.05$). The molecular function mainly included structural constituent of ribosome, RNA binding and so on ($P < 0.05$).

KEGG enrichment analysis showed that DEG was significantly enriched in Ribosome, Leishmaniasis, and Natural killer cell mediated cytotoxicity pathways ($P < 0.05$).

3.3 Prediction of PPI and hub genes

PPIs were constructed using the STRING tool for the screened DEGs, and the top 10 hub genes were screened using Cytosacpe's Cytphubba plug-in: RPL21, RPL23A, RPL6, RPS18, RPL5, RPL14, RPL23, RPS15A, RPL26, RPL7.

4. Discuss

Sepsis is a kind of systemic inflammatory response syndrome caused by severe infection. In addition to the source of infection, vasodilation, increased capillary permeability and accumulation of inflammatory factors in multiple organs and tissues of the body can lead to ischemia and hypoxia of tissues and organs, and finally develop into multiple organ dysfunction syndrome, which is life-threatening in severe cases [3]. In 2017, an epidemiological survey based on sepsis in China showed that the incidence of sepsis was 461 / 100,000 and the mortality rate was 79 / 100,000 [4]. Another survey data showed that [5], the mortality rate of sepsis was 12.6 %.At present, the clinical research on the pathogenesis of acute lung injury in sepsis has made some progress, but the deep and specific pathogenesis research is not detailed enough. Therefore, the detailed pathogenesis of sepsis-induced acute lung injury still needs to be systematically studied in the future to provide a theoretical basis for the selection of clinical therapeutic drugs.In this study, 713 DEGs were screened and enriched. GO enrichment analysis showed that DEG was significantly enriched in neutrophil detoxication, translation, and antibacterial humoral response. The top 10 hub genes screened by PPI were: RPL21, RPL23A, RPL6, RPS18, RPL5, RPL14, RPL23, RPS15A, RPL26, RPL7. These genes may be involved in the occurrence and development of sepsis-induced lung injury.RPL21 (ribosomal protein L21) is a protein-coding gene. The system associated with RPL21 is immunity. The related pathways include viral mRNA translation and rRNA processing in the nucleus and cytoplasm. Gene ontology (GO) annotations related to this gene include RNA binding and structural components of ribosomes.RPL23A has a strong correlation with immune cells[6].Immune is closely related to the occurrence and development of sepsis and lung injury[7].Diseases associated with RPL6 include human T-cell leukemia virus type 1 and T-cell acute lymphoblastic leukemia.Regulation of the HDM2-p53 pathway by RPL6 in response to ribosomal stress[8].Alveolar epithelial progenitor cells (AEP) are a kind of progenitor cells that can develop into alveolar cells. RPS18 plays an important role in determining cell differentiation[9].The RP-RPL5 − / RPL11-mediated p53 monitoring system plays an important regulatory role in lung cancer progression[10].RPL14 may be a potential marker of chronic obstructive pulmonary disease and play an important role in lung disease[11].Triptolide disrupts rRNA synthesis and induces RPL23-MDM2-p53 pathway to inhibit lung cancer cells[12].The inhibition of RPS15 A can induce the reduction of proliferation through cell cycle arrest. RPS15 A is a new potential oncogene involved in lung cancer [13].

In summary, through systematic bioinformatics analysis, we identified some hub genes and explained the biological functions and signal transduction pathways related to sepsis-induced lung injury. In addition, we also identified 10 hub genes related to sepsis-induced lung injury, which are not only related to other organ damage caused by sepsis, but also closely related to sepsis-induced lung injury.

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