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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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ORIGINAL ARTICLE

Clinical and Translational Research

BCAR3 and *BCAR3*-related competing endogenous RNA expression in hepatocellular carcinoma and their prognostic value

Hui-Qin Shi, Shu Huang, Xin-Yue Ma, Zhen-Ju Tan, Rui Luo, Bei Luo, Wei Zhang, Lei Shi, Xiao-Lin Zhong, Mu-Han Lü, Xia Chen, Xiao-Wei Tang

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is a malignant tumor that has a high incidence and mortality worldwide. Despite extensive studies, the detailed molecular mechanism of HCC development remains unclear. Studies have shown that the occurrence and development of HCC are closely related to abnormal gene expression. *BCAR3* has been shown to be overexpressed in a variety of malignant tumors. However, the role of *BCAR3* in HCC remains unclear.

AIM

To investigate the expression of *BCAR3* and *BCAR3*-related competing endogenous RNAs (ceRNAs) in HCC and their clinical significance, in order to provide new ideas for the diagnosis and treatment of HCC.

METHODS

The data of HCC were obtained from the Cancer Genome Atlas database and The Genotype Tissue Expression, including transcriptome data and clinical information. Multiple common databases, including UALCAN, Timer 2.0, cBioPortal, LinkedOmics, starBase, Gene Ontology and Kyoto Encyclopedia of Genes and Genomes, were used to analyse the expression of *BCAR3*, prognostic value, genetic alteration, co-expressed genes, differentially expressed genes, *BCAR3* gene-related ceRNAs and functional enrichment analysis in HCC patients. Kaplan-Meier analysis, univariate and multivariate Cox regression analysis were used to analyze survival prognosis and the Spearman test was used to measure correlations between *BCAR3* and immune functions. And R language package was used to analyze the correlation between *BCAR3* and immune invasion of HCC.

RESULTS

Our study indicated that *BCAR3* was differentially expressed in various tumor tissues. The over-expression of *BCAR3* gene was an unfavorable prognostic indicator for HCC patients, and associated with unfavorable cytogenetic risk and gene mutations. Moreover, most immune cells were positively correlated with *BCAR3* ($P < 0.05$). According to the results of functional enrichment analysis, *BCAR3* was involved in the positive regulation of epidermal growth factor receptor signaling pathway and ERBB signaling pathway, and was related to DNA replication and GTPase regulator activity. Finally, our study found that based on *RAB30-DT* and *miR-19b-3p* pathways, targeting *BCAR3* might promote the occurrence and development of HCC.

CONCLUSION

Collectively, this study indicated that the *BCAR3* gene was involved in the occurrence and development of HCC, and it might be a new biomarker and therapeutic target for HCC, but the specific mechanism remains to be further verified.

Key Words: Hepatocellular carcinoma; Breast cancer anti-estrogen-resistant protein 3; Bioinformatics; Prognosis; Immunoassay

Core Tip: *BCAR3* gene was over-expressed in a variety of malignant tumors, and its high expression was significantly associated with poor prognosis of cancer patients. In hepatocellular carcinoma (HCC), the expression of *BCAR3* was observably higher in cancer tissues than in normal tissues, and the expression level was higher in HCC tissues with *TP53* mutation compared to those without. *BCAR3* was positively correlated with a variety of immune cells in HCC tissues, and might play an important role in the immune micro-environment of tumors. In addition, the *BCAR3/miR-19b-3p/RAB30-DT* competing endogenous RNA regulatory axis may be involved in the development of HCC.

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INTRODUCTION

Primary hepatocellular carcinoma (HCC) is one of the most prevalent malignant tumors with the fourth highest mortality rate globally, among which HCC is the most predominant, accounting for approximately 80% of primary HCC[1,2]. Chronic infection with hepatitis B virus or hepatitis C virus, high alcohol consumption, excess body weight, and smoking are the major pathogenic factors of HCC[3]. HCC lacks effective early diagnosis methods compared with other malignant tumors, and advanced HCC demonstrates a very poor prognosis, with mortality approaches the worldwide incidence. A large number of studies have revealed that HCC occurrence and development are closely associated with abnormal gene expression[4]. Therefore, effective biomarkers related to HCC diagnosis and prognosis were searched from the molecular level.

BCAR3, namely *NSP2* or *AND-34*, is a member of the novel Src homology 2 (SH2) containing protein family[5]. Studies revealed that *BCAR3* expression was associated with the occurrence and development of various cancers. *BCAR3* played an important role in the metastasis and invasion of breast cancer cells and promoted the proliferation and migration of triple-negative breast cancer by regulating MET signaling[6,7]. The experiment by Hou *et al*[8] confirmed that *BCAR3* knockout significantly inhibited cell migration and colorectal cancer cell invasion, but did not affect tumor cell proliferation. In contrast, high *BCAR3* expression was strongly associated with a better prognosis in multiple myeloma[9]. However, the association between *BCAR3* expression and HCC prognosis, as well as the role of *BCAR3* in HCC remains unclear.

Competing endogenous RNAs (ceRNAs) are a class of non-coding RNAs (ncRNAs) that competitively bind to shared miRNAs and play a regulatory role at the post-transcriptional level[10]. The ceRNA hypothesis suggested that ceRNAs act as miRNA sponges *via* miRNA response elements and thus play a role in proliferation, metastasis, and drug resistance in several common tumors, such as gastric cancer, gallbladder cancer, and HCC[11-13]. Therefore, we aimed to investigate the association of *BCAR3* and its related ceRNAs with HCC and the prognosis of patients with HCC through bioinformatics analysis, to provide new ideas for HCC diagnosis and treatment.

MATERIALS AND METHODS

Download and clean data from public databases

RNA-sequencing expression profiles for 33 tumors were downloaded from The Cancer Genome Altas (TCGA) database (https://portal.gdc.com), including 9807 tumor tissues. RNA-seq data of normal tissues were downloaded from TCGA and The Genotype Tissue Expression (GTEx). Meanwhile, *BCAR3* gene expression data were extracted from GTEx and TCGA datasets for subsequent analyses. Furthermore, 424 RNA-seq data and corresponding clinical information of HCC from the TCGA database were used to investigate the associations between *BCAR3* expression and clinicopathological factors of patients with HCC.

Analysis of BCAR3 expression in tumor and normal tissues

The UALCAN database (http://ualcan.path.uab.edu/), containing RNA-seq and clinical data of 33 cancer types from the TCGA data set, was used for *BCAR3* expression analysis in different tumor sample types and downloaded the box plots. The GTEx (https://www.gtexportal.org/home/), containing RNA-seq data from 31 normal tissues, was utilized for *BCAR3* expression analysis in different normal tissues and downloaded the box plots.

Two-group data performed by the Mann-Whitney *U* test were used to investigate the differential expression of *BCAR3* between tumors and normal tissues across different cancer types from GTEx and TCGA datasets. *P*-value of < 0.05 indicated statistical significance ($^{a}P < 0.05$).

Analysis of clinical prognostic factors

Timer 2.0 (http://timer.comp-genomics.org) was usually applied to investigate the prognostic significance of genes in different cancer types. We investigated the prognostic values of *BCAR3* expression for overall survivals (OS) in pancancers using these two databases. Kaplan-Meier survival analysis and the log-rank test were conducted to calculate the *P*-value.

Genetic alteration analysis

Pan-cancer analysis of *BCAR3* genetic alterations was performed with cBioPortal web (https://www.cbioportal.org/), including genetic alteration frequency, mutation type, and copy number alteration among different tumors.

BCAR3 immune correlation analysis in HCC

The R software pheatmap package was used to investigate the correlation analyses between *BCAR3* and various immune cells. Spearman's correlation analysis was utilized to describe the correlation between quantitative variables without a normal distribution. *P*-values of < 0.05 were considered statistically significant.

Coexpression genes and differently expressed genes analysis

The LinkedOmics database (http://www.linkedomics.orglogin.php) was applied to identify the co-expressed genes correlated with *BCAR3* expression in the RNA-seq data of patients with HCC from the TCGA database. The Pearson correlation analysis was utilized to calculate the correlation, and the volcano map of the co-expressed genes was plotted from the LinkedOmics website. The Limma package in R 4.2.1 was used to collect the differently expressed genes (DEGs) of HCC, with *P* adj of < 0.05 and LogFC of ≥ 1 as the screening conditions. Finally, the co-expressed genes and the DEGs were intersected to obtain overlapping genes, which were visualized to obtain the heat map.

Functional enrichment analysis

Functional enrichment analyses screened the above-mentioned overlapping genes, including Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways, and tissue enrichment analysis, performed using the Metascape database.

Establishment of mRNA-miRNA-long-stranded ncRNA co-expression network and survival analysis of miRNA and long-stranded ncRNA

The *BCAR3*-related miRNA and long-stranded ncRNA (lncRNA) data were downloaded from the starBase database (http://starbase.sysu.edu.cn/), with a program number of ≥ 2 as the miRNA screening criteria. The corresponding lncRNA was then screened out based on the miRNA obtained under the above conditions.

Statistical analysis

Wilcox-on rank-sum test was used to compare the difference between the two groups. "DESeq2" and "survival" R

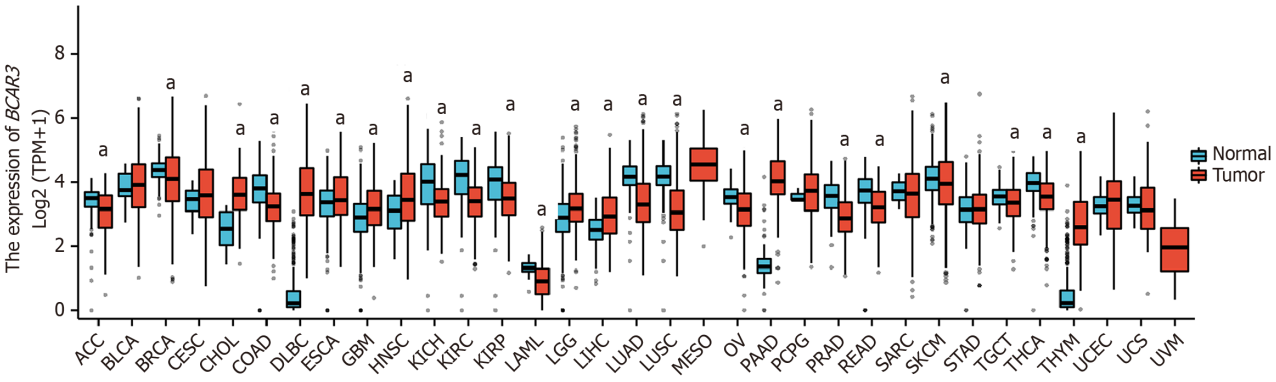

Figure 1 Differential expression of *BCAR3* in cancer tissues and normal counterparts from The Cancer Genome Altas and Genotype Tissue Expression databases, analyzed by Mann-Whitney *U* test. [a]*P* < 0.05. ACC: Adrenalcortical carcinoma; BLCA: Bladder urothelial carcinoma; BRCA: Breast invasive carcinoma; CESC: Cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL: Cholangiocarcinoma; COAD: Colon adenocarcinoma; DLBC: Diffuse large B cell lymphoma; ESCA: Esophageal carcinoma; GBM: Glioblastoma multiforme; HNSC: Head and Neck squamous cell carcinoma; KICH: Kidney chromophobe; KIRC: Kidney renal clear cell carcinoma; KIRP: Kidney renal papillary cell carcinoma; LAML: Acute myeloid leukemia; LGG: Brain lower grade glioma; LIHC: Liver hepatocellular carcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; MESO: Mesothelioma; OV: Ovarian serous cystadenocarcinoma; PAAD: Pancreatic adenocarcinoma; PCPG: Pheochromocytoma and paraganglioma; PRAD: Prostate adenocarcinoma; READ: Rectum adenocarcinoma; SARC: Sarcoma; SKCM: Skin cutaneous melanoma; STAD: Stomach adenocarcinoma; TGCT: Testicular germ cell tumor; THCA: Thyroid carcinoma; THYM: Thymoma; UCEC: Uterine corpus endometrial carcinoma; UCS: Uterine carcinosarcoma; UVM: Uveal melanoma.

software were used for differential expression data analysis. Kaplan-Meier survival analysis was used for receiver operating characteristic (ROC) curve analysis and univariate and multivariate Cox regression analysis. The Spearman test was utilized to measure correlations between *BCAR3* and immune functions. A *P*-value of < 0.05 indicated a significant threshold.

RESULTS

BCAR3 expression in pan-cancer

Based on the TCGA and GTEx databases, *BCAR3* was expressed in 33 kinds of malignant tumor tissue samples, among which 24 demonstrated significant differences in *BCAR3* expression level (Figure 1). *BCAR3* was down-regulated in cholangial carcinoma, diffuse large B-cell lymphoma, esophageal carcinoma, glioblastoma multiforme, neck squamous cell carcinoma, brain lower-grade glioma, liver HCC, pancreatic adenocarcinoma, and thymoma compared with para-cancer normal tissues. On the contrary, *BCAR3* was under-expressed in adrenocortical carcinoma, breast invasive carcinoma, colon adenocarcinoma, kidney chromophobe, kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, acute myeloid leukemia, lung adenocarcinoma, lung squamous cell carcinoma, ovarian serous cystadenocarcinoma, prostate adenocarcinoma, rectum adenocarcinoma, skin cutaneous melanoma, testicular germ cell tumor, and thyroid carcinoma. Whereas, no statistical difference in *BCAR3* expression level was found in bladder urothelial carcinoma, cervical squamous cell carcinoma and endocervical adenocarcinoma, pheochromocytoma and paraganglioma, sarcoma, stomach adenocarcinoma, uterine corpus endometrial carcinoma (UCEC), uterine carcinosarcoma, and their corresponding normal tissues. Additionally, mesothelioma and uveal melanoma were excluded due to a lack of normal tissue samples.

BCAR3 was a diagnostic and prognostic factor for patients with HCC

BCAR3 was significantly more expressed in HCC tissue compared with para-cancer normal tissues ($P < 0.01$; Figure 2A). Moreover, *BCAR3* expression level in HCC was correlated with the mutation status of *TP53*. *BCAR3* expression was higher in the *TP53*-mutated HCC tissue samples ($P < 0.001$; Figure 2B).

Subsequently, we analyzed the important value of the *BCAR3* gene in HCC diagnosis and prognosis. The sensitivity analysis revealed that the diagnostic ROC curve of the target gene *BCAR3* demonstrated an area under the curve (AUC) of 0.7, indicating that the high *BCAR3* expression indicated the diagnostic value for HCC (Figure 3A). More importantly, the prognostic ROC curve of *BCAR3* revealed that the AUCs were 0.674, 0.572, and 0.566 at 1, 2, and 3 years, respectively (Figure 3B). Additionally, we revealed that the OS, disease-specific survival, and progression-free interval of patients with HCC with high expression of *BCAR3* were worse than those with low *BCAR3 expression* based on Kaplan-Meier curves and log-rank test analysis (Figure 3C-E, Table 1). Univariate Cox regression analysis revealed that high *BCAR3* expression, tumor status, and tumor pathological T stage (T3 and T4) were correlated with poor OS in patients with HCC (Figure 3F), whereas multivariate Cox regression analysis indicated that *BCAR3* expression level was not an independent prognostic risk factor for HCC (Table 2). In conclusion, *BCAR3* was a prognostic risk factor for HCC.

Table 1 Association between *BCAR3* expression and the clinical parameters in patients with hepatocellular carcinoma in The Cancer Genome Altas, *n* (%)

Characteristics	Low expression of *BCAR3*	High expression of *BCAR3*	*P* value
n	187	187	
Gender			0.912
Male	127 (34)	126 (33.7)	
Female	60 (16)	61 (16.3)	
Age			0.275
≤ 60	94 (25.2)	83 (22.3)	
> 60	93 (24.9)	103 (27.6)	
Tumor status			0.014
Tumor free	111 (31.3)	91 (25.6)	
With tumor	64 (18)	89 (25.1)	
Pathologic T stage			0.085
T1 and T2	146 (39.4)	132 (35.6)	
T3	37 (10)	43 (11.6)	
T4	3 (0.8)	10 (2.7)	
Pathologic M stage			0.667
M0	138 (50.7)	130 (47.8)	
M1	3 (1.1)	1 (0.4)	
AFP (ng/mL)			0.056
≤ 400	110 (39.3)	105 (37.5)	
> 400	42 (15)	23 (8.2)	
Histological type			0.996
Fibrolamellar carcinoma	1 (0.3)	2 (0.5)	
Hepatocellular carcinoma	183 (49.9)	181 (49.3)	
Overall survival event			0.017
Alive	133 (35.6)	111 (29.7)	
Dead	54 (14.4)	76 (20.3)	
Disease specific survival event			0.009
No	153 (41.8)	134 (36.6)	
Yes	29 (7.9)	50 (13.7)	
Progression free interval event			0.005
No	109 (29.1)	82 (21.9)	
Yes	78 (20.9)	105 (28.1)	

AFP: Alpha-fetoprotein.

Genetic and epigenetic alterations of BCAR3 in HCC

The genetically altered status of the *BCAR3* gene in different types of cancers in the TCGA cohort was then investigated at the cBioPortal website. The highest alteration frequency of *BCAR3* (approximately 6%) was observed in patients with UCEC with "mutation," "amplification," and "multiple alterations" as the primary changes. Additionally, genetic alterations of the *BCAR3* gene were observed in HCC cases, mainly "mutation" and "amplification" (Figure 4A). Moreover, genetic changes of the *BCAR3* gene were found in HCC cases, mainly "mutation" and "amplification," with two mutation sites of "SH2" and "RasGEF," the mutation rate was approximately 1.8% (Figure 4B and C).

Table 2 Univariate Cox regression and multivariate Cox regression analysis of prognosis-related risk factors in hepatocellular carcinoma

Characteristics	Total (*N*)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95%CI)	*P* value	Hazard ratio (95%CI)	*P* value
Pathological T stage	370		< 0.001		
T1	183	Reference		Reference	
T2	94	1.428 (0.901-2.264)	0.129	1.368 (0.846-2.212)	0.201
T3 and T4	93	2.949 (1.982-4.386)	< 0.001	2.458 (1.610-3.751)	< 0.001
Tumor status	354		< 0.001		
Tumor free	202	Reference		Reference	
With tumor	152	2.317 (1.590-3.376)	< 0.001	1.864 (1.261-2.755)	0.002
BCAR3	373		0.029		
Low	187	Reference		Reference	
High	186	1.472 (1.038-2.088)	0.030	1.245 (0.859-1.805)	0.247
Gender	373		0.204		
Female	121	Reference			
Male	252	0.793 (0.557-1.130)	0.200		
Age	373		0.293		
≤ 60	177	Reference			
> 60	196	1.205 (0.850-1.708)	0.295		

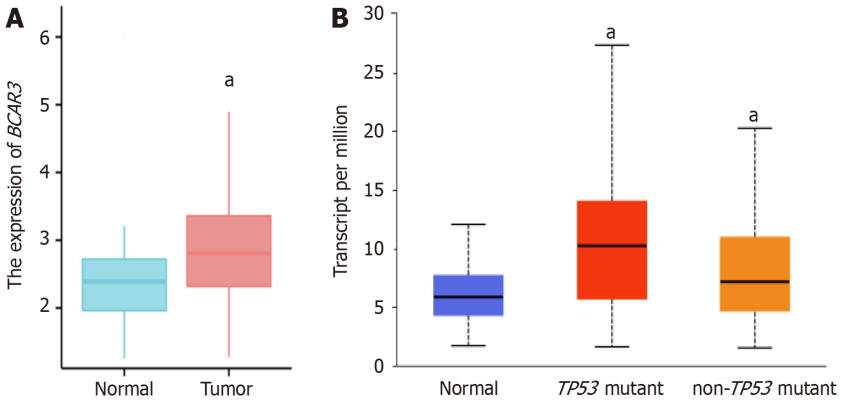

Figure 2 Differential expression of *BCAR3*. A: The difference of *BCAR3* expression in normal tissue and liver cancer tissue; B: Expression difference of *BCAR3* in normal, *TP53* mutant and non-*TP53* mutant hepatocellular carcinoma tissues. [a]*P* < 0.05.

Correlation of BCAR3 with various immune cells in HCC

We analyzed the correlations between immune cells and the levels of immune infiltration for *BCAR3* and revealed that B cells, T cells CD4+, T cells CD8+, neutrophil, macrophage, and myeloid dendritic cells were positively correlated with *BCAR3* (Figure 5, R > 0.2, *P* < 0.01).

BCAR3 co-expressed gene analysis in patients with HCC

In HCC tissues, 451 co-expressed genes from the TCGA database that were significantly associated with *BCAR3* were determined through the LinkedOmics database (false discovery rate < 0.05, *P* < 0.05, |cor| ≥ 0.3). Among them, 286 genes were positively correlated with *BCAR3* expression, whereas 164 genes were negatively correlated with *BCAR3* expression (Figure 6A). Subsequently, single-gene differential analysis of target gene *BCAR3* was conducted through an online tool website (https://www.xiantao.love/), and 881 DEGs in HCC were obtained. After the intersection of DEGs and the above co-expressed genes, 16 overlapping genes and their volcano maps were collected for further analysis (Figure 6B).

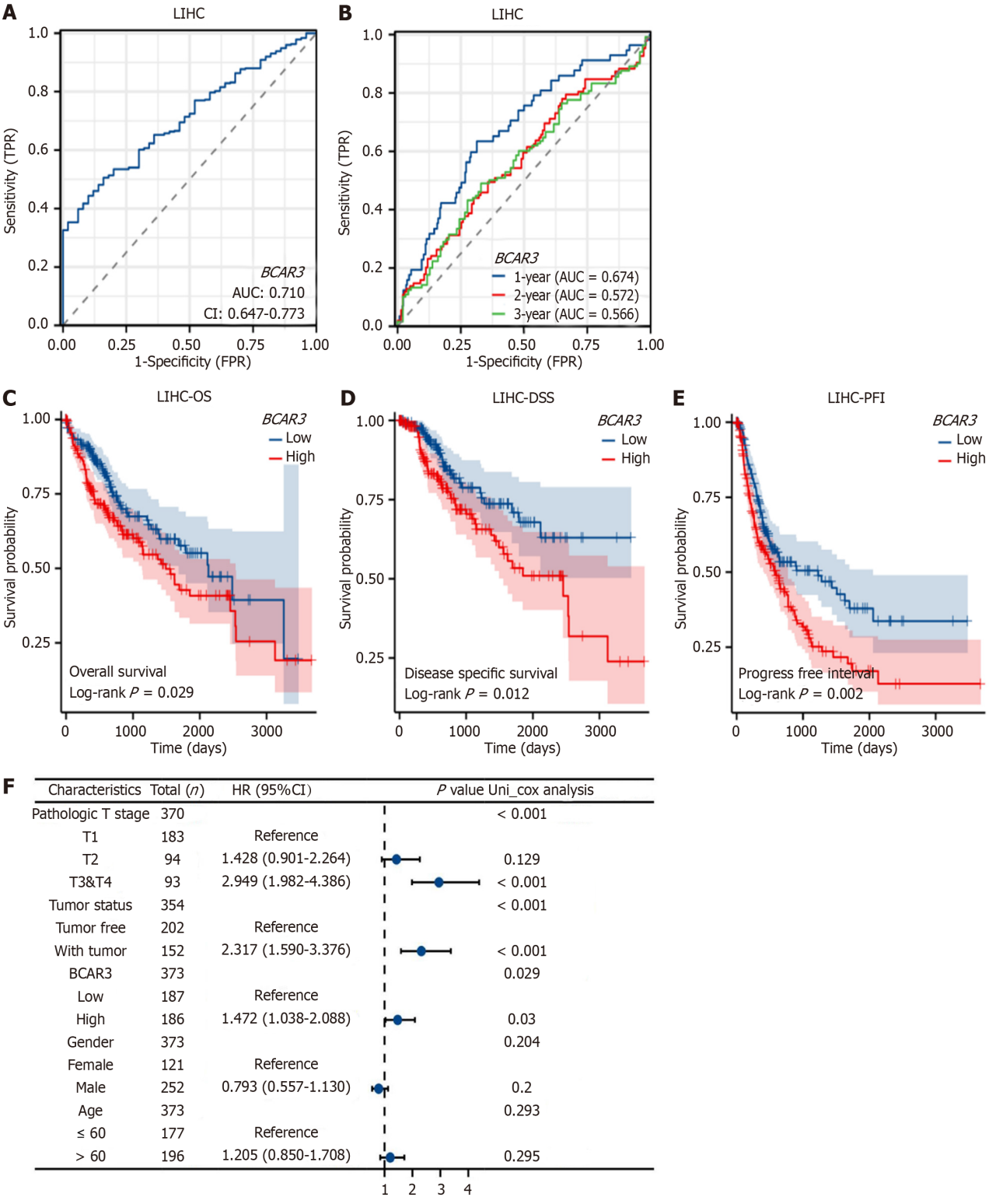

Figure 3 Effect of *BCAR3* on diagnosis and prognosis of hepatocellular carcinoma. A: Receiver operating characteristic (ROC) curve and area under curve (AUC) value of *BCAR3* gene expression in diagnosing hepatocellular carcinoma (HCC). The blue curve represents the ROC curve and AUC = 0.71; B: ROC curve and AUC value of *BCAR3* gene expression in predicting the 1, 2 and 3 year survival time of HCC patients. Larger AUC values corresponding to better prediction performance; C-E: Effects of *BCAR3* expression on overall survival (OS), disease specific survival and progression free interval of HCC. Comparison between high expression group and low expression group was performed by Log rank; F: Forest plot for univariate cox regression analysis of *BCAR3* expression with OS in HCC with different clinicopathologic features. High expression of *BCAR3* is a risk factor for HCC. AUC: Area under curve.

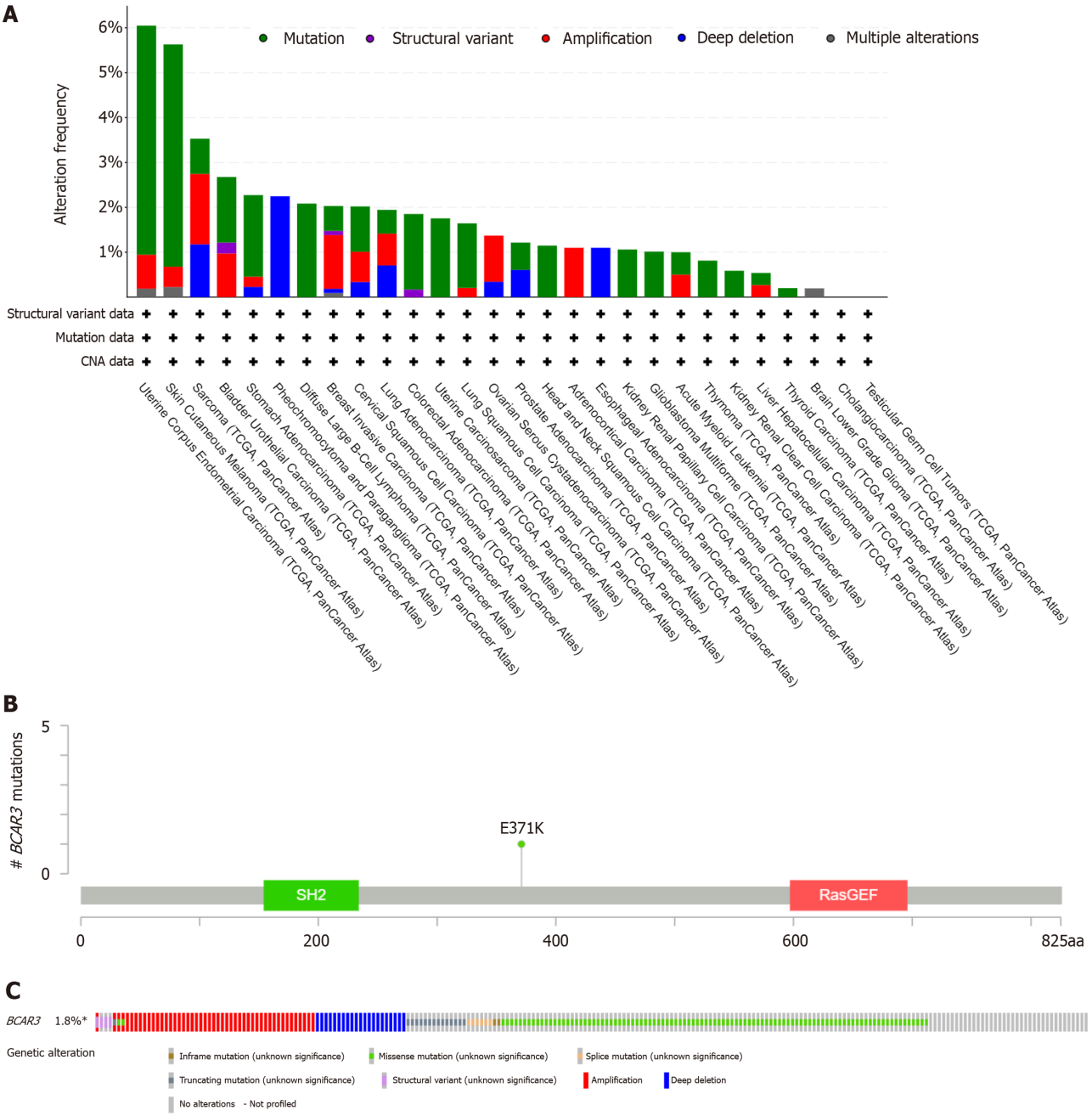

Figure 4 Genetic and epigenetic alterations of *BCAR3* in hepatocellular carcinoma patients from The Cancer Genome Altas dataset. A: Genetic features of *BCAR3*, including, including mutation, structural variant, amplification, deep deletion and multiple alteration, in different tumors of The Cancer Genome Altas analyzed by cBioPortal; B: Mutation site of *BCAR3* in hepatocellular carcinoma (HCC); C: The mutation rate of *BCAR3* in HCC.

Functional enrichment analysis of BCAR3 in HCC

Metascape database was used for GO/KEGG analysis to investigate the biological functions of 16 overlapping genes. The results revealed that *BCAR3* and its related genes were functional mediators of immune regulation, including positive epidermal growth factor receptor (EGFR) signaling pathway regulation, ERBB signaling pathway positive regulation, DNA replication positive regulation, guanyl-nucleotide exchange factor activity, GTPase regulator activity, and nucleoside-triphosphatase regulator activity (Figure 7A). These genes were involved in inflammatory processes, including responses to bacteria, tuberculosis, phagocytosis, macrophage activation, and endocytosis. Additionally, *BCAR3* expression was associated with MAPK cascade regulation and cell death (Figure 7B).

The co-expression network of BCAR3-related miRNA and lncRNA

We screened two groups of miRNAs that were co-expressed and negatively correlated with *BCAR3* ($r < -0.1$, $P < 0.01$) in preparation for the subsequent screening of potential targets and pathways after downloading the *BCAR3*-miRNA interaction data from the starBase database and using the R language package for the analysis (Figure 8A and B). Prognosis and survival curve analysis revealed that high expression level of *miR-19b-3p*-miRNA was associated with poor

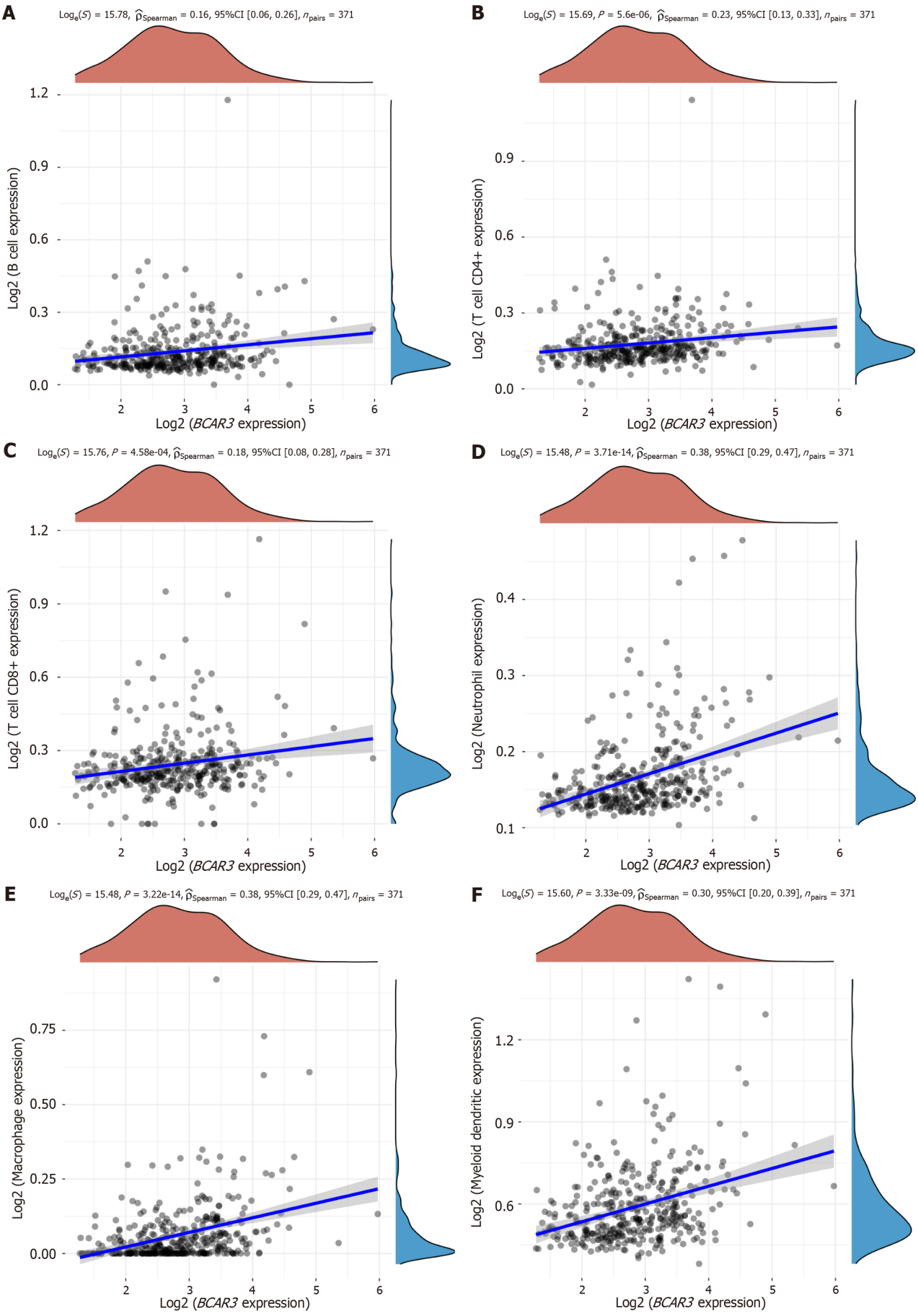

Figure 5 Relationship between the expression of *BCAR3* and immune invasion of hepatocellular carcinoma. A: B cells; B: T cells CD4+; C: T

cells CD8+; D: Neutrophil; E: Macrophage; F: Myeloid dendritic cells were positively correlated with *BCAR3*.

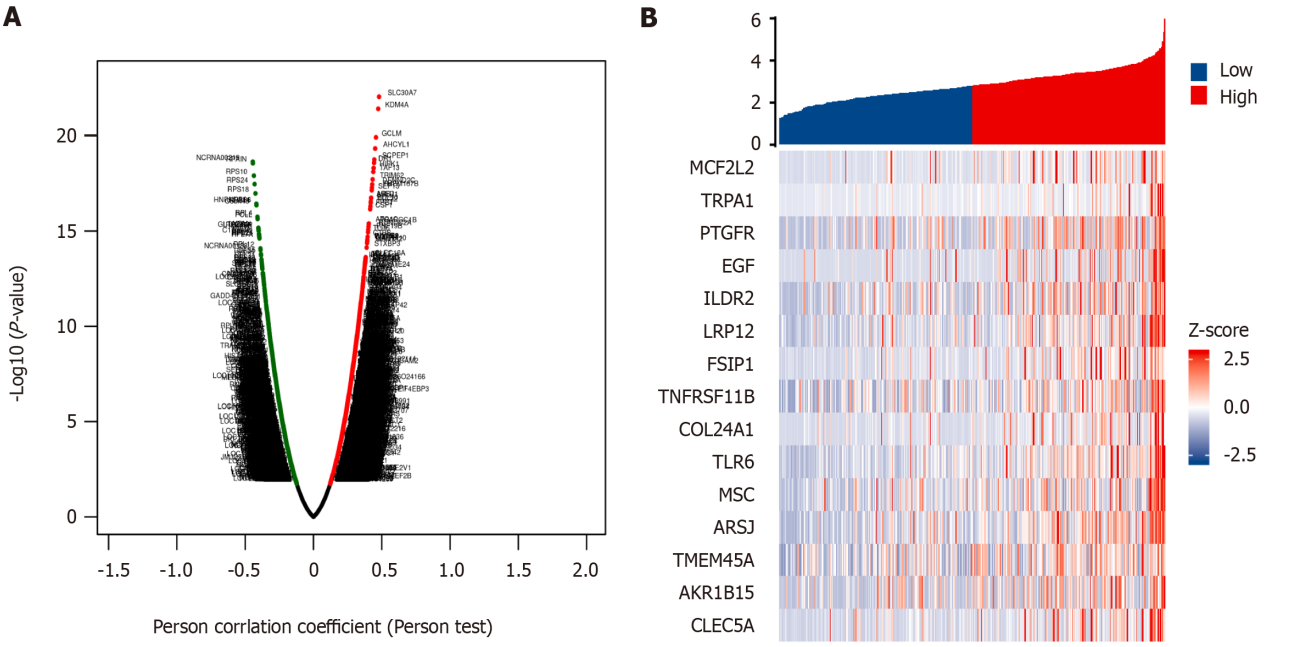

Figure 6 The co-expressed genes associated with *BCAR3* expression in hepatocellular carcinoma. A: Volcanic map of *BCAR3*-related co-expression genes obtained by the LinkedOmics. heat maps; B: Heat map of the top 15 differently expressed genes between high and low *BCAR3* expression groups.

prognosis of patients with HCC. However, the expression level of *miR-19a-3p*-miRNA was not correlated with the prognosis of patients with HCC (Figure 8C and D).

Thereafter, we downloaded the lncRNA data that interacted with *miR-19b-3p* from the starBase database and screened and analyzed the correlation coefficients. Finally, the *miR-19b-3p*-related lncRNAs, namely *MIR34AHG* (Figure 9A and B, $r < -0.1$, $P < 0.05$) and *RAB30-DT* (Figure 9C and D, $r > 0.1$, $P < 0.01$) were screened. The lncRNAs were differently expressed in between the normal and tumor groups, and high *RAB30-DT* expression was associated with poor prognosis (Figure 9E and F). Therefore, a *BCAR3*-related miRNA-lncRNA pathway was constructed to investigate HCC occurrence and development.

DISCUSSION

BCAR3 has been associated with several prevalent cancers, but its function in HCC remains unclear. First, we mainly discussed the differential expression of *BCAR3* in HCC and its effect on the survival and prognosis of patients with HCC and revealed that the *BCAR3* gene was differentially expressed in a variety of malignant tumors. Our study revealed that *BCAR3* expression in HCC was observably higher in cancer tissues than in normal tissues, and the expression level was higher in HCC tissues with *TP53* mutation compared to those without. *TP53* is one of the most prevalent mutated genes in human cancers[14]. The immune response of HCC with *TP53* mutation was significantly weakened compared with HCC without *TP53* mutation, which was detrimental to the survival of patients with HCC[15]. Additionally, *BCAR3* was positively correlated with various immune cells in HCC tissues and may play an important role in the immune micro-environment of tumors. However, the specific mechanism between *BCAR3* expression and *TP53* mutation in HCC remains unclear and may be associated with the immune landscape. Finally, we determined miRNAs and lncRNAs associated with *BCAR3* mRNA through the starBase database and revealed that the ceRNA regulatory network, composed of *BCAR3* mRNA-*miR-19b-3p* miRNA-*RAB30-DT* lncRNA, was significantly correlated with the prognosis of patients with HCC.

BCAR3, as a signal transduction regulator, was widely expressed in human tissues and was first discovered during the study of anti-estrogen resistance genes in breast cancer[16]. Further study revealed that *BCAR3* was closely associated with a variety of cell biological processes in the human body, such as cell migration, proliferation, and survival. *BCAR3* over-expression in breast cancer cells promoted cell migration and invasion[17]. *BCAR3* effectively binds to $p130^{Cas}$ (*BCAR1*)[18], thereby activating Rac1[19], regulating Src/$p130^{Cas}$ association and Src family tyrosine kinase activity and rapidly disrupting adhesion and causing tumor invasion[20,21]. *BCAR3* regulated the process of adhesion force between cells and extracellular matrix by affecting the organization of cytoskeleton and cell adhesion proteins, which was particularly crucial for cell migration and tissue remodeling. The over-expressed and hyper-activated protein of Rac1 in HCC played an important role in cancer cell proliferation, metastasis, and treatment resistance[22]. Therefore, *BCAR3* probably

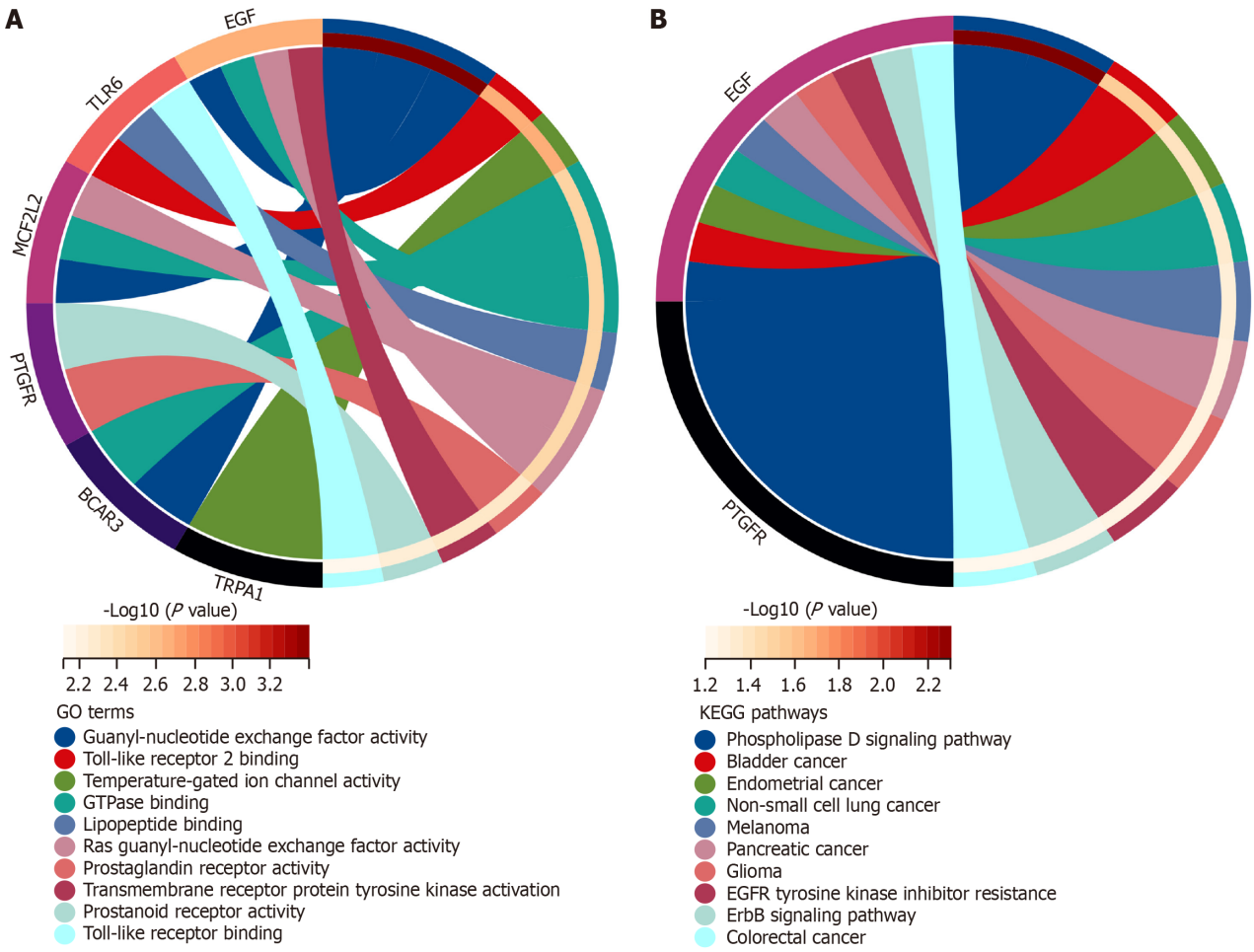

Figure 7 Functional enrichment analysis of *BCAR3* gene in hepatocellular carcinoma. A: Gene ontology enrichment analysis of *BCAR3* by Metascape, including positive regulation of guanyl-nucleotide exchange factor activity and GTPase regulator activity; B: Kyoto encyclopedia of genes and genomes pathway analysis of *BCAR3* expression by Metascape, including positive regulation of ERBB signaling pathway and positive regulation of epidermal growth factor receptor signaling pathway.

plays a similar role by activating Rac1 signaling pathways, thereby affecting the prognosis of patients with HCC, but further studies are warranted.

Our study revealed that *BCAR3* over-expression affected the immune infiltration of HCC cells and was involved in the positive regulation of the EGFR signaling pathway of tumors with related genes. Persistent and chronic liver inflammation promotes HCC development[23]. The previous study identified that the epidermal growth factor (EGF) promoted DNA synthesis and HCC cell regeneration, multiple inflammatory factor production and accumulation[24], and bound to EGFR to form EGF–EGFR pathway, which contributes to the formation of inflammation, angiogenesis, and distant HCC metastasis[25,26]. Thus, *BCAR3* promoted HCC progression by regulating the EGFR signaling pathway, causing poor prognosis in patients with HCC.

In recent years, the role of ceRNA in HCC occurrence and development received increasing attention. Multiple ceRNAs (including lncRNAs, miRNAs, and circRNAs) and corresponding ceRNA networks have been identified, which affect HCC development by regulating specific miRNAs and their target genes[27]. *MiR-122* is a hepato-specific miRNA. Studies revealed that lncRNA *HOTAIR* binds to *miR-122*, inhibits its activity through the "miRNA sponge effect," and promotes HCC proliferation, migration, and invasion[28,29]. Additionally, ceRNA plays a role by regulating important cell signaling pathways, such as regulating *Wnt/beta-catenin* signaling pathway activation to drive the aggressiveness and metastasis of liver cancer cells[30]. *UCA1* lncRNA promotes the survival of liver cancer cells by regulating downstream expression of *Bcl-2* and *Hexokinase 2* through interaction with *miR-216b* or miR-143[31]. Additionally, ceRNA regulates HCC development by affecting epigenetic mechanisms, thereby interfering with cell cycle and apoptosis[32]. In particular, *MEG3* affects liver cancer cell invasion by interacting with *miR-145-5p* to up-regulate disabled-2 expression [33]. Challenges remain in terms of clinical application despite the clear regulatory effects of these ceRNAs and networks in cell and animal models. This study obtained *BCAR3*-related mRNAs and lncRNAs by calculating the Pearson correlation coefficient, revealing a *BCAR3*-related miRNA-lncRNA pathway.

The miRNA-associated *BCAR3* mRNA was known as *miR-19b-3p*, which was a miRNA and a class of small molecular RNA that regulates gene expression. By regulating gene expression, *miR-19b-3p* could affect biological processes, such as cell growth, differentiation, and death, and be involved in cancer occurrence and development, including lung adenocarcinoma, esophageal squamous carcinoma, and intrahepatic cholangiocarcinoma[34-36]. Recent experimental studies

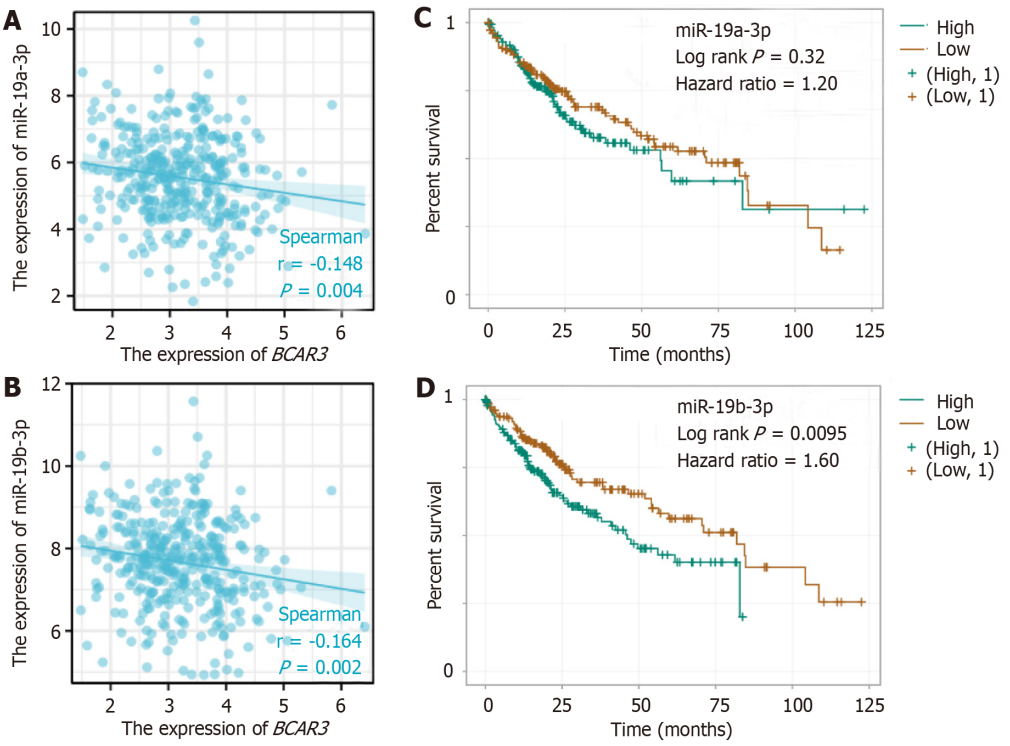

Figure 8 Correlation, and survival curve analyses between *BCAR3* and 2 miRNAs. A: Negative regulatory relationship between *BCAR3* and *miR-19a-3p*, analyzed by Spearman correlate analysis; B: Negative regulatory relationship between *BCAR3* and *miR-19b-3p*, analyzed by Spearman correlate analysis; C and D: Kaplan-Meier survival analysis of *miR-19a-3p* and *miR-19b-3p* expression in hepatocellular carcinoma (HCC) patients. Comparison between high expression group and low expression group was performed by Log rank. Hazard ratio (HR) represents the risk factor of the high expression group relative to the low expression group sample. HR > 1 indicates that the miRNA is a risk factor for HCC.

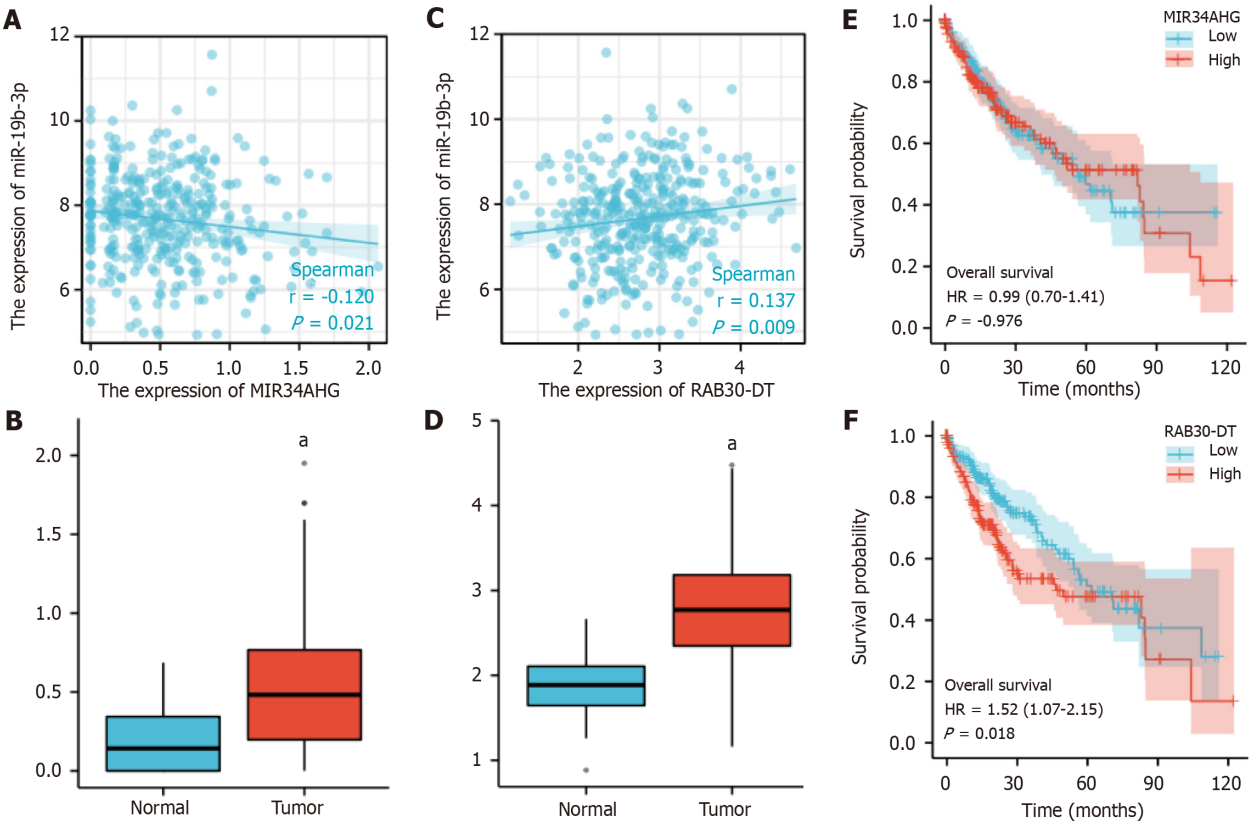

Figure 9 Correlation, difference, and survival curve analyses between *miR-19b-3p- BCAR3*-related long-stranded non-coding RNA and

miRNA in hepatocellular carcinoma, respectively. A: Negative regulatory relationship between *MIR34AHG* long-stranded non-coding RNA (lncRNA) and *miR-19b-3p*, analyzed by Spearman correlate analysis; B: Differential expression of *MIR34AHG* lncRNA in hepatocellular carcinoma (HCC) tissue; C: Positive regulatory relationship between *RAB30-DT* lncRNA and *miR-19b-3p*, analyzed by Spearman correlate analysis; D: Differential expression of *RAB30-DT* in HCC tissue; E: Kaplan-Meier survival analysis of *MIR34AHG* lncRNA expression in HCC patients; F: Kaplan-Meier survival analysis of *RAB30-DT* lncRNA expression in HCC patients. [a]*P* value < 0.05.

revealed that the up-regulated *miR-19b-3p* expression level in HCC inhibited ferroptosis and promoted HCC cell proliferation by inhibiting RBMS1 expression[37], and was closely associated with HCC malignancy and prognosis. Additionally, *miR-19b-3p* overexpression activated the *Wnt/β-catenin* signaling pathway and played a role in promoting HCC development[38]. Therefore, *miR-19b-3p* may promote HCC occurrence and progression by regulating *BCAR3* expression, but the specific mechanism remains unclear.

RAB30-DT is a lncRNA that belongs to a family of great interest in cancer, but information about this lncRNA is limited [39]. *RAB30-DT* demonstrated an abnormal expression level in HCC and a significantly higher expression level in HCC than that in normal liver tissue, which is significantly associated with the poor prognosis of patients with HCC. Some studies revealed that *miR-19b-3p* promoted tumor growth and intratumoral cell proliferation by targeting *PTEN*, causing PI3K/AKT signaling pathway activation[40]. Therefore, the possible mechanism by which *RAB30-DT* affected HCC occurrence and development was to reduce the inhibitory effect on the target gene *PTEN* by binding to *miR-19b-3p*, thereby improving the migration and invasion ability of HCC cells. More studies are warranted to investigate this process. In conclusion, *BCAR3* probably promoted the *RAB30-DT* expression by regulating *miR-19b-3p* expression, thereby playing a role in HCC pathogenesis.

Our study used TCGA and starBase databases to investigate and analyze the role of *BCAR3* and its related ceRNAs in HCC occurrence and development. Our results present very valuable direction and reference for the research of *BCAR3*, which may be utilized as a new potential biomarker to provide new ideas for the early diagnosis and treatment of HCC. However, our study has some limitations. Noteworthily, the study was based on bioinformatics analysis, so the validity of the results warrants further verification by basic experimental studies.

CONCLUSION

In conclusion, *BCAR3* plays an important role in HCC occurrence and development and is closely associated with HCC diagnosis and prognosis. *BCAR3* is expected to become a new prognostic indicator and therapeutic target and bring more accurate treatment for patients with HCC. However, the current study remains preliminary, and further research is required to investigate the mechanism of action of *BCAR3* in HCC as well as the application of this knowledge to clinical treatment.

FOOTNOTES

Author contributions: Tang XW was responsible for the design and conception of the research; Shi HQ and Huang S completed the writing and key revisions of the manuscript together; Ma XY, Tan ZJ, Zhang W, Shi L, Luo R, Luo B, Lü MH and Zhong XL jointly completed the data collection and analysis of the manuscript; Chen X and Tang XW completed the final revision and approval of the manuscript. All authors were involved in the critical review of the results and have contributed to read and approved the final manuscript. Shi HQ and Huang S contributed equally to this work as co-first authors. Chen X and Tang XW contributed to this work as co-corresponding authors. The reasons for designating Chen X and Tang XW as co-corresponding authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-corresponding authors authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-corresponding authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, Chen X and Tang XW contributed efforts of equal substance throughout the research process. The choice of these researchers as co-corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Chen X and Tang XW as co-corresponding authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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