Gene expression microarray in lupus nephritis by bioinformatic analysis


Background: Nephritis is one of the predominant causes of morbidity and mortality in patients with lupus. The lack of understanding regarding the molecular mechanisms of lupus nephritis (LN) hinders the development of specific targeted therapy for this progressive disease.

Objectives: In this study, we use bioinformatic methods to analyze the genes involved in regulating the potential pathogenesis of LN.

Methods: The expression profile of LN (GSE104948 and GSE2591) was obtained from the GEO database. GSE104948 was a memory chip, which included 32 LN glomerular biopsy tissues and 15 monocytes in SLE patients. GSE2591 dataset included 32 LN glomerular biopsy tissues and 15 glomerular tissues from living donors. The oligo package was used to process the data to obtain the expression matrix files of all the related genes. P<0.05 and log2(FC)>2 were setted as cut-off criteria for the DEGs. Ggplot2, heatmap packages were used to DEGs visualization. Metascape online tool was used to annotate DEGs for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis performed. We used STRING online database to construct protein-protein interaction (PPI) network. Hub genes were identified by Cytoscape.

Results: In differential expression analysis, 357 DEGs were identified, including 248 up-regulated genes and 109 down-regulated genes. GO enrichment showed that these DEGs were primarily enriched in biological pathways, cell localization and molecular function and revealed that LN-related genes mainly involved in immune response. KEGG pathway annotation enrichment analysis revealed these DEGs were closely associated with Staphylococcus aureus infection, Complement and coagulation cascades (Figure 1D). Fourteen hub genes (IFT3, IRF7, OAS3, GBP2, RSAD2, MX1, IFT2, IF6, MX2, IS-F15, IFT1, OAS2, OASL, OAS1) were identified from PPI network (Figure 1E, F).

Figure 1: KEGG map of the top 10 up-regulated differentially expressed genes. Each small square represents a gene, the color indicates the expression level of the gene. Each column indicates the expression level of the gene in a sample, and the size indicates the expression level of a gene in different samples. The right side of the gene name, (A) KEGG map of gene expression. The horizontal axis is log2 FC, the vertical axis is log2(FC). Each dot represents a gene, blue indicates low expression genes, red indicates high. (B) KEGG map of GO enrichment analysis. (C) KEGG pathway enrichment analysis. (D) KEGG PPI network and hub gene identification. Top 4 hub genes in the PPI network were named by Cytoscape plugin cytohubba based on their degree value from red (high degree value) to yellow (low degree value).

Figure 4: (A) Volcano plots of DEGs between LN and healthy controls. Each dot represents a gene, where red represents up-regulated, blue represents down-regulated genes, and black represents genes with no significant differences. (B) Box-plot of the top 15 up-regulated and 15 down-regulated DEGs. (C) Bar graph of expression levels of top 15 different genes in different samples (D) Bar graph of enriched terms across input gene lists, colored by p-values. (E) PPI network and hub gene identification. Top 4 hub genes in the PPI network were named by Cytoscape plugin cytohubba based on their degree value from red (high degree value) to yellow (low degree value).

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determined in the routine laboratory. Based on the final diagnosis, we divided patients into two groups: A) initial diagnosis of SLE and B) Non-SLE mimicking condition.

**Results:** In 76 patients (32.3%) SLE was confirmed by fulfilling the EULAR / ACR 2019 classification criteria [5]. SIGLEC-1 was dramatically increased in patients with an initial diagnosis of SLE compared to patients without SLE (p<0.0001). For a threshold of 2500 molecule per monocyte, a sensitivity of 98.7%, a specificity of 82.1%, a negative predictive value (NPV) of 99.2%, and a positive predictive value (PPV) of 72.8% were calculated for SIGLEC-1. Adjusted to the prevalence of SLE in Germany (36.7 per 100,000 inhabitants [6]) NPV and PPV turned out to be > 99.9% and 0.2%. We further aimed to compare not only the performance of the tests at a given cutoff but also across all possible measured values. Therefore, we conducted ROC curves analyses (see figure 1). The area under the curve (AUC) of SIGLEC-1 test was significantly higher than that of ANA test (AUC=0.88, p=0.031), C3 (AUC = 0.83, p=0.001), C4 (AUC=0.83, p=0.002), but not than that of the Anti-dsDNA ELISA (AUC=0.90, p=0.163).

**Conclusion:** Our study shows that IFN activity is a hallmark at the onset of the disease and that the interferon biomarker SIGLEC-1 is valuable to rule out SLE in suspected cases.

**REFERENCES:**


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