Original Article
Screening of hepatocellular carcinoma hub genes and construction of a control network

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Abstract: Background: Hepatocellular carcinoma (HCC) is a malignant tumor that threatens human life and health. However, the molecular mechanisms of hepatocarcinogenesis remain unclear. Aim: The current study aimed to explore the molecular mechanisms of HCC through screening and functional analysis of differentially-expressed genes of HCC, providing a new method for diagnosis and treatment of HCC. Methods: Gene expression arrays of 14 pairs of HCC tissues and corresponding non-cancerous tissues were obtained from the GEO database. Next, this study identified differentially-expressed genes using the R program. The gene function and protein-protein interaction (PPI) network of DEGs was analyzed using the DAVID website and STRING database. Visualization was conducted with Cytoscape 3.7.0 software. An MCC algorithm was used to screen high connectivity hub genes. At the same time, a hub gene-miRNA regulatory network was constructed. Finally, verification of the hub genes was conducted using Kaplan-Meier and UALCAN websites. Results: A total of 285 DEGs were identified to be significantly associated with HCC tissues, including 56 upregulated and 229 downregulated genes. Gene ontology analysis revealed that downregulated genes were mainly involved in Redox and metabolic processes. Furthermore, 20 hub genes were screened. Five genes, including RRM2, CCNB1, CDK1, NCAPG, and KIF20A, were found to be highly regulated by miRNAs. Validation results showed that expression of 20 hub genes was significantly higher in HCC tissues and closely related to prognosis of HCC patients. Conclusion: Through bioinformatics analysis, the roles of DEGs in HCC were examined. Thus study may provide a new molecular target for diagnosis and treatment of HCC, providing a theoretical basis for further study of the molecular mechanisms of HCC.

Keywords: Hepatocellular carcinoma, bioinformatics, molecular mechanism, hub genes, control network

Introduction

Hepatocellular carcinoma (HCC) is a common malignant tumor type, worldwide, with extremely high morbidity and mortality rates, especially in China [1, 2]. The mortality rate of HCC ranks second among leading causes of among all cancer-associated deaths. According to statistics, approximately 600,000 patients die of HCC every year [3-6]. Although great progress has been made in diagnostic techniques, radiotherapy, interventional therapy, and surgical treatment in recent years, prognosis of HCC remains unsatisfactory, with five-year overall survival rates less than 5% [7, 8]. Moreover, liver cancer is not easily discovered. It often progresses to middle and late stages. Many patients lose the opportunity for surgery. Therefore, it is of great significance to study the molecular mechanisms of HCC, improving prevention, diagnosis, and treatment of HCC.

In recent years, with the landmark progress of gene sequencing along with the rapid spread of the internet, hundreds of biological databases have emerged rapidly. Through bioinformatics analysis, databases can be used to screen target genes, analyzing gene function conveniently and quickly. Bioinformatics provides a novel molecular target for HCC prevention, diagnosis, and treatment.
Methods

Microarray data acquisition

Expression profiles were downloaded from the Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/). Array data for GSE84402 (Experiment type: Expression profiling by array; Platforms: GPL570, Affymetrix Human Genome U133 plus 2.0 Array; Organism: Homo sapiens) contained 14 pairs of HCC tissues and corresponding adjacent tissues. All HCC samples were extracted and analyzed from pathologically diagnosed HCC tissues and corresponding non-cancerous tissues.

Processing data and identification of DEGs

R software (version 3.5.1, https://www.r-project.org/) is an excellent tool for statistical calculation and statistical mapping. It is used in the language and operating environment of statistical analysis and drawing. It can identify DEGs via the correlation R package and function. R software can be used to screen for DEGs that are differentially-expressed between hepatocellular carcinoma tissues and corresponding non-cancerous tissues. This study used R software to process and analyze raw data. First, background corrections and quantile normalization were performed on the raw data using the robust mult-array average (RMA) algorithm in R software [9]. Differentially-expressed gene (DEGs) between the tumor and normal group samples were analyzed using paired t-tests. Multiple testing was corrected by the Benjamini-Hochberg method, obtaining adjusted P-values [10]. Finally, genes with adjusted P-values < 0.05 and |log2 fold-change (log FC)| ≥ 2 indicated significance.

Gene ontology and pathway enrichment analysis of DEGs

The biological function of DEGs was predicted by Annotation, Visualization, and Integrated Discovery version 6.7 Database (DAVID, https://david.ncifcrf.gov/, accessed November 25, 2018). A comprehensive set of functional annotation tools [11], the DAVID database includes GO and KEGG analysis functions. It is an online bioinformatics analysis system that integrates biological information and analysis tools for large-scale gene and protein (gene ID, protein ID) analysis. This helps researchers access important biological information.

GO is composed of three parts: 1) cellular Components (CC), used to describe subcellular structures; 2) molecular Function (MF), used to describe gene function; and 3) biological Process (BP), used for ordered action of biomolecules, playing a broader role [12]. The Kyoto Encyclopedia of Genome and Genome (KEGG) is a database for systematic analysis of gene functions that integrates genomic, chemical, and systemic functional information. Many metabolic pathways and their relationships can be obtained by KEGG. DEGs in GSE84402 were identified by R software. They were further analyzed using DAVID online. The cut-off criteria were set at p < 0.05, indicating statistical significance.

Protein-protein interaction network analysis

Search Tool for the Retrieval of Interacting Genes (STRING) database (http://string-db.org/) is a database dedicated to evaluating protein-protein interactions (PPI), including direct and indirect associations [13]. Cytoscape is a graphical display, analysis, and editing software program, visualizing the network of proteins, genes, and other biomolecules [14]. Importing PPI data into Cytoscape, a protein-protein interaction network was constructed by STRING. It was visualized in Cytoscape. The Cytohubba plug-in for Cytoscape was used to screen hub genes from the PPI network. Data setting conditions: Experimentally validated interactions with a combined score > 0.4 were selected as significant. Only DEGs with a degree score ≥ 20 were selected as hub genes. The top 20 genes were obtained with the highest connectivity, designated as key genes. Subsequently, the MCODE plug-in was detected using a molecular complex, using degree cutoff = 2 node score cutoff = 0.2 K-core = 2G and max. The depth = 100 truncation criterion was used to screen out the PPI module. The signal path of the fundamental factor in each module was analyzed by DAVID.

Construction of hub gene-miRNA regulatory network

Researchers downloaded miRNAs from the MiRDB database (http://mirdb.org) that might regulate the hub gene. Numerical setting: Interaction score between miRNAs and Hub genes was ≥ 80. The hub gene-miRNA regulatory network was constructed by Cytoscape software.
Figure 1. Heatmap of the first 25 upregulated genes and the first 25 downregulated genes. The red part represents upregulated, while the green part represents downregulated.
Hepatocellular carcinoma hub gene

Table 1. Gene ontology analysis of downregulated DEGs associated with HCC

<table>
<thead>
<tr>
<th>Category</th>
<th>ID</th>
<th>Term</th>
<th>Count</th>
<th>%</th>
<th>P</th>
<th>FDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>GO:00055114</td>
<td>Oxidation-reduction process</td>
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<td>17.22</td>
<td>1.32E-13</td>
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<td>BP</td>
<td>GO:0042738</td>
<td>Exogenous drug catabolic process</td>
<td>7</td>
<td>3.89</td>
<td>7.50E-10</td>
<td>1.19E-06</td>
</tr>
<tr>
<td>BP</td>
<td>GO:0006805</td>
<td>Xenobiotic metabolic process</td>
<td>11</td>
<td>6.11</td>
<td>4.79E-09</td>
<td>7.63E-06</td>
</tr>
<tr>
<td>BP</td>
<td>GO:0019373</td>
<td>Epoxygenase P450 pathway</td>
<td>7</td>
<td>3.89</td>
<td>1.43E-08</td>
<td>2.28E-05</td>
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<tr>
<td>BP</td>
<td>GO:0071294</td>
<td>Cellular response to zinc ion</td>
<td>7</td>
<td>3.89</td>
<td>2.08E-08</td>
<td>3.31E-05</td>
</tr>
<tr>
<td>CCa</td>
<td>GO:0005576</td>
<td>Extracellular region</td>
<td>42</td>
<td>23.33</td>
<td>2.91E-09</td>
<td>3.42E-06</td>
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<tr>
<td>CC</td>
<td>GO:0007062</td>
<td>Extracellular exosome</td>
<td>56</td>
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<td>CC</td>
<td>GO:0005615</td>
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<td>1.03E-02</td>
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<tr>
<td>CC</td>
<td>GO:0031090</td>
<td>Organelle membrane</td>
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<td>1.67E-12</td>
<td>1.96E-09</td>
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<tr>
<td>CC</td>
<td>GO:0072562</td>
<td>Blood microparticle</td>
<td>14</td>
<td>7.78</td>
<td>2.10E-09</td>
<td>2.47E-06</td>
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<tr>
<td>MFb</td>
<td>GO:0005506</td>
<td>Iron ion binding</td>
<td>14</td>
<td>7.78</td>
<td>2.92E-09</td>
<td>4.12E-06</td>
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<tr>
<td>MF</td>
<td>GO:0020037</td>
<td>Heme binding</td>
<td>13</td>
<td>7.22</td>
<td>8.58E-09</td>
<td>1.21E-05</td>
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<tr>
<td>MF</td>
<td>GO:0004497</td>
<td>Monooxygenase activity</td>
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<tr>
<td>MF</td>
<td>GO:0004252</td>
<td>Serine-type endopeptidase activity</td>
<td>10</td>
<td>5.56</td>
<td>8.45E-04</td>
<td>1.18E+00</td>
</tr>
<tr>
<td>MF</td>
<td>GO:0019825</td>
<td>Oxygen binding</td>
<td>10</td>
<td>5.56</td>
<td>5.82E-10</td>
<td>8.20E-07</td>
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</table>

1BP biological process, 2CC cell component, 3MF molecular function. 4FDR False discovery rate (E-n: ×10).

Table 2. KEGG pathway analysis of downregulated DEGs associated with HCC

<table>
<thead>
<tr>
<th>Pathway ID</th>
<th>Term</th>
<th>Count</th>
<th>%</th>
<th>P</th>
<th>FDR</th>
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<tr>
<td>Hsa01100</td>
<td>Metabolic pathways</td>
<td>41</td>
<td>22.78</td>
<td>9.26E-07</td>
<td>1.11E-03</td>
</tr>
<tr>
<td>Hsa00830</td>
<td>Retinol metabolism</td>
<td>12</td>
<td>6.67</td>
<td>2.87E-09</td>
<td>3.45E-06</td>
</tr>
<tr>
<td>Hsa05204</td>
<td>Chemical carcinogenesis</td>
<td>11</td>
<td>6.11</td>
<td>3.60E-07</td>
<td>4.34E-04</td>
</tr>
<tr>
<td>Hsa00982</td>
<td>Drug metabolism-cytochrome P450</td>
<td>11</td>
<td>6.11</td>
<td>7.43E-08</td>
<td>8.94E-05</td>
</tr>
<tr>
<td>Hsa03320</td>
<td>PPAR signaling pathway</td>
<td>5</td>
<td>2.78</td>
<td>2.00E-02</td>
<td>2.16E+01</td>
</tr>
</tbody>
</table>

1E-n: ×10.

Background

UALCAN expression analysis and Kaplan-Meier survival analysis based on TCGA database

Expression and prognosis were verified by UALCAN and Kaplan-Meier plotter websites based on the TCGA database.

Results

Identification of DEGs in HCC

According to conditional analysis, 285 DEGs were identified in GSE84402. Of these, 56 were upregulated genes and 229 downregulated genes. This study compared 50 DEGs with significant differences (25 upregulated genes and 25 downregulated genes). The heat map is shown in Figure 1.

Gene ontology and KEGG pathway enrichment analyses

Gene functional and pathway information of the 285 DEGs were analyzed by DAVID. According to the results of GO analyses, downregulated DEGs were significantly enriched in the oxidation-reduction process, xenobiotic metabolic process, epoxygenase P450 pathways, and cellular responses to zinc ion biological processes. Cell components showed that downregulated DEGs were involved in the extracellular region, extracellular exosome, extracellular space, membrane attack complex, and integral components of the plasma membrane. Downregulated DEGs were enriched in molecular functional, including iron ion binding, heme binding, monooxygenase activity, and oxidoreductase activity (Table 1). Downregulated KEGG pathways were significantly enriched by metabolic pathways, retinol metabolism, chemical carcinogenesis, drug metabolism-cytochrome P450, and PPAR signaling pathways (Table 2). Because of the small number of upregulated genes, there were no significant enrichment results in GO and KEGG.

Module analysis of DEGs

A total of 285 DEGs (log FC > 2) were analyzed using String 10.5. Cytocape software was used
Figure 2. A. 285 DEGs were used to construct a protein-protein interaction (PPI) network by on-line analysis of String data (upregulated genes are displayed in red and downregulated genes in blue); B. Hub proteins of protein-protein interaction (PPI) network (top20).
to visualize the construction of the PPI network of DEGs (Figure 2A). Using the MCC algorithm, screening of the first 20 Hub genes and the color depth were used to represent the scores predicted by the MCC algorithm (Figure 2B). These 20 hub genes were highly expressed in hepatocellular carcinoma tissues (Table 3). Furthermore, MOCDE analysis used to group the most closely connected genes in the PPI network to form multiple modules. Results showed that the first three modules had higher scores (Figure 3). The most rated module 1 contained 20 Hub genes. Interactions between other genes were more dispersed.

Construction of hub gene-miRNA regulatory network

In constructing the regulatory network of the Hub gene-miRNA (Figure 4), a total of 72 miRNA were shown to be involved. Of these, RRM2 (connectivity = 12), CCNB1 (connectivity = 10), KIF20A (connectivity = 10), NCAPG (connectivity = 9), and CDK1 (connectivity = 6) had higher connectivity, indicating that these mRNAs were highly regulated by the miRNA network.

Tumorigenesis, progression, and metastasis of HCC, like most other cancers, is a complex process that is the result of a combination of multiple factors and multiple pathways, involving a large number of abnormalities in genes and pathways [15-17]. However, the molecular mechanisms of its occurrence and development have not been elucidated. To improve diagnosis and treatment of HCC, it is vitally important to find these abnormal genes or pathways, aiming to understand their roles in the molecular mechanisms of HCC. With the development of microarray and high throughput technologies, researchers have been able to detect cancer etiology by examining aberrations in whole-genome levels. These technologies have been widely used to predict potential therapeutic targets for various cancers [18].

In this study, a total of 285 differentially-expressed genes were screened by analyzing GSE84402 data of gene expression profiles in the GEO database. Differential-genes were analyzed by GO and KEGG enrichment analysis. Results showed that these DEGs were mainly involved in the biological processes of redox and other biological processes. The metabolic

Table 3. Twenty hub genes highly expressed in hepatocellular carcinoma tissues

<table>
<thead>
<tr>
<th>Gene</th>
<th>Expression</th>
<th>Log FC</th>
<th>P Value</th>
<th>Adj.P.Val</th>
</tr>
</thead>
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<tr>
<td>BUB1B</td>
<td>UP</td>
<td>2.207781</td>
<td>7.80E-08</td>
<td>1.63E-05</td>
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<tr>
<td>CDK1</td>
<td>UP</td>
<td>2.153406</td>
<td>1.97E-08</td>
<td>6.68E-06</td>
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<tr>
<td>NDC80</td>
<td>UP</td>
<td>2.000320</td>
<td>5.17E-08</td>
<td>1.27E-05</td>
</tr>
<tr>
<td>CCNB1</td>
<td>UP</td>
<td>2.890837</td>
<td>3.27E-11</td>
<td>1.19E-07</td>
</tr>
<tr>
<td>NUF2</td>
<td>UP</td>
<td>2.038862</td>
<td>4.73E-07</td>
<td>5.90E-05</td>
</tr>
<tr>
<td>ZWINT</td>
<td>UP</td>
<td>2.233690</td>
<td>2.86E-07</td>
<td>4.20E-05</td>
</tr>
<tr>
<td>AURKA</td>
<td>UP</td>
<td>2.089909</td>
<td>1.05E-09</td>
<td>1.01E-06</td>
</tr>
<tr>
<td>KIF20A</td>
<td>UP</td>
<td>2.046271</td>
<td>3.57E-08</td>
<td>9.59E-06</td>
</tr>
<tr>
<td>NCAPG</td>
<td>UP</td>
<td>2.011597</td>
<td>1.50E-06</td>
<td>0.000136</td>
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<tr>
<td>TPX2</td>
<td>UP</td>
<td>2.120467</td>
<td>5.16E-09</td>
<td>2.77E-06</td>
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<tr>
<td>BIRC5</td>
<td>UP</td>
<td>2.002120</td>
<td>6.10E-09</td>
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<tr>
<td>TOP2A</td>
<td>UP</td>
<td>3.206744</td>
<td>8.58E-10</td>
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<td>PBK</td>
<td>UP</td>
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<td>2.088389</td>
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<td>TTK</td>
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<td>ASPM</td>
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<td>RRM2</td>
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<td>PTTG1</td>
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<td>2.014036</td>
<td>1.71E-08</td>
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</table>

Expression and prognosis validation of hub genes based on TCGA database

Expression levels of hub genes were verified by the UALCAN database. Results showed that expression of Hub genes in HCC tissues was significantly higher than that in normal liver tissues. Expression levels of 10 Hub genes (Figure 5), including PTTG1, CCNB1, ZWINT, NUSAP1, AURKA, RRM2, CDK1, TPX2, TOP2A, and KIAA0101, were the most significant (mean > 4). This was consistent with the results of the gse84402 dataset. The survival curve of hub genes was drawn using the Kaplan-Meier survival curve method. Results showed that overall survival rates of the low expression group were better than those of the high expression group. Survival rates of the 5 hub genes, CDK1, ZWINT, PTTG1, NDC80, and AURKA, were the most significant (Figure 6).

Discussion
Figure 3. A. Module 1; B. Module 2; C. Module 3.
Figure 4. miRNAs and Hub gene control network: The red part represents Hub genes, the white part represents miRNAs.
Figure 5. Verification of expression levels of hub genes. The red part represents upregulated, the blue part represents downregulated.
Hepatocellular carcinoma hub gene

Figure 6. Kaplan-Meier survival curve analysis of Hub genes of HCC.
reprogramming of cancer cells could lead to increases in oxidative stress due to metabolism-induced changes in microenvironment. Therefore, maintaining the redox balance, cancer cells maintain redox homeostasis by enhancing their antioxidant capacity through a variety of mechanisms [19]. These genes are mainly involved in the cellular composition of extracellular bodies, organelle membranes, and membrane attack complexes. Along with glycosylation, amino acid metabolism, and other molecular functions, tumors continue to compete with the body for nutrients, especially amino acids, during the rapid growth process. Studies have shown that amino acids are an important in maintaining the growth and proliferation of tumor cells. Glutamine, leucine, and valine provide nutrients for tumor growth [20]. A total of 41 DEGs were found to be enriched in metabolic-related pathways by KEGG pathway enrichment. It also relates to PPAR signaling pathways. Peroxisome proliferate-activated receptor (PPAR) is a family of peroxisome proliferators-activated receptors, including PPAR-α, PPAR-β/δ, and PPAR-γ phenotypes. Of these, PPAR-γ plays an important role in regulating glucose metabolism and tumorigenesis and development. It has been proven that PPAR-α is highly expressed in the liver and has protective effects on liver cells [21]. In addition, PPAR-α is involved in oxidative stress and cell cycle regulation. Analysis of genes was conducted in the most closely connected and important nodes of the DEGs in the PPI network using Cytoscape software. A total of 20 Hub genes, including RRM2, CCNB1, CDK1, NCAPG, KIF20A, and other genes with the highest connectivity, were screened out. Through the construction of the hub gene-miRNA regulatory network, 70 related miRNAs were screened out. These miRNAs may have synergistic or inhibitory regulatory effects on hub genes. RRM2, CCNB1, CDK1, NCAPG, and KIF20A are highly regulated by multiple miRNAs. In subsequent verification, 20 hub genes were significantly overexpressed in HCC tissues. High expression of hub genes was shown to be closely related to poor prognosis in HCC patients.

Combining hub genes and expression and prognosis verification, the current study focused on the research progress of CDK1, PTTG1, ZWINT, NDC80, and AURKA, aiming to provide the basis for future experiments. Research has proven that CDK1 is involved in the regulation of cell cycle [22]. Kawamoto et al. found that CDK1 over-proliferates in breast cancer [23]. Previous studies have suggested that CDK1 is highly expressed in various types of cancer, including lung, colorectal, and renal cancer [24-26]. Furthermore, the activity of CDK1 has been demonstrated to play an important role in angiogenesis, energy metabolism, and tumor development by regulation. The activity of CDK1 has also been shown to be regulated by p53 pathways [27].

Pituitary tumor-transforming gene 1 (PTTG1) plays an important role in the regulation of transcription, mitosis, cell cycle regulation, chromosome stability, DNA repair, and apoptosis [28]. Many studies have shown that PTTG1 is highly expressed in most tumors, such as thyroid cancer, colorectal cancer, ovarian cancer, thymic cancer, hepatocellular carcinoma, lung cancer, and esophageal cancer [29]. Fujii [30] reported that expression of PTTG1 mRNA in HCC tissues was significantly higher than that in para-cancerous liver tissues and PTTG1 protein was highly expressed in HCC tissues, but not in para-cancerous liver tissues. Moreover, high expression of PTTG1 in HCC tissues was mainly related to the level of α-l-fucosidase, tumor size, and differentiation degree [31]. In addition, it has been proven that pituitary adenoma transforming gene 1 can promote hepatitis B virus replication and hepatitis progression by inhibiting p53 [32]. PTTG1 gene silencing can inhibit weight gain and activity of HCC cells [33].

The protein encoded by ZWINT genes is the key regulation protein of mitotic checkpoint. It mainly participates in mitosis and regulates the cell cycle. It has been reported that ZWINT is associated with chromosomal instability (CIN), suggesting that ZWINT may promote tumorigenesis and development [34]. In addition, some experiments have proven that ZWINT protein promotes the proliferation ability of hepatoma cells by regulating cell cycle [35].

Mitotic cyclin 80 (nuclear division cycle 80 (NDC80) plays an important role in cell mitosis. One study showed that ndc80 induces hepatocarcinoma mainly through its effect of promoting proliferation and anti-apoptosis [36]. In addition, NDC80 is highly expressed in osteosarcoma [37], colon cancer [38], and breast cancer [39].
AURKA is a member of the serine/threonine kinase family. It is a Ras binding protein, playing an important role in regulating cell mitosis. It has been suggested that AURKA may be related to MAPK signal transduction pathways mediated by Ras. This may be a new target for diagnosis and treatment of HCC [40].

Conclusion

In summary, using bioinformatics, the current study provides information on DEGs and hinge genes that may be involved in liver cancer. However, this analysis was limited. It does not capture the expression of these genes in different HCC subtypes. Another limitation of this work is that the reliability of the genes screened was not experimentally proven. Although the current work demonstrates the benefits and usefulness of microarray analysis in extracting DEGs and hub genes that could be potential diagnostic and therapeutic targets for HCC, there is a need for improved analysis and prospective clinical research. However, the current study is useful in understanding the potential molecular mechanisms of liver cancer, providing guidance for subsequent experimental studies.

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Disclosure of conflict of interest

None.

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References


