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Integrative analysis of gene expression profiling reveals deregulation of the immune response genes during different phases of chronic hepatitis B infection

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Background: The natural history of the CHB infection can be widely sub-divided into four phases including, immune tolerance, immune clearance (or immune active), inactive HBsAg carrier, and reactivation phase. However, utilizing high-throughput data, the distinct immunological mechanisms of these phases have been insufficiently investigated. The aim of present study was to determine candidate disease-associated genes and significantly altered biological processes for different phases of CHB infection.

Material/methods: The gene expression profiles of 83 CHB patients (22 immune tolerance, 50 immune clearance, and 11 inactive carrier phase) were utilized from gene expression omnibus (GEO dataset: GSE65359) and were analyzed by bioinformatics tools. Several plugins of the Cytoscape software were used to construct protein-protein interaction (PPI) networks and measure their topological properties. Subsequently, functional annotation and signaling pathway enrichment were carried out using the Database for Annotation, Visualization and Integrated Discovery (DAVID), Kyoto Encyclopedia of Genes and Genomes (KEGG) and Signaling Pathway Enrichment using the Experimental Datasets (SPEED) databases. The connections between differentially expressed genes

and GO terms, a DEG-GO network was constructed with the GO terms and DEGs using the Cytoscape Software.

Results: 449 and 452 deregulated genes were identified in immune tolerant-immune clearance and immune clearance-inactive carrier patients, respectively. Gene ontology and KEGG pathway analyses showed that immune response genes were upregulated in the immune clearance phase. By contrast, immune response genes were significantly downregulated in the inactive carrier phase. LCK (encoding a tyrosine kinase) was determined as the most important hub gene of both constructed PPI networks. However, the LCK gene expression was significantly upregulated in the immune clearance phase compared to the inactive carrier phase. Furthermore, other immune response associated genes were found to be the important hub genes in clinical phases of CHB. The degree of any particular gene was determined by the number of GO terms regulated by the gene in the network. The CD24 (18 degrees), CORO1A (17 degrees), INFG (15 degrees), CD74 (15 degrees), HLA-DMA (14 degrees) and LCK (13 degrees) were significantly regulated differentially in immune tolerant samples compared to the immune clearance samples. The important GO terms, defined as the most highly regulated by the altered DEG, were involved in immune response (71 degrees).

Conclusions: The immune response related pathways were upregulated in the immune clearance phase of CHB, but not in the inactive carrier phase. LCK hub gene might help the pathogenesis of different phases of CHB and serve as a therapeutic target for the treatment of hepatitis B virus.