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Exploring hub genes in hepatocellular carcinoma using a systems biology approach

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Abstract

- Liver cancer is the sixth most common cancer in the world and has a poor prognosis despite advances in diagnosis and treatment. Therefore, deciphering the molecular mechanisms involved in this disease is very important. In the current study, gene expression profile GSE76427 was downloaded from Gene Expression Omnibus database. A total of 493 differentially expressed genes(DEGs) were identified using GEO2R which included 92 upregulated and 401 downregulated genes. The protein-protein interaction (PPI) network of the DEGs was constructed based on the STRING database. According to degree levels, six genes including JUN, ESR1, IGF1, AURKA, CRP, and CDC20 were identified as hub genes. In conclusion, these identified DEGs (and especially hub genes) might have critical roles in the progression of HCC, and could be used as potential early diagnostic biomarkers and therapeutic targets.
- **Keywords**: Differentially Expressed Genes, Hepatocellular Carcinoma, Enrichment Analysis, Hub genes

Introduction

- Hepatocellular carcinoma (HCC) as a prevalent malignancy is the fourth leading cause of cancer-related death worldwide (Yang et al., 2019). Most patients in the early stages of the disease can be treated by surgical resection and liver transplantation but it should be noted that most individuals present symptoms of progression at the time of identification which can complicate the treatment process with conventional therapies like chemotherapy and radiotherapy(Huang et al., 2013). For this reason, despite tangible advances in early diagnosis and development of new therapies, the prognosis of these patients is still poor and the 5-year survival rate is less than 25%(Yan & Liu, 2019). Therefore, further research to elucidate the molecular mechanisms of HCC to develop novel methods for treatment and early diagnosis is extremely urgent. Recently, analysis of gene expression profiles using bioinformatics tools has opened a new way to achieve this goal.

Materials and Methods

- The datasets of HCC gene expression profiling by microarray techniques with high data quality were searched in the Gene Expression Omnibus (GEO) database (www.ncbi.nlm.nih.gov/geo). As a result, gene expression profile GSE76427 was downloaded which contained 167 samples including, 115 primary tumor tissue samples and 52 adjacent non-tumor tissue samples derived from 115 HCC patients(Grinchuk et al., 2018). Differentially expressed genes (DEGs (were identified using GEO2R using the Benjamini-Hochberg method. |log2 fold change| >1 and adjusted p-value<0.05 were defined as threshold criteria for identifying DEGs. Then, gene ontology (GO) functional enrichment analysis was performed for the DEGs using BiNGO in the Cytoscape (v. 3.7.1) software, with a threshold of p-value <0.05. Furthermore, the protein-protein interaction (PPI) network of the DEGs was constructed based on the search tool for the retrieval of interacting genes/proteins (STRING) database.

Results

- Based on the threshold criteria, a total of 493 DEGs were obtained, including 92 upregulated and 401 downregulated genes. The upregulated genes were significantly enriched in the cell cycle and cellular component organization, while the downregulated genes were mainly enriched in the metabolic process and respond to a stimulus. Interactions between the identified DEGs were revealed by constructing a PPI network (Figure 1). In total, there were 481 nodes and 2435 edges in the network. According to degree levels, the top six hub nodes were JUN (degree, 46), ESR1 (degree, 45), IGF1 (degree, 45), AURKA (degree, 43), CRP (degree, 43), and CDC20 (degree, 42).

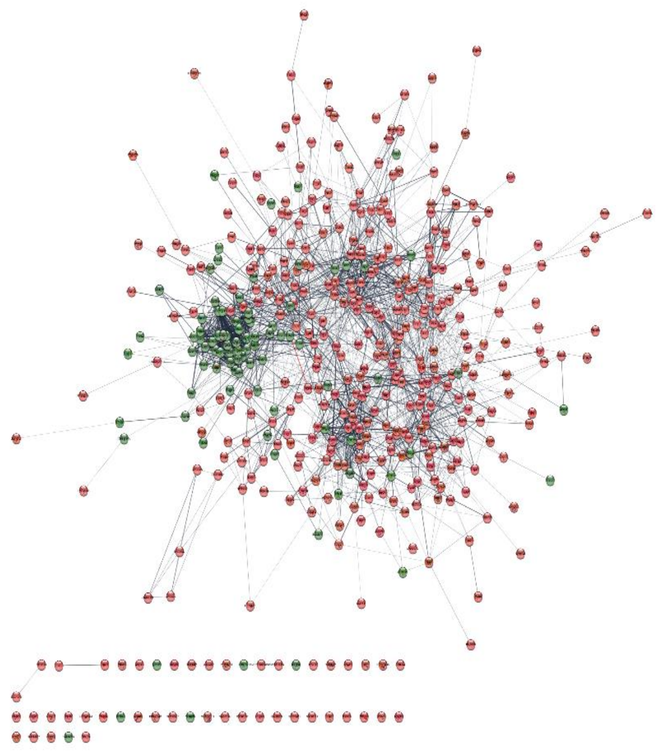

Figure 1. PPI network constructed from the DEGs. The nodes represent proteins and the edges represent the interaction of proteins. Green and red circles indicate upregulated and downregulated DEGs, respectively.

Discussion, Conclusion and Suggestions

- The importance of the top six hub genes in HCC has been demonstrated in previous studies (Chen et al., 2017; Li, Gao, Du, Huang, & Wei, 2014). Such results imply that the identified DEGs (and especially hub genes) might have critical roles in the progression of HCC, and could be used as potential diagnostic biomarkers and therapeutic targets. Although they were identified using a systems biology approach, the specific roles and underlying molecular mechanisms in HCC require further experimental confirmation.

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