Integrated Bioinformatics Analysis on Differentially Expressed Genes and Pathways in NASH and NASH-HCC

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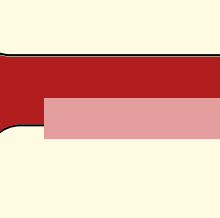
BACKGROUND

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the fourth leading cause of cancer-related deaths globally. Non-alcoholic steatohepatitis (NASH), a severe form of non-alcoholic fatty liver disease (NAFLD), is now recognized as a significant risk factor for HCC, especially in patients with cirrhosis.



A study by Motta et al (2023)

HCC is the most common primary liver cancer comprising 75-85% of cases

NASH can contribute to HCC development

OBJECTIVE

To identify key genes involved in NASH-related HCC and investigate their associated pathways.

METHODS

1. Gene Expression Omnibus was used to find datasets relating NASH with HCC.

2. GEO2R was used to group and analyze the differentially expressed genes in GSE164760.

3. Microsoft excel was used to screen the genes with a p value < 0.05 and a log Fold change of > 1 or < 1.

4. Enrichr was used to conduct the Kyoto KEGG and gene ontology (GO) analysis.

5. Cytoscape was used to create string protein-protein interaction network (PPI). The proteins with no interactions were removed. The remaining PPI genes were ranked using Cytohubba based on degree.

Keywords

NASH and HCC and “geo2r”[filter]

RESULTS

Table 1. Characteristics of included studies

Study	Dataset	Samples (n)		Tissue	Protocol Design
		NASH patients	NASH-HCC patients		
Llovet JM, Pinyol R, Torrecilla S (2021)	GSE164760	74	53	Liver	Affymetrix Human Genome U219 Array

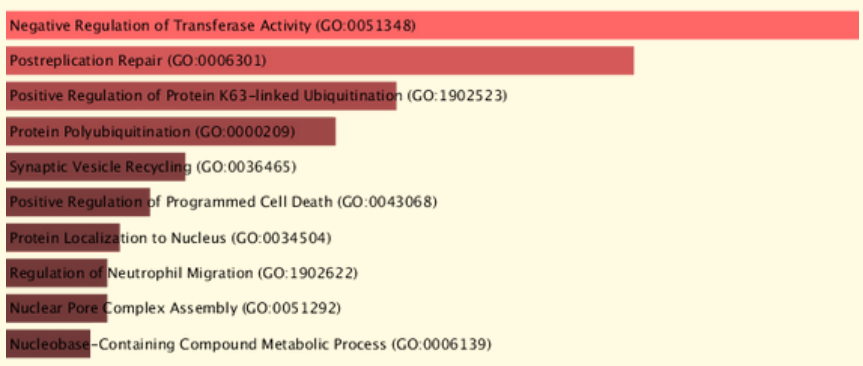


Figure 1. GO Biological Process (BP) of upregulated DEGs

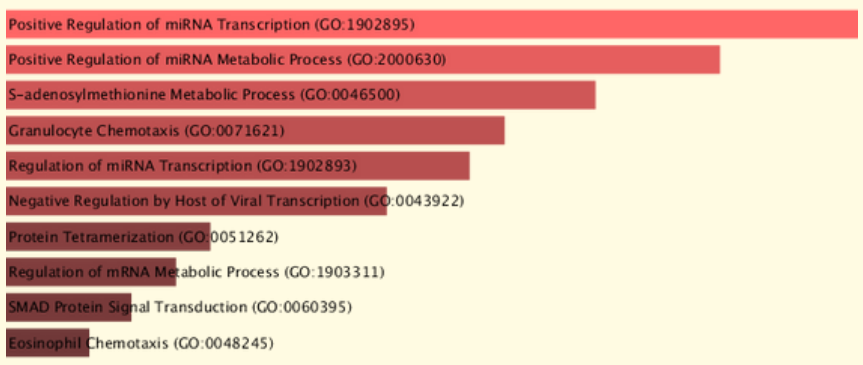


Figure 2. GO Biological Process (BP) of downregulated DEGs

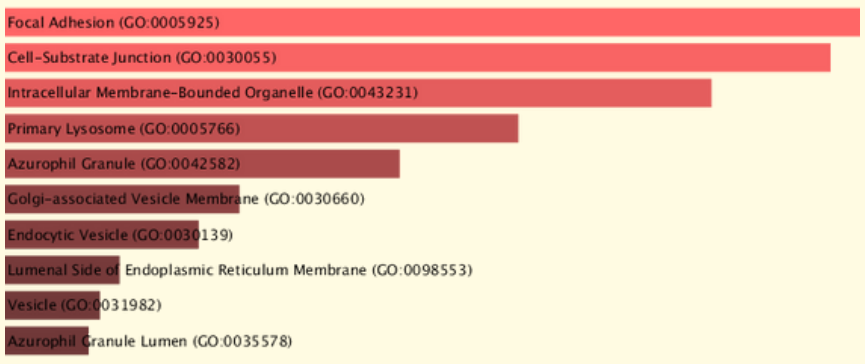


Figure 3. GO Cellular Components (CC) of upregulated DEGs

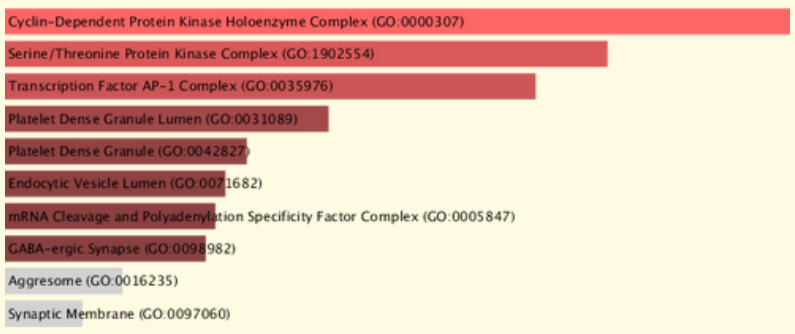


Figure 4. GO Cellular Component (CC) of downregulated DEGs

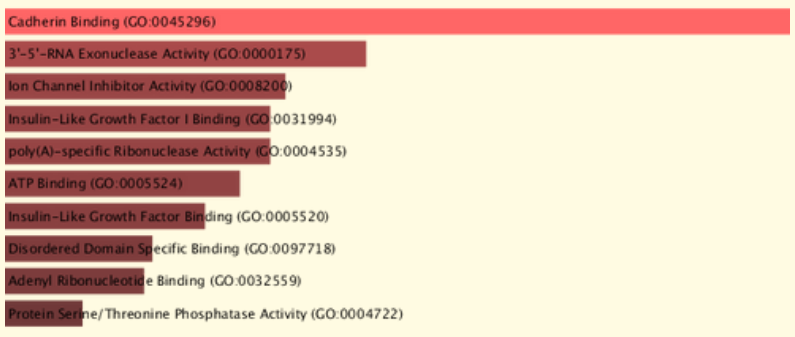


Figure 5. GO Molecular Function (MF) of upregulated DEGs

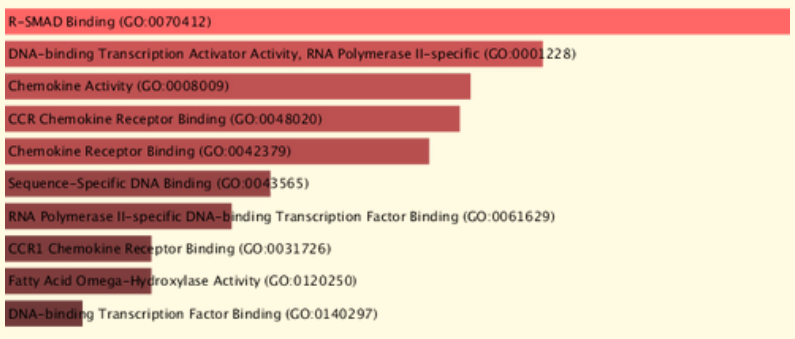


Figure 6. GO Molecular Function (MF) of downregulated DEGs

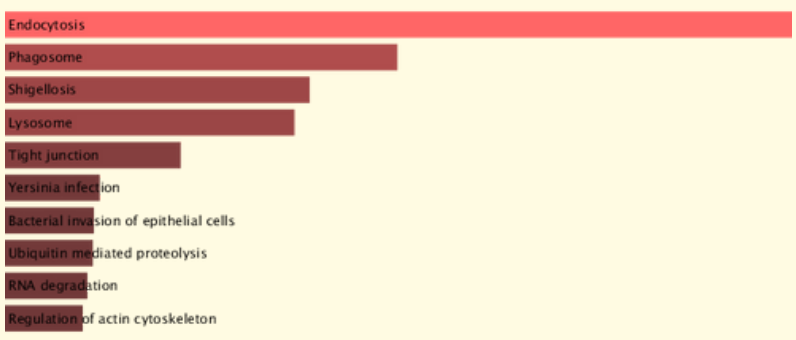


Figure 7. KEGG pathway analysis of upregulated DEGs

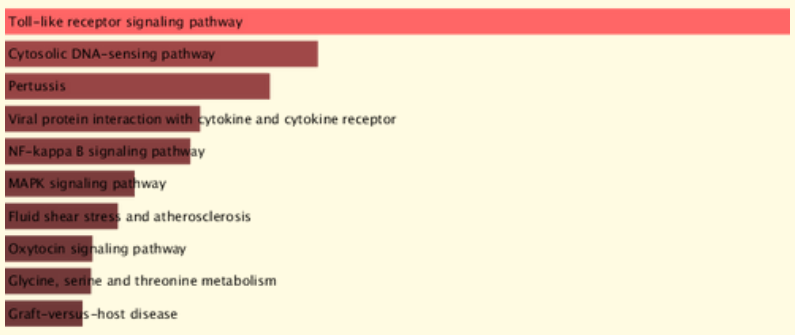


Figure 8. KEGG pathway analysis of downregulated DEGs

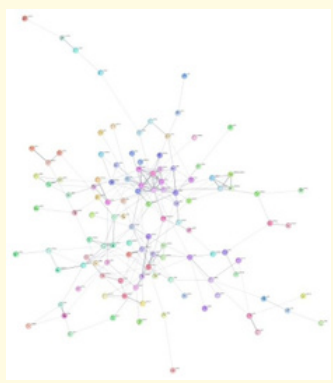


Figure 9. String Network for DEGs

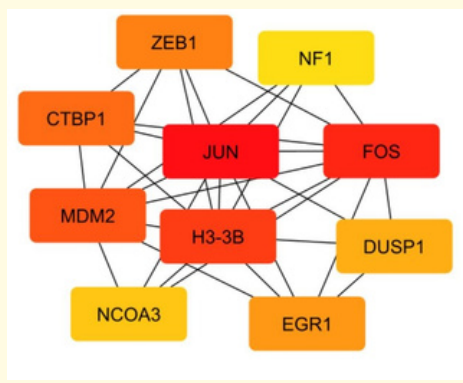


Figure 10. Top 10 ranked PPI DEGs

DISCUSSION

Upregulated DEGs

Suppression of transferase activity → possible compensatory mechanism → counteract excessive post-translational modifications (drive inflammation and fibrosis)

The enrichment of focal adhesion and cadherin binding → enhanced extracellular matrix (ECM) remodeling and disrupted cell-cell adhesion → epithelial-mesenchymal transition (EMT) hallmark → key process in fibrosis and HCC metastasis

Upregulation of endocytosis → reflect altered trafficking of growth factor receptors (EGFR, TGF-β) → sustain pro-fibrotic and oncogenic signaling in disease progression

Downregulated DEGs

Reduced miRNA transcription → loss of tumor-suppressive miRNAs (miR-122, miR-34a) → unchecked proliferation and inflammation

Downregulation of cyclin-dependent kinase complexes → cell cycle dysregulation → from DNA damage or senescence in pre-malignant NASH → may later escape these controls in HCC

Diminished R-SMAD binding → disrupted TGF-β signaling → aberrant fibrogenesis

The suppression of TLR signaling → may indicate immune exhaustion or evasion → enable chronic inflammation to persist → promote tumorigenesis

CONCLUSION

The overlapping DEGs between NASH and NAS-HCC reveal distinct molecular signatures driving disease progression. The GO/KEGG analysis for upregulated DEGs suggest enhanced ECM remodeling and pro-tumorigenic signaling, while the one for the downregulated DEGs indicate impaired tumor suppression and immune dysfunction. These findings highlight key pathways contributing to fibrosis, inflammation, and malignant transformation, providing potential therapeutic targets to disrupt the progression from NASH to HCC.

REFERENCES