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FROM DIFFERENTIAL EXPRESSION TO INTERACTION NETWORKS: UNCOVERING HUB GENES IN HEPATOCELLULAR CARCINOMA

Zeynep Kucukakcali[1]*, Ipek Balikci Cicek [1]

Inonu University Faculty of Medicine, Department of Biostatistics and Medical Informatics, 44280, Malatya, Turkey.

***Corresponding Author: Zeynep Kucukakcali**

Inonu University Faculty of Medicine, Department of Biostatistics and Medical Informatics, 44280, Malatya, Turkey.

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ABSTRACT

Objective: Hepatocellular carcinoma (HCC) is a molecularly heterogeneous malignancy with high mortality. This study aimed to identify differentially expressed genes (DEGs) between tumor and non-tumor liver tissue and, through protein–protein interaction (PPI) network analysis, to reveal hub genes central to HCC pathogenesis. **Materials and Methods:** Using the GSE76427 dataset from the Gene Expression Omnibus, 115 HCC tumor tissues were compared with 52 non-tumor liver tissues. Differential expression analysis was performed with the limma package (adj. P. Val < 0.05, |logFC| ≥ 1). The most strongly dysregulated genes were submitted to the STRING database to construct a PPI network, and the network topology was evaluated. Results: A total of 362 probes were differentially expressed (95 up-regulated, 267 down-regulated). The roughly three-fold excess of down-regulated genes reflects loss of liver-specific metabolic and detoxification programs. PPI analysis revealed a network significantly richer in interactions than expected (enrichment $p = 4.67 \times 10^{-5}$); the cell-cycle– and mitosis-related proteins PCLAF, PRC1, MCM2, UBE2T and TUBA1C formed a tightly connected proliferation module that constituted the network core, whereas down-regulated genes associated with sinusoidal endothelium, innate immunity and hepatocyte metabolism appeared largely as isolated nodes. **Conclusion:** The findings indicate that the HCC phenotype is driven mainly by a proliferation-centered interaction network accompanied by loss of liver-specific differentiation. The hub proteins within this proliferation module stand out as candidate biomarkers and therapeutic targets for HCC.

KEYWORDS: Hepatocellular carcinoma, differential gene expression, GSE76427, protein–protein interaction network, hub gene, bioinformatics.

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the predominant histological subtype, accounting for 75–90% of primary liver cancers, and is one of the leading causes of cancer-related deaths worldwide.[1] GLOBOCAN 2022 data rank liver cancer sixth in incidence and third in mortality, reporting approximately 900,000 new cases and over 750,000 deaths annually.[2] Although the disease burden has traditionally been concentrated in East Asia and Sub-Saharan Africa, the incidence is steadily increasing in Europe and North America as well, due to the rising prevalence of steatotic liver disease associated with obesity and metabolic dysfunction3.[] This situation has transformed HCC from a purely regional issue into a global health problem requiring new diagnostic and treatment strategies.

The development of HCC is a process that unfolds over many years and involves the contribution of numerous factors. Chronic hepatitis B and C infections, alcohol-related liver disease, aflatoxin exposure, and steatotic liver disease associated with metabolic dysfunction constitute the primary etiological causes; the common outcome of these factors is a clinical picture characterized by chronic inflammation, fibrosis, and cirrhosis.[1,3] Genetic and epigenetic changes accumulating in hepatocytes during repeated damage–repair cycles disrupt proliferation control, suppress

apoptosis, and accelerate angiogenesis, paving the way for malignant transformation.[4] The fact that tumor behavior varies significantly even among patients with similar etiologies demonstrates that HCC is a highly heterogeneous disease from a molecular perspective.[4]

In cases detected at an early stage, curative options such as surgical resection, liver transplantation, or local ablation may be applied; however, a significant proportion of patients are diagnosed at an advanced stage or experience high recurrence rates following treatment.[1] In recent years, the combined use of immune checkpoint inhibitors and anti-angiogenic agents—such as the atezolizumab–bevacizumab combination—has improved survival in advanced HCC.[5] However, treatment responses vary significantly among patients, and acquired drug resistance remains a current challenge.[4] This situation necessitates a more detailed understanding of the molecular basis of the disease and the identification of new therapeutic targets that play a central role in HCC biology.

Advances in cancer biology have shown that HCC cannot be explained by a single gene or a disruption in a single signaling pathway. The disease is a multilayered process in which genomic, epigenetic, and transcriptional changes are intertwined with dysregulations in protein expression and intracellular signaling networks.[6] Due to this complexity, multi-omics approaches—which integrate genomic, transcriptomic, and proteomic data are playing an increasingly central role in identifying biomarkers and new therapeutic targets.[7]

High-throughput microarray and RNA sequencing technologies have revolutionized the molecular study of cancer by enabling the simultaneous measurement of expression levels of thousands of genes.[8] The Gene Expression Omnibus (GEO), one of the most comprehensive platforms for sharing such data via open access, makes expression data from various diseases and experimental designs available to researchers.[9] Differential gene expression (DEG) analyses conducted on these datasets identify genes that show significant changes between tumor and control groups, thereby contributing to the mapping of disease-related biological processes.[10]

However, merely identifying differentially expressed genes is not sufficient for functional interpretation, as cellular processes are governed by complex interaction networks formed by numerous proteins. Therefore, the biological significance of these genes should also be evaluated at the protein level. The concept of network medicine approaches diseases not as the consequence of individual genes, but as the result of interconnected molecular networks.[11] To this end, the STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) database integrates experimental evidence, curated databases, computational predictions, co-expression analyses, and text mining to construct comprehensive protein–protein interaction (PPI) networks.[12] A critical step in the analysis of these networks is the identification of hub genes, which are highly connected nodes that play central roles in maintaining network integrity, which are highly connected nodes that play central roles in maintaining network integrity. Tools such as cytoHubba enable the identification of these key proteins based on network topology.[13] Hub proteins are frequently involved in essential biological processes, including cell proliferation, DNA repair, mitosis, and cell cycle regulation. Owing to their central roles in these processes, they are considered promising therapeutic targets as well as key regulators of network stability.[11]

In this study, the GSE76427 gene expression dataset from the Gene Expression Omnibus (GEO) database was used to identify differentially expressed genes (DEGs) between hepatocellular carcinoma (HCC) tumor tissues and adjacent non-tumor liver tissues. The identified DEGs were subsequently used to construct a protein–protein interaction (PPI) network using the STRING database. Based on the topology of this network, hub genes were identified and evaluated with respect to their potential roles in HCC pathogenesis, as well as their value as potential biomarkers and therapeutic targets.

2. MATERIALS AND METHODS

2.1. Selection of the Dataset and Study Design

In this study, the publicly available microarray dataset GSE76427 from the NCBI Gene Expression Omnibus (GEO) database was used. The dataset consists of human liver tissue expression profiles generated on the Illumina HumanHT-12 V4.0 expression beadchip platform. As part of the analysis, 115 hepatocellular carcinoma (HCC) tumor tissue samples were compared with 52 adjacent non-HCC liver tissue samples as two independent groups. Sample grouping was based on tissue type information from the sample metadata associated with the series.

2.2. Differential Gene Expression (DEG) Analysis

Raw gene expression data were log2-transformed and normalized according to the characteristics of the microarray platform. Differential expression between tumor and non-tumor liver tissues was evaluated using the linear modeling framework implemented in the limma package. For each probe, the moderated t-statistic, raw p-value, B-statistic, and log2 fold change (logFC) were calculated. Multiple testing correction was performed using the Benjamini–Hochberg false discovery rate method.

Differentially expressed genes were identified according to the following combined criteria:

- Adjusted p-value < 0.05
- $|\log FC| \geq 1$

An absolute logFC value of at least 1 corresponds to a minimum two-fold change in gene expression. Probes with $\log FC \geq 1$ were classified as upregulated, whereas

probes with logFC ≤ −1 were classified as downregulated. Probes with −1 < logFC < 1 were not considered differentially expressed, even when their adjusted p-values were statistically significant.

Probes without an annotated gene symbol were excluded from subsequent analyses. When multiple probes corresponded to the same gene, the probe with the highest absolute logFC value was retained as the representative probe. The overall distribution of differentially expressed genes was visualized using a volcano plot, with log2 fold change on the x-axis and −log10 adjusted p-value on the y-axis.

2.3. Construction of a Protein–Protein Interaction (PPI) Network

The top 10 upregulated and top 10 downregulated differentially expressed genes (DEGs) were uploaded to the STRING database (Homo sapiens), and a protein–protein interaction (PPI) network was constructed.

3. RESULTS

3.1. Differentially Expressed Genes

When the thresholds of adjusted P value < 0.05 and |logFC| ≥ 1 were applied simultaneously, a total of 362 probes were identified as differentially expressed between 115 HCC tumor tissues and 52 adjacent non-tumor liver tissues. Among these, 95 probes were upregulated, whereas 267 were downregulated in tumor tissues. The approximately threefold higher number of downregulated genes compared with upregulated genes suggests a marked loss of the normal liver-specific metabolic and detoxification programs in HCC tissues (Table 1).

Table 1: Summary of differential gene expression analysis in the GSE76427 dataset.

Category	Applied threshold	Number of probes	Percentage (%)
Total DEGs	Adjusted P value < 0.05 and |logFC| ≥ 1	362	100.0
Upregulated (in tumor)	logFC ≥ +1	95	26.2
Downregulated (in tumor)	logFC ≤ −1	267	73.8

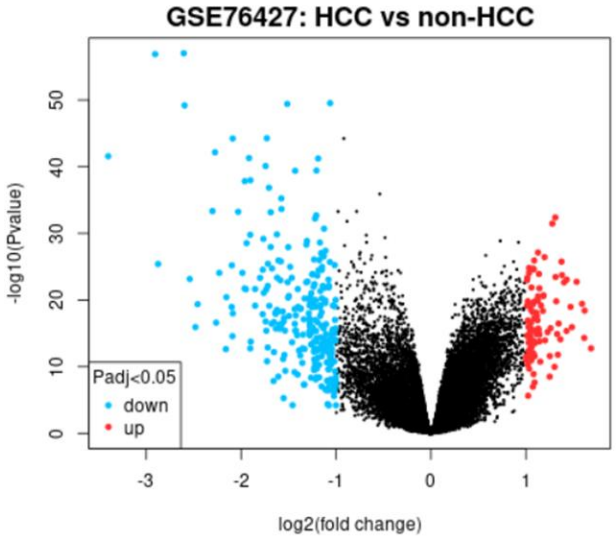

Figure 1: Volcano plot showing the differential gene expression analysis comparing HCC and non-HCC samples in the GSE76427 dataset. The x-axis represents the log2 fold change (log2FC), and the y-axis represents the −log10(P value). Blue dots indicate downregulated genes (logFC ≤ −1), red dots indicate upregulated genes (logFC ≥ +1), and black dots represent probes that did not meet the significance thresholds (adjusted P value < 0.05 and |logFC| ≥ 1).

The top ten upregulated genes with the highest fold changes are presented in Table 2. This gene set is predominantly composed of genes involved in cell cycle progression and DNA replication, including PCLAF (KIAA0101), PRC1, MCM2, UBE2T, and PTTG3P, reflecting the enhanced proliferative activity characteristic of HCC tissues.

Table 2: Top 10 upregulated genes with the highest log2 fold change.

Rank	Gene symbol	Log2FC	adj. P. Val	Gene name
1	UGT1A6	1.687	5.50×10^{-12}	UDP glucuronosyltransferase family 1 member A6
2	KIAA0101 (PCLAF)	1.619	4.50×10^{-17}	PCNA clamp associated factor
3	TMEM14A	1.615	2.23×10^{-13}	Transmembrane protein 14A

4	PRC1	1.591	5.67×10^{-18}	Protein regulator of cytokinesis 1
5	PTTG3P	1.534	6.56×10^{-21}	Pituitary tumor-transforming 3, pseudogene
6	MCM2	1.486	8.22×10^{-15}	Minichromosome maintenance complex component 2
7	TUBA1C	1.470	1.44×10^{-17}	Tubulin alpha 1c
8	UBE2T	1.430	3.36×10^{-21}	Ubiquitin conjugating enzyme E2 T
9	CAP2	1.429	2.58×10^{-14}	Adenylate cyclase-associated protein 2
10	RPLP0	1.401	7.73×10^{-21}	Ribosomal protein lateral stalk subunit P0

In contrast, the top ten most strongly downregulated genes (Table 3) represent key components of normal liver physiology, including sinusoidal endothelial and innate immune markers (CLEC1B, CLEC4G, and FCN2), enzymes involved in lipid and hormone metabolism (LCAT, SHBG, and CYP26A1), and hepatocyte-specific transporters and structural proteins (SLC25A47, ECM1, CDHR2, and CRHBP). The reduced expression of these genes indicates a marked loss of liver-specific differentiated functions within the tumor microenvironment.

Table 3: Top 10 downregulated genes with the lowest log2 fold change.

Rank	Gene symbol	Log2FC	adj. P. Val	Gene name
1	CLEC1B	−3.400	1.25×10^{-38}	C-type lectin domain family 1 member B
2	CLEC4G	−2.906	3.08×10^{-53}	C-type lectin domain family 4 member G
3	SLC25A47	−2.875	2.55×10^{-23}	Solute carrier family 25 member 47
4	FCN2	−2.604	3.08×10^{-53}	Ficolin 2
5	ECM1	−2.596	6.02×10^{-46}	Extracellular matrix protein 1
6	CYP26A1	−2.541	2.74×10^{-21}	Cytochrome P450 family 26 subfamily A member 1
7	SHBG	−2.481	8.20×10^{-15}	Sex hormone binding globulin
8	LCAT	−2.458	6.40×10^{-18}	Lecithin-cholesterol acyltransferase
9	CDHR2	−2.302	9.98×10^{-31}	Cadherin related family member 2
10	CRHBP	−2.275	3.63×10^{-39}	Corticotropin releasing hormone binding protein

3.2. Protein–Protein Interaction (PPI) Network Analysis

The top 20 genes with the greatest fold changes (10 upregulated and 10 downregulated), presented in Tables 2 and 3, were uploaded to the STRING protein–protein interaction database to evaluate their functional relationships at the protein level. Since PTTG3P, a non-protein-coding pseudogene, could not be mapped, the analysis was performed on 19 nodes. The resulting network consisted of 19 nodes and 10 edges, with an average node degree of 1.05 and an average local clustering coefficient of 0.526 (Figure 2, Table 4).

Table 4: Basic statistics of the STRING protein–protein interaction network.

Parameter	Value	Description
Number of nodes	19	Number of proteins mapped to the network
Number of edges	10	Number of observed protein–protein interactions
Expected number of edges	2	Expected number of interactions for a random gene set of the same size
Average node degree	1.05	Average number of interactions per node
Average local clustering coefficient	0.526	Degree of interconnectedness among neighboring nodes
PPI enrichment *p*-value	4.67×10^{-5}	Statistical significance of observing more interactions than expected by chance

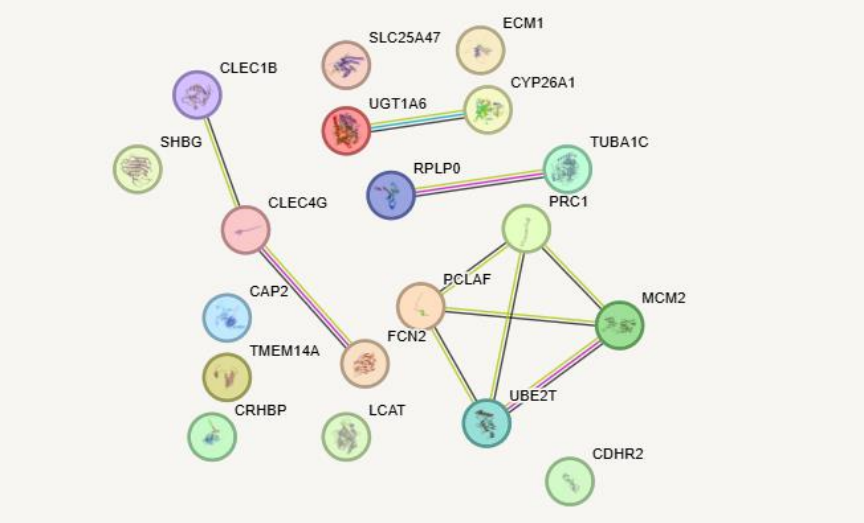

Figure 2: STRING protein–protein interaction (PPI) network of the top 20 differentially expressed genes with the largest fold changes. Each node represents a protein, while each edge represents a known or predicted functional interaction between two proteins. The tightly connected cluster in the upper right (PCLAF, PRC1, MCM2, UBE2T, and TUBA1C) constitutes the upregulated proliferation module, whereas most of the downregulated genes appear as isolated nodes. Since the pseudogene PTTG3P could not be mapped to the STRING database, the network consists of 19 nodes.

For a random gene set of the same size, the expected number of edges was only 2, whereas the observed network contained 10 edges, indicating approximately five times more interactions than expected by chance. The statistical significance of this enrichment was confirmed by a PPI enrichment p-value of 4.67×10^{-5}. In STRING, the statement "significantly more interactions than expected" indicates that the proteins in the network exhibit substantially more functional associations than would be anticipated if an equivalent number of genes were randomly selected from the genome. Therefore, these findings suggest that the identified proteins do not represent an arbitrary collection of unrelated molecules but instead constitute a biologically connected group involved, at least in part, in common functional processes.

Examination of the network topology revealed a tightly connected central module composed predominantly of upregulated proteins. Proteins associated with cell cycle progression, mitosis, and DNA replication including PCLAF (KIAA0101), PRC1, MCM2, and UBE2T formed the most densely interconnected region of the network, while TUBA1C and RPLP0 were positioned adjacent to this proliferative core. Although the overall average node degree was relatively low (1.05), the comparatively high average local clustering coefficient (0.526) indicates that the limited number of interactions was concentrated within a specific subnetwork. Thus, the network is globally sparse but locally enriched around a proliferation-associated functional module.

In contrast, most downregulated proteins (SHBG, ECM1, SLC25A47, LCAT, CDHR2, CRHBP, TMEM14A, and CAP2) appeared as isolated nodes with few or no interactions. Only limited interactions were observed within the CLEC1B–CLEC4G–FCN2 cluster, which is associated with liver sinusoidal endothelial function and innate immunity, as well as between UGT1A6 and CYP26A1. The largely disconnected nature of these downregulated proteins suggests that they do not represent the coordinated disruption of a single protein complex but rather reflect the concurrent suppression of multiple liver-specific metabolic and immunological functions.

Overall, the PPI analysis demonstrates that the transcriptomic alterations observed in HCC are also reflected at the proteomic interaction level, supporting the notion that the HCC phenotype is primarily driven by a functional interaction network centered on cell cycle regulation and cellular proliferation.

4. DISCUSSION

Hepatocellular carcinoma (HCC) is characterized by profound molecular heterogeneity, involving coordinated alterations in multiple signaling pathways that regulate cell proliferation, cell cycle progression, metabolism, immune responses, and genomic stability. Rather than acting in isolation, these molecular alterations operate through interconnected biological networks that collectively drive tumor initiation and progression. Consequently, evaluating transcriptomic alterations within the context of protein–protein interaction (PPI) networks provides a more comprehensive understanding of the functional organization of tumor biology than differential gene expression analysis alone. Network-based approaches facilitate the identification of central molecular modules and key regulatory proteins that may play critical roles in HCC pathogenesis and may represent promising biomarkers or therapeutic targets.

In this study, evaluation of the differentially expressed genes identified from the GSE76427 dataset at the protein–protein interaction (PPI) level revealed that the transcriptomic reprogramming in hepatocellular carcinoma (HCC) exhibits a biphasic organizational pattern. The PPI network constructed from the 20 genes with the greatest fold changes contained approximately five times more interactions than expected by chance, and this enrichment was statistically significant ($p = 4.67 \times 10^{-5}$), indicating that these genes do not constitute a random collection but rather encode functionally related proteins involved in common biological processes. This interaction pattern is consistent with the concept of network medicine, which proposes that disease phenotypes arise not from individual genes but from functionally interconnected molecular modules.[11]

The most prominent feature of the network was a tightly connected proliferation module composed of upregulated genes. The proteins forming this central core PCLAF (KIAA0101), PRC1, MCM2, UBE2T, and TUBA1C—are all involved in distinct stages of the cell cycle and mitosis, and each has been associated with poor prognosis in hepatocellular carcinoma (HCC) in independent studies. Among these, MCM2, a key component of the DNA replication licensing machinery, is consistently overexpressed in HCC and has been linked to unfavorable clinical outcomes. Previous studies have further demonstrated that MCM2 promotes stem cell–like properties and sorafenib resistance through activation of the Hippo/YAP signaling pathway. Notably, these observations have been validated across multiple independent transcriptomic datasets, including the GSE76427 cohort analyzed in the present study. .[14] Similarly, PCLAF (KIAA0101), a proliferating cell nuclear antigen (PCNA)-binding factor involved in DNA replication and repair, is consistently overexpressed in HCC. Its elevated expression has been independently associated with advanced tumor stage, early postoperative recurrence, and poor overall survival, highlighting its potential value as both a prognostic biomarker and a therapeutic target.[15] PRC1, a microtubule-associated regulator of cytokinesis, is a direct downstream target of the Wnt/β-catenin signaling pathway and establishes a positive feedback loop that promotes early recurrence of HCC.[16] Elevated expression of the ubiquitin-conjugating enzyme UBE2T promotes proliferation and migration in HCC cells and predicts poor prognosis, whereas high expression of the α-tubulin isoform TUBA1C has been associated with cell cycle progression, proliferation, and metastatic potential.[17,18]

The topological properties of the network further support these findings. Although the average node degree was low (1.05), the relatively high average local clustering coefficient (0.526) indicates that the network is globally sparse, while the observed interactions are concentrated around the proliferation module. Such locally dense subnetworks represent the primary regions in which central hub proteins are expected to reside. Accordingly, a formal topology-based centrality analysis (e.g., using cytoHubba) would most likely identify PCLAF, PRC1, MCM2, UBE2T, and TUBA1C as the principal hub gene candidates.[13] The fact that each of these genes has demonstrated prognostic value in independent cohorts indicates that this proliferation-associated hub signature is reproducible across different datasets, thereby reinforcing the robustness and reliability of our findings.

In contrast, the downregulated genes reflect a distinct biological process. The fact that the number of downregulated genes was approximately three times greater than that of upregulated genes, and that these genes appeared largely as isolated nodes within the PPI network, suggests the simultaneous suppression of multiple liver-specific functional programs rather than the disruption of a single protein complex. These genes include markers associated with liver sinusoidal endothelial function and innate immunity (CLEC1B, CLEC4G, and FCN2), enzymes involved in lipid and hormone metabolism (LCAT, SHBG, CYP26A1, and UGT1A6), and hepatocyte-specific transporters and structural proteins (SLC25A47, ECM1, CDHR2, and CRHBP). Notably, CLEC1B, CLEC4G, and FCN2 have also been consistently identified in independent bioinformatics studies of HCC as genes that are significantly downregulated in tumor tissues and are closely associated with the normal immunological and sinusoidal endothelial functions of the liver.[19] The dispersed distribution of these proteins within the network suggests a loss of liver-specific differentiated functions (dedifferentiation) in the tumor microenvironment.[4]

Overall, the PPI analysis indicates that the HCC phenotype is primarily driven by a functional interaction network centered on cell cycle regulation and cellular proliferation, whereas liver-specific metabolic and immunological programs are coordinately suppressed. The hub proteins within the proliferation module represent strong candidates as both diagnostic/prognostic biomarkers and therapeutic targets. Given the limited and variable response rates to current systemic therapies, as well as the frequent development of acquired resistance,[4] evaluating these proteins through structure-based drug discovery approaches represents a logical next step. Nevertheless, several limitations of this study should be acknowledged. First, the findings are based on a single microarray dataset. Second, the PPI analysis was performed using only the 20 genes with the greatest fold changes. Finally, the results are derived exclusively from in silico analyses. Therefore, independent validation of the expression patterns and prognostic significance of the identified hub genes at the protein level in external cohorts (e.g., TCGA) and in experimental or clinical samples will be essential to strengthen the biological and clinical relevance of these findings.

REFERENCES

1. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. Nature reviews Disease primers, 2021; 7(1): 6.
2. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 2024; 74(3): 229-63.
3. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. Journal of clinical gastroenterology, 2013; 47 Suppl(0): S2-6.
4. Llovet JM, Pinyol R, Kelley RK, El-Khoueiry A, Reeves HL, Wang XW, et al. Molecular pathogenesis and systemic therapies for hepatocellular carcinoma. Nature cancer, 2022; 3(4): 386-401.
5. Casak SJ, Donoghue M, Fashoyin-Aje L, Jiang X, Rodriguez L, Shen YL, et al. FDA Approval Summary: Atezolizumab Plus Bevacizumab for the Treatment of Patients with Advanced Unresectable or Metastatic Hepatocellular Carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research, 2021; 27(7): 1836-41.
6. Villanueva A. Hepatocellular Carcinoma. The New England journal of medicine, 2019; 380(15): 1450-62.
7. Hasin Y, Seldin M, Lusis A. Multi-omics approaches to disease. Genome biology, 2017; 18(1): 83.
8. Wang Z, Gerstein M, Snyder M. RNA-Seq: a revolutionary tool for transcriptomics. Nature reviews Genetics, 2009; 10(1): 57-63.
9. Barrett T, Wilhite SE, Ledoux P, Evangelista C, Kim IF, Tomashevsky M, et al. NCBI GEO: archive for functional genomics data sets--update. Nucleic acids research, 2013; 41(Database issue): D991-5.
10. Ritchie ME, Phipson B, Wu D, Hu Y, Law CW, Shi W, et al. limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic acids research, 2015; 43(7): e47.
11. Barabási AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. Nature reviews Genetics, 2011; 12(1): 56-68.
12. Szklarczyk D, Kirsch R, Koutrouli M, Nastou K, Mehryary F, Hachilif R, et al. The STRING database in 2023: protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. Nucleic acids researc, 2023; 51(D1): D638-d46.
13. Chin CH, Chen SH, Wu HH, Ho CW, Ko MT, Lin CY. cytoHubba: identifying hub objects and sub-networks from complex interactome. BMC systems biology, 2014; 8 Suppl 4(Suppl 4): S11.
14. Zhou X, Luo J, Xie H, Wei Z, Li T, Liu J, et al. MCM2 promotes the stemness and sorafenib resistance of hepatocellular carcinoma cells via hippo signaling. Cell death discovery, 2022; 8(1): 418.
15. Yuan RH, Jeng YM, Pan HW, Hu FC, Lai PL, Lee PH, et al. Overexpression of KIAA0101 predicts high stage, early tumor recurrence, and poor prognosis of hepatocellular carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research, 2007; 13(18 Pt 1): 5368-76.
16. Chen J, Rajasekaran M, Xia H, Zhang X, Kong SN, Sekar K, et al. The microtubule-associated protein PRC1 promotes early recurrence of hepatocellular carcinoma in association with the Wnt/β-catenin signalling pathway. Gut., 2016; 65(9): 1522-34.
17. Ren X, Li A, Ying E, Fang J, Li M, Yu J. Upregulation of ubiquitin-conjugating enzyme E2T (UBE2T) predicts poor prognosis and promotes hepatocellular carcinoma progression. Bioengineered, 2021; 12(1): 1530-42.
18. Wang J, Chen W, Wei W, Lou J. Oncogene TUBA1C promotes migration and proliferation in hepatocellular carcinoma and predicts a poor prognosis. Oncotarget, 2017; 8(56): 96215-24.
19. Wang S, Song Z, Tan B, Zhang J, Zhang J, Liu S. Identification and Validation of Hub Genes Associated With Hepatocellular Carcinoma Via Integrated Bioinformatics Analysis. Frontiers in oncology, 2021; 11: 614531.