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Construction of a circRNA-miRNA-mRNA Network and Prognostic Model to Unveil Prognosis and Immunotherapy Prospects of Hepatocellular Carcinoma

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ABSTRACT

Background: This study aimed at understanding the mechanisms underlying the pathogenesis of hepatocellular carcinoma (HCC) and to provide biomarkers for prognosis as well as immunotherapy and chemotherapy by constructing a circular (circ)RNA-micro (mi)RNA-mRNA ceRNA network and risk model.

Methods: High-throughput sequencing data including circRNA, miRNA, and mRNA expression profiles for HCC were downloaded from the Gene Expression Omnibus (GEO) database. Differentially expressed circRNAs, miRNAs, and mRNAs were identified and screened by Limma package in R language. Based on circRNA-miRNA pairs and miRNA-mRNA pairs, a ceRNA network was constructed. The potential functions of differentially expressed circRNAs were analyzed using gene ontology (GO) and the Kyoto encyclopedia of genes and genomes (KEGG) enrichment analysis. mRNAs with a significant prognosis were screened using Univariate COX regression analysis, and were used to construct a prognosis model using Lasso regression. The prognostic value of the model was then evaluated by performing a survival analysis and establishing a ROC curve. Finally, the predictive ability of the model for immunotherapy and sensitivity to chemotherapy was analyzed.

Results: A total of 72 up-regulated circRNAs, 49 down-regulated circRNAs, 8 up-regulated miRNAs, 5 down-regulated miRNAs, 772 up-regulated mRNAs, and 929 down-regulated mRNAs were differentially expressed in HCC. A ceRNA network composed of target genes was constructed, incorporating 7 circRNAs, 4 miRNAs, and 10 differently expressed genes (mRNAs). A prognostic model was constructed based on 4 prognosis-related mRNAs (PSMD10, RAB15, ESR1, and PPARGC1A) and tested in HCC patients divided into training and validation groups, with AUC = 0.704 in the training group and AUC = 0.661 in the validation group. Univariate and multivariate COX regression demonstrated that the proposed model could be used as an independent prognostic model in HCC. The expression of PD-1 in the high-risk group was found to be higher than that in the low-risk group. Moreover, the IC50 of cisplatin and paclitaxel was lower in the high-risk group.

Conclusions: Our study provides a rationale for the circRNA-miRNA-mRNA regulatory network as a promising tool for mechanism research and biomarker identification of occurrence and prognosis of HCC patients. The constructed prognostic model based on 4 prognosis-related mRNAs (PSMD10, RAB15, ESR1, and PPARGC1A) is proposed as a new indicator in guiding immunotherapy and chemotherapy management in HCC.

Keywords: Hepatocellular Carcinoma; ceRNA Network; Prognostic Model; Immunotherapy; Chemotherapy

Abbreviations: GEO: Gene Expression Omnibus; GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; HCC: Hepatocellular Carcinoma; UTR: Untranslated Region

Introduction

Hepatocellular carcinoma (HCC) is a malignancy that poses the greatest threat to human life and is currently the main cause of cancer deaths worldwide [1-3]. Despite the gradual improvements in effective therapy for HCC, there are still a large number of patients who do not receive a timely diagnosis due to unremarkable early symptoms and the lack of effective biomarkers, and thus, face short survival [4,5]. Therefore, rigorous mechanism modeling and the identification of objective, precise biomarkers are a high priority for early diagnosis and timely treatment for HCC. It is known that non-coding RNAs, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), are involved in the occurrence and development of tumors, including HCC [6-8]. MiRNAs induce either translational repression or mRNA degradation via binding to complementary sequences in the 3'-untranslated region (UTR) of target mRNAs [9]. The prognostic miRNA signature in colon cancer and cervical cancer has been deeply investigated by the recent studies [10]. CircRNAs are novel coding or non-coding RNA with a covalent closed-loop structure believed to be formed by erroneous transcription during splicing [11]. Due to the lack of a 5' cap structure and 3' polyA tail, circRNAs have a longer half-life and stronger resistance to RNase than linear RNA [10,12].

CeRNA transcripts are mutually regulated at the post-transcriptional level by competing shared miRNAs. When two transcripts contain the same miRNA response elements (MRE), they are able to competitively bind to miRNA. The upregulation of one transcript can result in further binding of the shared miRNA, thereby reducing the expression of the other transcript [13]. The ceRNA network links the functions of protein-encoding mRNA and non-encoding RNA (microRNA, circRNA, lncRNA) [13]. MiRNA sponging by circRNA is another property that has captured increasing attention [14]. In HCC, the circRNA Cdr1as can be used as a competing endogenous RNA (ceRNA) to directly bind to miR-1270, and thus, up-regulate the expression of the target gene AFP, promoting the occurrence, development, and metastasis of HCC [15]. Some studies have found circMAT2B exhibits therapeutic and diagnostic value associated with its role in promoting glycolysis and HCC progression by activating the circMAT2B/miR-338-3p/PKM2 axis under hypoxia [16]. These findings indicate that ceRNA interactions can be an underlying player in the occurrence and development of HCC. A comprehensive analysis of the circRNA-miRNA-mRNA regulatory network is conducive to clarifying the role of circRNA in HCC and provides a rationale for clinical studies.

In this study, we downloaded circRNA (GSE97332), miRNA (GSE108724), and mRNA (GSE46408) microarray datasets related to HCC from the Gene Expression Omnibus (GEO) database and identified differentially expressed circRNAs (DECs), differentially expressed miRNAs (DEMIs), and differentially expressed mRNAs (DEMs). The gene network of circRNA-miRNA pairs and miRNA-mRNA pairs was constructed based on gene expression profiling to screen the most relevant mRNAs. Gene ontology (GO) functional processes and Kyoto encyclopedia of genes and genomes (KEGG) enrichment analysis was conducted to confirm the underlying molecular functions and the participating pathways by which mRNAs facilitated HCC onset and progression. By conducting a univariate COX analysis, mRNAs significantly associated with prognosis in the CERNA network were screened. Lasso regression was used to construct a prognostic model based on the data from TCGA database, the accuracy of the model was evaluated, and the efficacy of immunotherapy and chemotherapy for HCC patients was predicted. The current study characterizes the mechanisms underlying circRNA involvement in regulating the occurrence and development of HCC through the ceRNA network as well as the prognosis and immunotherapy/chemotherapy prospects of the constructed risk model in HCC.

Materials and Methods

Data Collection and Preprocessing

All available microarray datasets from HCC studies were collected from GEO (http://www.ncbi.nlm.nih.gov/gds/). CircRNA (GSE97332), miRNA (GSE108724), and mRNA (GSE46408) microarrays consisted of 7, 7, and 6 pairs of human HCC and matched non-tumor tissues, respectively. The expression matrix files were analyzed in bulk. The original probe file was converted into circRNA, miRNA, and mRNA matrix files. Subsequently, the circRNA matrix (not a standard gene name) was converted into each standard gene symbol based on circBase (http://circrna.org/) for further analysis.

Differential Analysis of CircRNA, miRNA, and mRNA Expressions

Within the R software environment, the Bioconductor Limma package was used for data quality control and expression normalization before differential analysis of microarray data [17]. Various circRNAs and miRNAs were screened, for which the filtration conditions were an adjusted P-value < 0.05 and |Log2FC| > 2. In addition, different mRNAs were filtered by the adjusted P-value < 0.05 and |Log2FC| > 1. The above data were clustered and analyzed in R, and visualized as heatmaps.

Construction of the ceRNA Network

The cancer-specific circRNA database (http://gb.whu.edu.cn/CSCD/,CSCD) was used to obtain the structure of circRNAs and to identify target miRNAs binding to DECs, and those also binding to DEMIs (GSE108724). Then, we mined the miRDB (http://www.mirdb.org/) and miRTarBase (http://mirtarbase.mbc.nctu.edu.tw/) databases to find miRNA-target pairs, and targeted mRNAs recognized by both databases. The intersected mRNAs for circRNA-miRNA and miRNA-mRNA pairs were included for the generation and analysis of the circRNA-miRNA-mRNA ceRNA network based on ceRNA theory [18]. The network was visualized using Cytoscape software (http://www.Cytoscape.org/), with genes and their interactions displayed by nodes and connections.

Functional Enrichment Analysis

We further investigated the potential biological functions and pathways of the targeted mRNAs using GO functional and KEGG pathways enrichment analysis and the clusterProfiler package in R [19]. GO analysis screened molecular functions (MFs), biological processes (BPs), and cell components (CCs) most associated with the targets, with a significance level of $P < 0.05$. Finally, KEGG analysis was performed to explore top pathways involved in HCC development.

Construction of the Prognostic Model and Sensitivity Analysis for Immunotherapy and Chemotherapy

The filtering condition was set at $P = 0.05$, and mRNAs potentially significantly associated with prognosis in the ceRNA network were screened via univariate Cox analysis and a forest map was drawn. Based on the expression of prognosis-related genes, Lasso regression was used to construct the prognosis model. The samples were then divided into training and validation groups, in which each accounted for 50% of the cases. The coefficients obtained by Lasso regression were used to construct the formula for the risk model [20], which was defined as the expression amount of prognosis-related genes multiplied by it respective coefficient. Next, risk scores of patients in the training and validation groups were calculated and HCC patients were divided into high- and low-risk groups according to the median value of the risk scores in the training group. A receiver operating characteristic (ROC) curve was constructed to verify the accuracy of the model. Subsequently, univariate and multivariate COX analyses verified whether the proposed model could be used as an independent prognostic predictor. The expression of the immunosuppressant PD-1 as well as the sensitivity to chemotherapy drugs cisplatin and paclitaxel in the high- and low-risk groups were analyzed using the "ggpubr" R package.

Results

Identification of DECs, DEMIs, and DEMs

According to the experimental plan, we collected circRNA, miRNA, and mRNA expression profiles in HCC and matched non-tumor tissues and the corresponding clinical information using the GSE97332, GSE108724, and GSE46408 datasets. In total, 2698 circRNAs, 393 miRNAs, and 19,199 mRNAs were extracted from the raw data. After rigorous filtering, 121 DECs, 13 DEMIs, 1701 DEMs, 72 up-regulated circRNAs, 49 down-regulated circRNAs (Figure 1A), 8 up-regulated miRNAs, 5 down-regulated miRNAs (Figure 1B), 772 up-regulated mRNAs, and 929 down-regulated mRNAs (Figure 1C) associated with hepatocarcinogenesis were selected.

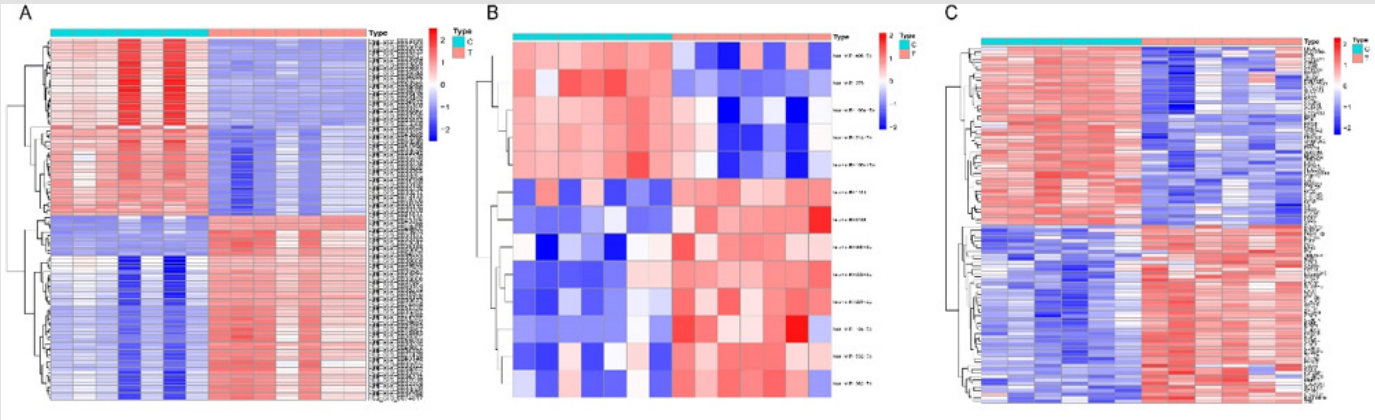

Figure 1: Differentially expressed circRNAs, miRNAs, mRNAs identified from the GEO datasets. (A) 49 down-regulated circRNAs, (B) 8 up-regulated miRNAs, and (C) 929 down-regulated mRNAs were differentially expressed between HCC and matched normal tissues.

Construction of the ceRNA Network

Gene expression profiles of 98 circRNAs and clinical information were identified as associated with HCC in CSCD after removing duplicates from the initial 121 circRNAs. Subsequently, 2090 miRNAs binding to the 98 circRNAs were identified. After circRNA-miRNA pairs were intersected, 10 miRNAs were obtained (Figure 2A). A total of 405 potential target genes of the 10 miRNAs were predicted by miRTarBase and miRDB, and 26 intersected mRNAs were identified (Figure 1B). Ultimately, a circRNA-miRNA-mRNA ceRNA network was constructed based on 7 circRNAs, 4 miRNAs, and 10 mRNAs (Figure 2C) and visualized as heatmaps and boxplots (Figures 3A-3F). Structure of the circRNAs involved in the ceRNA network is shown in (Figure 4).

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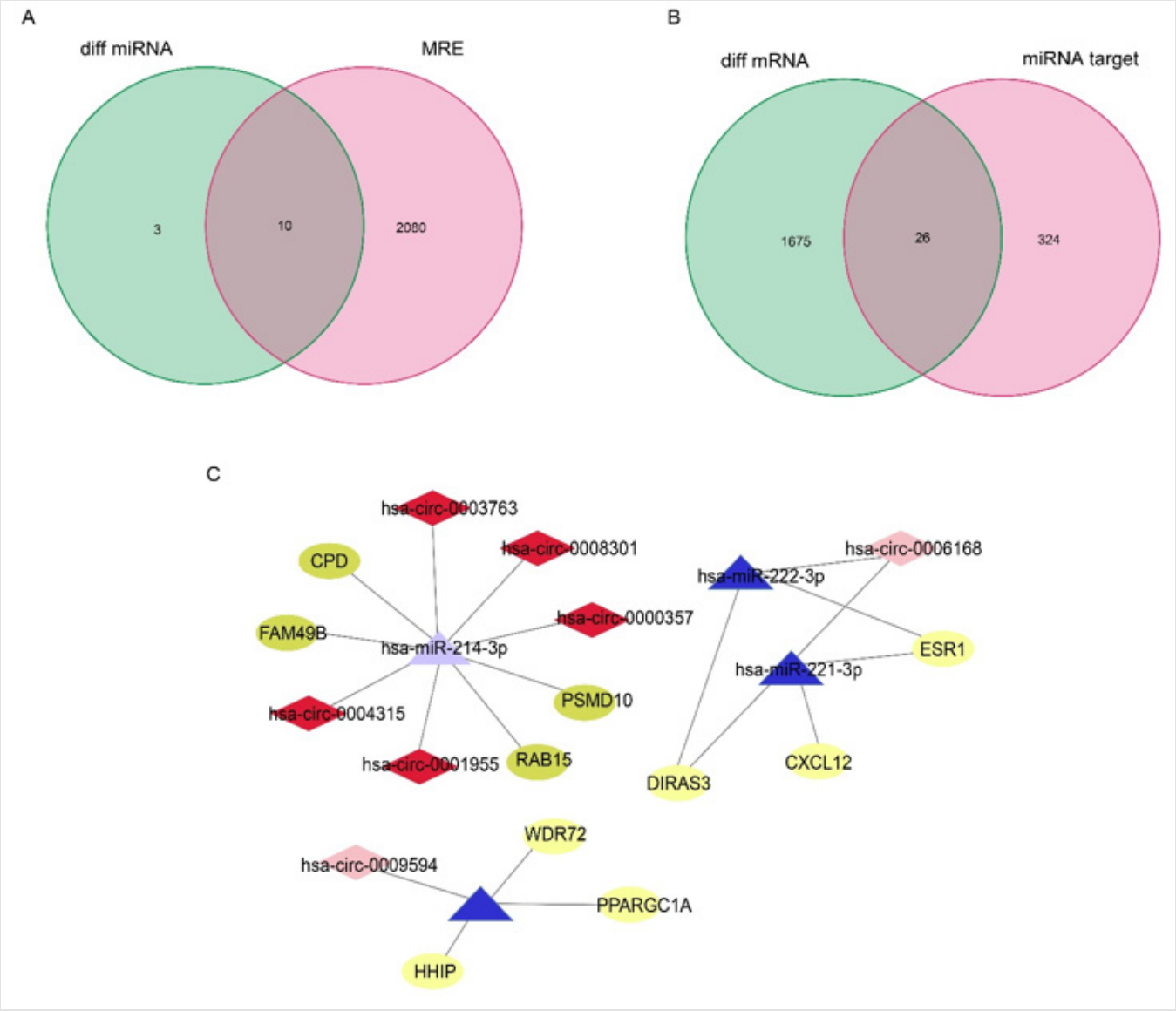

Figure 2: Construction of the circRNA-miRNA-mRNA ceRNA network in HCC. (A) The intersection between the MRE predicted by CSCD and differentially expressed miRNAs was conducted. (B) The intersection between miRNAs target predicted by miRDB and miRTarBase and differentially expressed mRNAs. (C) the construclted ceRNA network. Crimson rhombuses, up-regulated circRNAs; light red rhombuses, down-regulated circRNAs; dark blue triangles, up-regulated miRNAs; light blue triangles, down-regulated miRNAs; saffron yellow ellipses, up-regulated mRNAs; and light yellow ellipses, down-regulated mRNAs.

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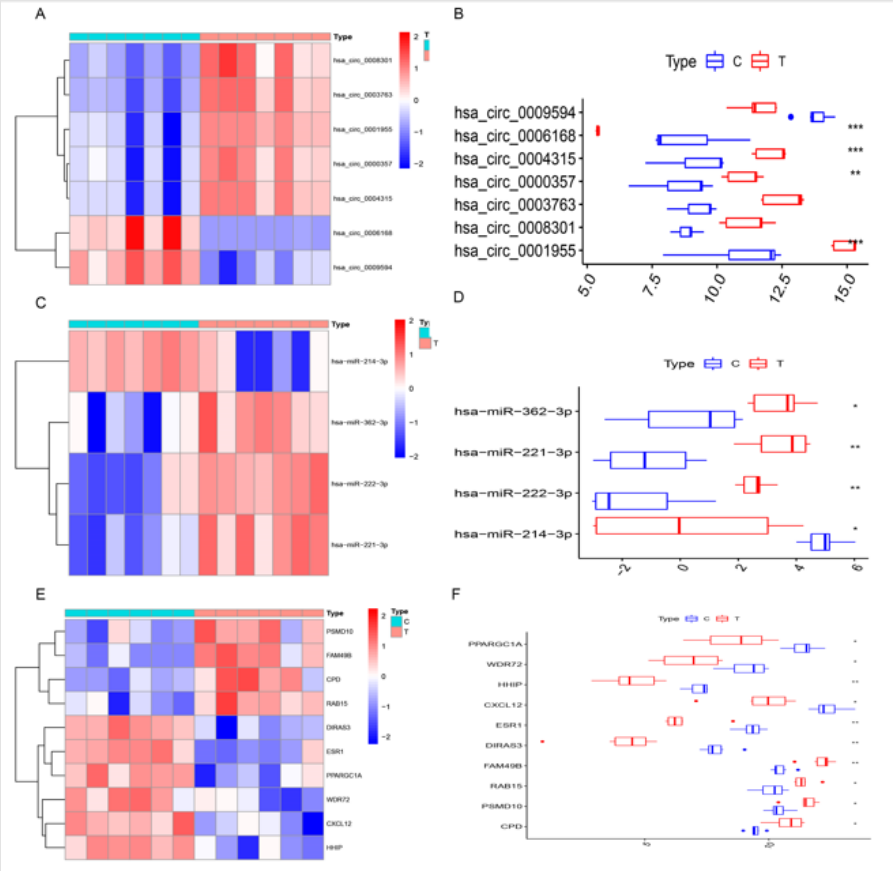

Figure 3: Heatmaps and boxplots of ceRNA interactions. The heatmaps and boxplots of (A, B) circRNAs, (C, D) miRNAs, and (E, F) mRNAs.

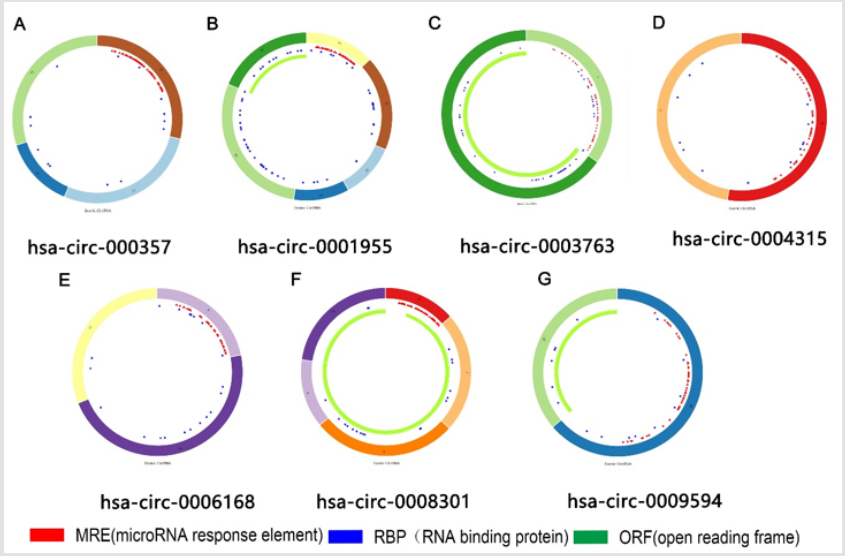

Figure 4: Structural patterns of the 7 circRNAs involved in the ceRNA network. (A-J) The structures were obtained from the circRNA website ().

Enrichment Analysis for Targeted mRNAs in HCC

A total of 10 mRNAs (CPD, PSMD10, RAB15, FAM49B, DIRAS3, ESR1, CXCL12, HHIP, WDR72, and PPARGC1A) were included in the ceRNA network and were subsequently utilized for functional enrichment analysis. GO analysis revealed that the top four BP (androgen metabolism process, cellular response to estradiol stimulus, negative regulation of mitochondrion organization response to hypoxia), CC (insulin-responsive compartment proteasome regulatory particle, base subcomplex, apical dendrite), and MF items (estrogen receptor binding, steroid hormone receptor binding, nuclear receptor binding, nuclear hormone receptor binding) were enriched in the 10 target mRNAs (Figures 5A-5C). Furthermore, the most relevant pathways enriched in the target genes included the intestinal immune network for IgA production, endocrine and other factor-regulated calcium reabsorption, and Hedgehog signaling pathways (Figure 5D).

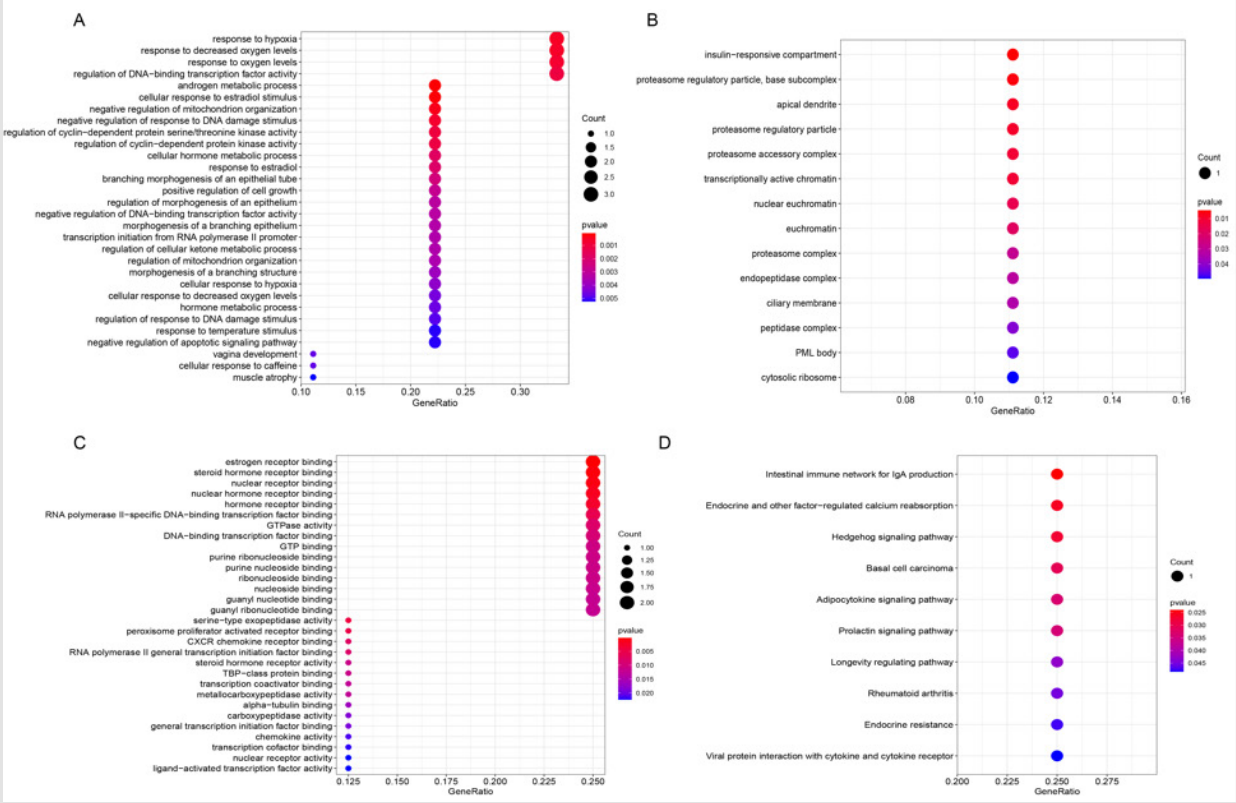

Figure 5: GO functional and KEGG pathways enrichment analyses of the differentially expressed mRNAs in the ceRNA network. (A) The biological processes, (B) cellular components, and (C) molecular functions mediated by the expression of differentially expressed mRNAs. (D) KEGG pathways enriched in the target genes. A P-value < 0.05 was considered statistically significant.

Construction of Prognostic Model and Drug Sensitivity Analysis

Four mRNAs (PSMD10, RAB15, ESR1, and PPARGC1A) with the highest significant prognosis were identified via univariate COX analysis, and a forest map was drawn (Figure 6A). In order to study the influence of these four mRNA on the prognosis of HCC patients, a prognosis model was constructed using Lasso-Cox regression, and the risk scores of the training and validation groups were calculated according to the model formula, after which the HCC patients from TCGA database (clinical data is shown in Supplementary Material: Additional file 7) were divided into high- and low-risk groups. A total of 101 high-risk patients and 101 low-risk patients were in the training group, and 117 high-risk patients and 83 low-risk patients were in the validation group. The results of the survival analysis demonstrated that the survival rate in the low-risk group of the training and validation groups was significantly higher than that in the high-risk group (Figures 6B & 6C). In order to verify the accuracy of the model, a ROC curve was drawn, which showed an AUC = 0.661 in the validation group (Figure 6D) and an AUC = 0.704 in the training group (Figure 6E). Accordingly, the proposed model was observed to be moderately accurate in predicting patient survival. The univariate and multivariate COX regression results showed that the riskScore with a P < 0.05 in our model could be used as an independent predictor of prognosis (Figures 7A-7D). Finally, whether the proposed model could guide immunotherapy and chemotherapy in HCC patients was evaluated. The results showed that the expression of PD-1 in the high-risk group was higher than that in the low-risk group, while the half maximal inhibitory concentration (IC50) of cisplatin and paclitaxel was lower in the high-risk group (Figures 8A-8D).

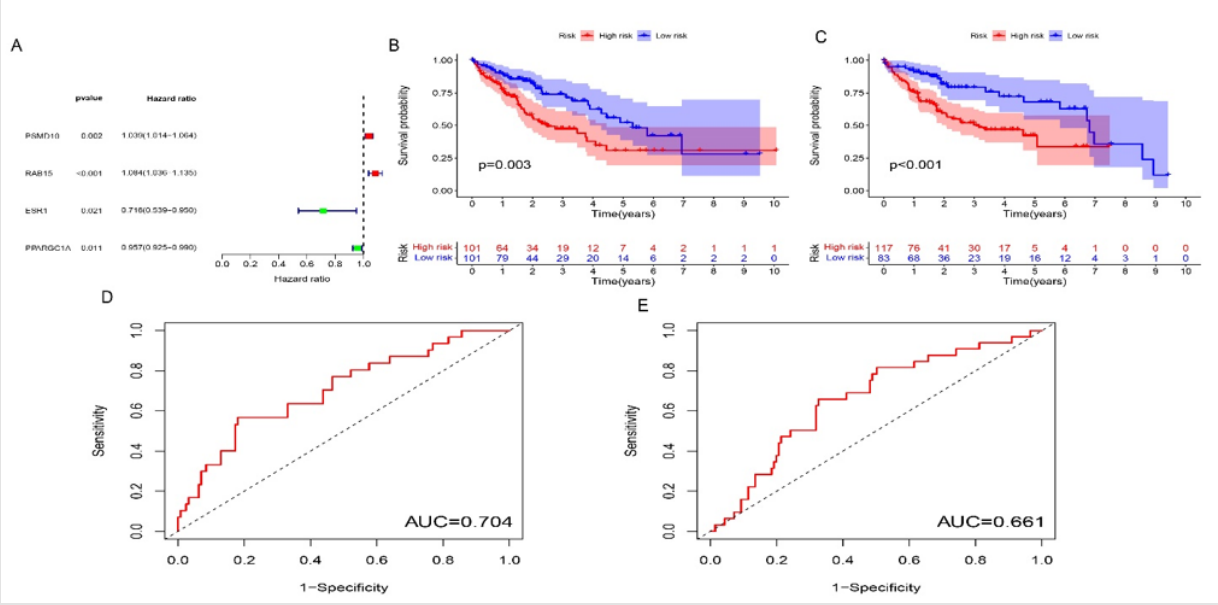

Figure 6: Construction of a scoring model based on the four prognosis-related mRNA and the prognostic significance. (A) Forest map showing four prognostic mRNAs (PSMD10, RAB15, ESR1, and PPARGC1A) identified via univariate COX analysis. (B, C) The survival curves for low- and high-risk HCC patients in the training (panel B) and validation (panel C) cohorts. (D, E) ROC survival curves showing the patient survival in the training (panel D) and validation (panel E) cohorts.

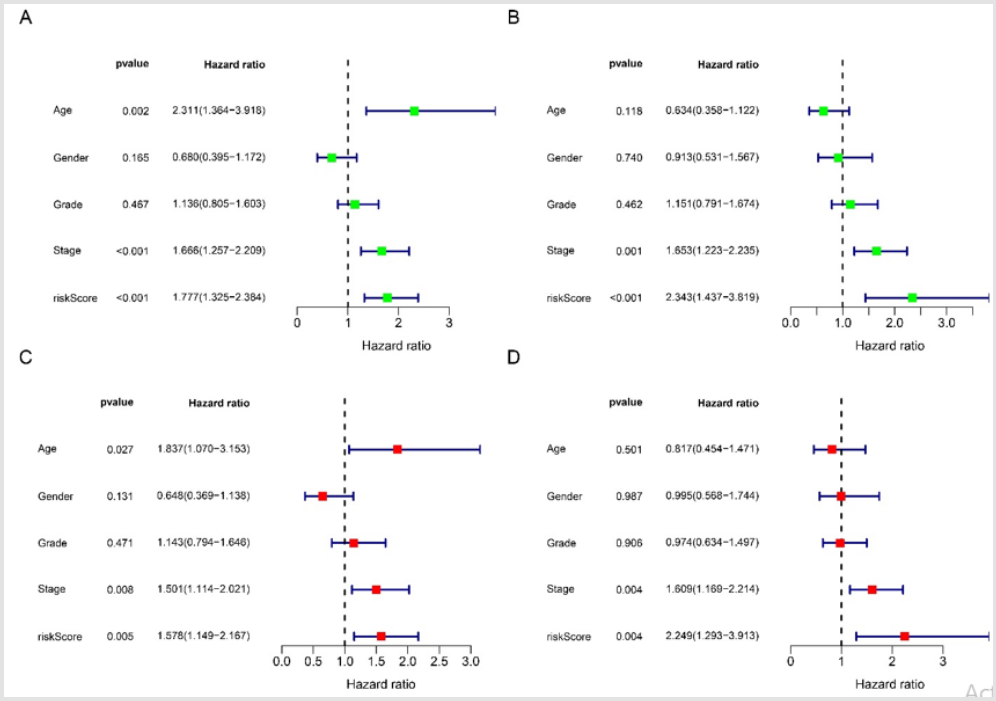

Figure 7: The scoring model serves as an independent prognostic predictor for HCC patient outcomes. Univariate COX analysis of the training (panel A) and validation (panel B) cohorts for prognosis. Multivariate COX analysis of the training (panel C) and validation (panel D) cohorts for prognosis.

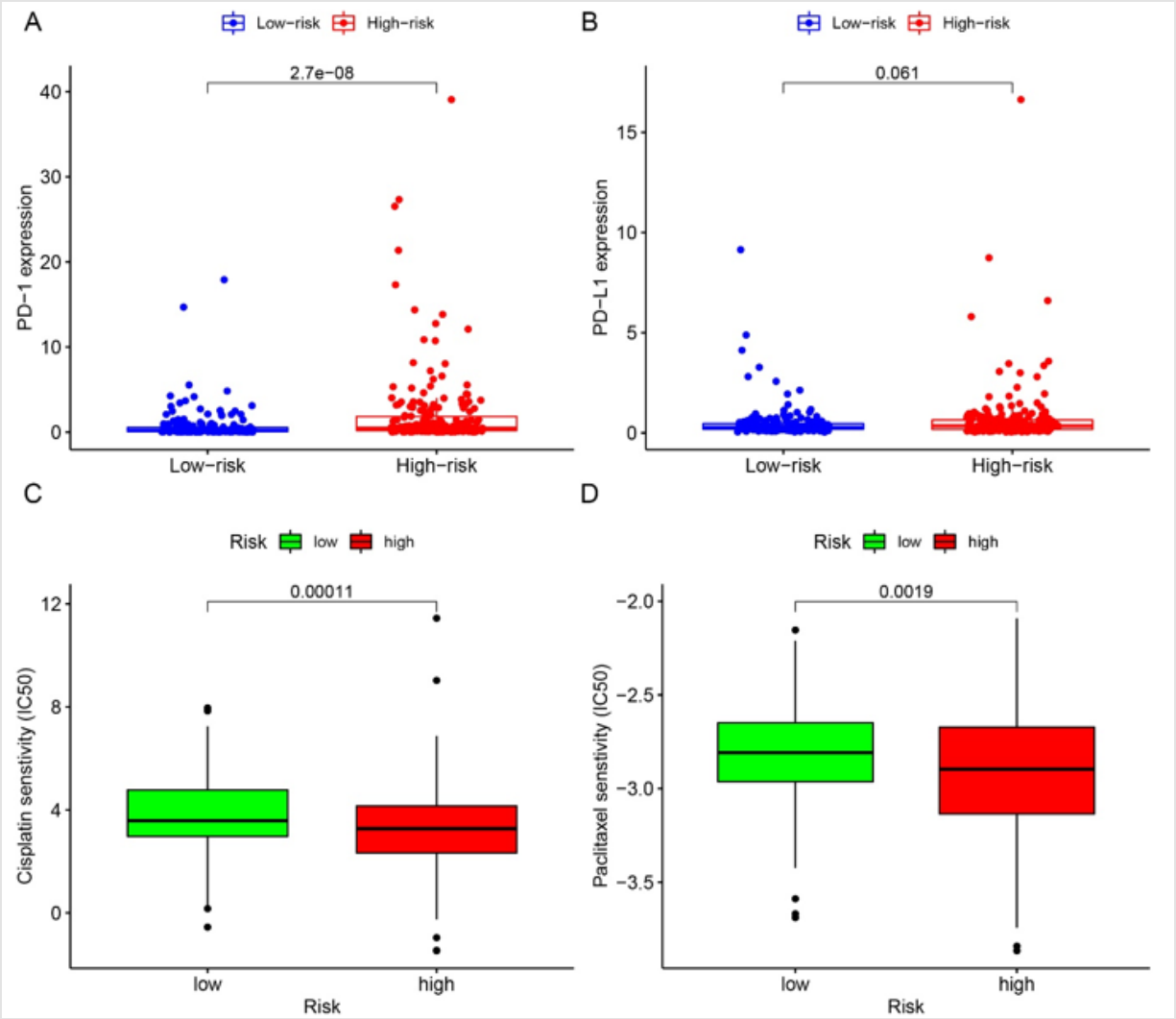

Figure 8: Differences in PD-1/PD-L1 gene expressions and patients' response to common chemosensitivity agents between low- and high-risk HCC patients stratified by RiskScore. (A, B) PD-1/PD-L1 gene expressions. (C, D) Comparison of IC50 values of cisplatin, paclitaxel between the two risk groups.

Discussion

CeRNAs are transcripts that decrease miRNA activity by competing for shared miRNA response elements, thus regulating mRNAs at the transcriptional or post-transcriptional level [21]. In particular, interest in circRNA research has recently surged as these genes have been demonstrated to harbor abundant conserved miRNA response elements [14]. CircRNA is a novel and unique type of coding/non-coding endogenous RNAs and shows tissue and cell specificity [11]. CircRNA formation from exon or intron sequences is regulated by specific cis-acting elements and trans-acting factors [11,22,23]. In recent years, an increasing number of studies have found that the interaction of molecules in the ceRNA network is involved in the occurrence and development of tumors [7]. Studies have found that circRNAs contain multiple MREs, which can bind to miRNAs, downregulate the cytoplasmic level of miRNAs, and release their downstream target mRNAs [9]. Moreover, hsa-circ-0004015 has been shown to play a role in the microRNA-1183/PDPK1 regulatory axis to selectively promote the invasion and metastasis of lung cancer. Additionally, upregulation of hsa-circ-0004015 can significantly improve the drug resistance of tumor cells. Therefore, the underlying ceRNA network of circRNAs may serve an important role in chemotherapy resistance [7]. A study by Zou et al. screened 543 differentially expressed circRNAs in gastrointestinal stromal tumors (GISTs) through the GEO database [24].

A ceRNA regulatory network comprised of 6 circRNA, 30 miRNAs, and 308 mRNAs was also constructed, which revealed the key mechanism of GIST occurrence and development. Similarly, in HCC, circRNA can regulate the occurrence and development of HCC via the ceRNA network, which serves as a therapeutic target for HCC. Circ-

TRIM33-12 has been found to upregulate the expression of TET1 via microRNA-191, resulting in a significant decrease in the level of 5-hydroxymethylcytosine (5hmC) in HCC cells, thereby inhibiting the proliferation, invasion, and metastasis of HCC [25]. CircMTOR can promote the expression of P21 through the sponge effect of miR-9 while inhibiting the progression of HCC [19]. Studying RNA interactions at the molecular level is helpful in better understanding the gene regulatory network in HCC. In this study, the circRNA-miRNA-mRNA network was constructed by analyzing the high-throughput data of non-coding RNA in HCC. Furthermore, functional analysis and survival prognosis analysis were carried out to identify the circRNAs that regulate the occurrence and development of HCC. Our analysis was performed using circRNA, miRNA, and mRNA microarray data of HCC patients from GEO. Initially, 121 DECs, 13 DEMIs, and 1,701 DEMs were identified for subsequent screening. The circRNA-miRNA-mRNA regulatory network was constructed based on the finally confirmed target genes. Enrichment analyses revealed the biological functions and metabolic pathways the target genes were involved in, such as the regulation of sex steroid hormones and their receptors. These results indicated the role of the circRNA-miRNA-mRNA ceRNA network in HCC.

Accordingly, previous studies have found that dehydroepiandrosterone (DHEA), a precursor of estrogens and androgens, can enhance hepatocarcinogenesis after induction of N-nitrosomorpholine (NNM) [26]. The genetic viability of estrogen receptors may be associated with HCC, and estrogen has been reported to act as a promoter of hepatocarcinogenesis [27,28]. The results of the KEGG showed that the Hedgehog signaling pathway may serve as an important enrichment term of target mRNA in ceRNA. It has been reported that inactivation of the Hedgehog signaling pathway can inhibit the growth of HCC while increasing the radiosensitivity of HCC [15,18]. Therefore, inhibition of this pathway may be used as an effective targeted therapy for HCC. In order to further examine the role of mRNA in the ceRNA network in HCC, four mRNAs (PSMD10, RAB15, ESR1, and PPARGC1A) with a significant prognosiswere screened via univariate COX analysis. Studies have previously found that miR-18a can reduce the expression of ESR1 in HCC and promote the proliferation of HCC, suggesting that ESR1 can play a protective role in the progression of HCC [29]. ESR1 was also found to implicated in the Hedgehog signaling pathway that we screened by KEGG analysis [30]. The expression of PPARGC1A is known to be decreased in HCC, and TSPY can inhibit the expression of PPARGC1A, resulting in poor prognosis and shortened survival time of patients. TSPY is a unique proto-oncogene located on the male Y chromosome, which may also explain why HCC incidence may show differences according to sex [31].

However, as a member of the RAS oncogene family, the role of RAB15 in HCC has been rarely reported. Accurate prediction of the prognosis of cancer patients is very important for formulating personalized treatment plans and optimizing treatment strategies. Therefore, a prognostic model was constructed to evaluate the prognostic value of the aforementioned four mRNAs. HCC patients from TCGA database were divided into training and validation groups for validation of the model. The risk scores of HCC patients were calculated and the median value of the risk scores of the training group was used to divide patients into high- and low-risk groups. The survival rate of patients in the high-risk group was found to be significantly lower than that in the low-risk group. The areas under the ROC curve in the training and validation group were 0.702 and 0.661, respectively, demonstrating that the model based on the four mRNAs had good accuracy in predicting patient outcomes. These results from TCGA further supported the accuracy of our findings from GEO database. PD-1 is an inhibitory surface receptor that is expressed on activated T cells [32]. PD-1 ligands, PD-L1 and PD-L2, are expressed in tumor cells or immune cells, including invasive tumors [33]. Activation of the PD-1/PD-L pathway leads to the inhibition of the cytotoxic T cell response [16].

In this study, an important finding was that the expression of PD-1 in the high-risk group was found to be higher than that in the low-risk group, suggesting that the novel prognostic model based on 4 prognosis-related mRNAs may be rated as a new indicator in guiding immunotherapies in HCC. Moreover, the IC50 of cisplatin and paclitaxel, which are common chemotherapy drugs used in HCC, was observed to be lower in the high-risk group, hinting that they may be highly sensitive to these drugs. Nonetheless, there are many limitations to be considered in our analyses, including the marginal amount of sample data. As a result, the clinical applicability of the proposed model must be verified through further experiments. In conclusion, we constructed a circRNA-miRNA-mRNA network, as well as a prognostic risk model based on four mRNAs for HCC. The proposed prognostic model may act as an indicator for guiding immunotherapy and chemotherapy choices for HCC patients.

Acknowledgements

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