

Mining database and verification of PIK3CB as a marker predicting prognosis and immune infiltration in renal clear cell carcinoma

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Abstract

Background: Kidney renal clear cell carcinoma (KIRC) was the most prevalent malignancy of urinary system. Phosphatidylinositol 3-kinase pathway exerted a vital function in tumor proliferation, invasion, and survival by integrating extracellular growth signals.

Methods: The expression and clinical significance of PIK3CB in KIRC was explored using bioinformatics analysis. And qRT-PCR was performed to verify our results.

Results: PIK3CB was downregulated at mRNA and protein level in KIRC. KIRC patients with low PIK3CB expression indicated a worse overall survival, progression free survival, and disease-free survival. A predictive nomogram was constructed and demonstrated that the predicted calibration plots for 1-year, 3-year, and 5-year OS probabilities showed good agreement compared with the actual OS of KIRC patients. Validation research demonstrated a downregulation of PIK3CB in KIRC tissues and a poor overall survival in KIRC patients with low PIK3CB expression. Furthermore, Cox regression analysis revealed that PIK3CB expression was an independent prognostic factor for KIRC. PIK3CB expression showed positive correlation with the abundance of immune cells. Moreover, enrichment analysis revealed that PIK3CB and associated genes were mainly associated with RNA splicing and JAK-STAT signaling pathway.

Conclusion: Our study suggested that PIK3CB was a potential biomarker for prognosis and correlated with immune infiltrates in KIRC.

Abbreviations: GO = Gene Ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes, KIRC = kidney renal clear cell carcinoma, PI3K = phosphatidylinositol 3-kinase, TCGA = The Cancer Genome Atlas.

Keywords: immune infiltration, PIK3CB, prognostic biomarker, renal cell carcinoma

1. Introduction

Kidney renal clear cell carcinoma (KIRC) is the most prevalent malignancy of urinary system, ranking almost 75% of all kidney cancers.^[1] An estimated of 73,750 patients were diagnosed with kidney cancer and 14,830 patients died in 2020 globally.^[2] KIRC be characterized by high recurrence, metastasis, radiotherapy, and resistance to chemotherapy.^[3,4] Despite multidisciplinary synthetic therapy, including chemotherapy, immunotherapy, and targeted therapy being applied for KIRC, the prognosis of KIRC was

still poor, with the 5-year disease specific survival of less than 10% in stage IV.^[5,6] Hence, it is significant to identify novel prognostic biomarkers for KIRC.

The phosphatidylinositol 3-kinase (PI3K) pathway exerted a vital function in tumor proliferation, invasion, and survival by integrating extracellular growth signals.^[7] Previous studies revealed that PI3K/AKT pathway is modestly mutated but highly activated in KIRC, representing a promising drug target for KIRC.^[8] Class IA PI3Ks are heterodimeric lipid kinases including

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Code availability is not applicable.

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p110 α /PIK3CA, p110 β /PIK3CB, p110 δ /PIK3CD, and a p85 regulatory subunit.^[9] PIK3CB acted as a prognosis biomarker in cancer progression and regulated biological process.^[7,10] However, the role of PIK3CB in KIRC was still a mystery.

Herein, we explored the expression and prognosis value of PIK3CB and its association with immune infiltrates using multi-dimensional analysis methods. Our study result may provide more evidence for further study surrounding the role of PIK3CB in KIRC.

2. Methods

2.1. TIMER

TIMER (www.cistrome.shinyapps.io/timer/) is a comprehensive bioinformatics tool for immune-infiltrate analysis.^[11] In our study, “Diff Exp” module was applied to detect differential PIK3CB expression across various tumors. We utilized the “Gene” and “correlation” module for analysis of PIK3CB expression correlation with abundance of immune cell infiltrates with Spearman correlation test using The Cancer Genome Atlas (TCGA) KIRC dataset (n=538).

2.2. UALCAN

UALCAN (www.ualcan.path.uab.edu/analysis.html) is a comprehensive bioinformatics tool for cancer research.^[12] PIK3CB was submitted to the TCGA analysis module, which could analyze PIK3CB expression and its correlation with clinical features of KIRC patients using TCGA KIRC dataset (n=538). Student *t* test was applied to evaluate the significance of different subgroups and *P* value < .05 was a threshold for statistical significance.

2.3. The Human Protein Atlas

The Human Protein Atlas (www.proteinatlas.org) is a Swedish-based program build for showing map all the human proteins in cells, tissues, and organs.^[13] The Tissue Atlas and The Pathology Atlas of this program was used to explore the protein level of PIK3CB in renal tissue and KIRC tissue.

2.4. Prognosis analysis

Kaplan-Meier survival analysis was conducted to explore the prognosis value of PIK3CB in KIRC using TCGA KIRC dataset (n=538). The *P* value and hazard ratio with 95% confidence interval was calculated with a log-rank test. A nomogram was developed based on the results of univariate and multivariate Cox proportional hazards analysis.

2.5. Clinical specimens and Real-time quantitative PCR (qRT-PCR)

After obtained informed consent from patients of Affiliated hospital of Jingchu University of Technology, we obtained KIRC tissues and pair-normal renal tissues (n=46) from these patients. Our study was approved by the ethics committee of affiliated hospital of Jingchu University of Technology. None of patient received local or systemic treatment preoperatively. TRIzol reagent (Vazyme, Nanjing, China) was used to isolate total RNA. The synthesis of cDNAs corresponding to the mRNAs of interest was conducted with PrimeScript RT-polymerase (Vazyme). SYBR-Green Premix

(Vazyme) and specific PCR primers (Sangon, China). The primers used in this study for qRT-PCR analysis obtained from BioSune Biotechnology (Shanghai, China) and listed as follows: PIK3CB: Forward, 5'-TATTTGGACTTTGCGACAAGACT-3' and Reverse, 5'-TCGAACGTACTGGTCTGGATAG-3'; β -actin: Forward, 5'-GCACCGCAAATGCTTCTA-3' and Reverse, 5'-GGTCTTTACGGATGTCAACG-3'. The 2- $\Delta\Delta$ Ct method was used to calculate fold-changes. The difference of the expression of PIK3CB and the prognosis of PIK3CB in KIRC were explored with Student *t* test and Kaplan-Meier analysis, respectively.

2.6. Functional enrichment analysis

After obtained the genes (PIK3CB, PKB, mTOR, AMPK, GSK3A, GSK3B, PDK1, CK2, DNAPK, eNOS, MELK, MAPKAP-K1, S6K1, S6K2, PI4K, PIKfyve, PTEN, CREB) associated with PI3K/AKT pathway, we then performed Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) with “ggplot2” package in R software v4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

2.7. Open Targets

Open Targets (www.targetvalidation.org) is an online platform that integrates evidence from genomics, transcriptomics, and scientific literature, which allows for scoring and ranking of target-disease associations for drug target identification.^[14] PIK3CB was submitted to this platform for further allocating the diseases that were associated with PIK3CB.

2.8. LinkedOmics and GeneMANIA

LinkedOmics (www.linkedomics.org) is a comprehensive bioinformatics tool for genomic analysis with TCGA dataset.^[15] After obtained the associated genes of PIK3CB with Pearson correlation test, we submitted these genes to the LinkInterpreter module and perform GO, KEGG, kinase targets, miRNA-target by gene set enrichment analysis. We then submitted the genes of Kinase_MAPK3 and MIR-381 network to GeneMANIA (www.genemania.org) to construct a Protein-Protein Interaction (PPI) network.

2.9. GSCALite

GSCALite (www.bioinfo.life.hust.edu.cn/web/GSCALite) is a comprehensive bioinformatics tool that helps us identify about the contribution of a gene to the cancer initiation, progress, diagnosis, prognosis, and therapy.^[16] The drug sensitivity of PIK3CB was analyzed using GSCALite.

3. Results

3.1. PIK3CB expression in KIRC

The differences of PIK3CB expression in tumor and normal tissues across various type of cancers was explored with the TIMER database. The result revealed low PIK3CB mRNA expression in colorectal cancer, KIRH, KIRC, KIRP, and THCA (Fig. 1A). Moreover, the data also suggested that PIK3CB mRNA expression was increased in CHOL, ESCA, HNSC, LIHC, LUAD, LUSC, and STAD (Fig. 1A). Based on the KIRC dataset of TCGA database, the result of UALCAN revealed that PIK3CB mRNA level was downregulated in KIRC tissues (Fig. 1B, *P* < .001). We then explored the protein level of PIK3CB

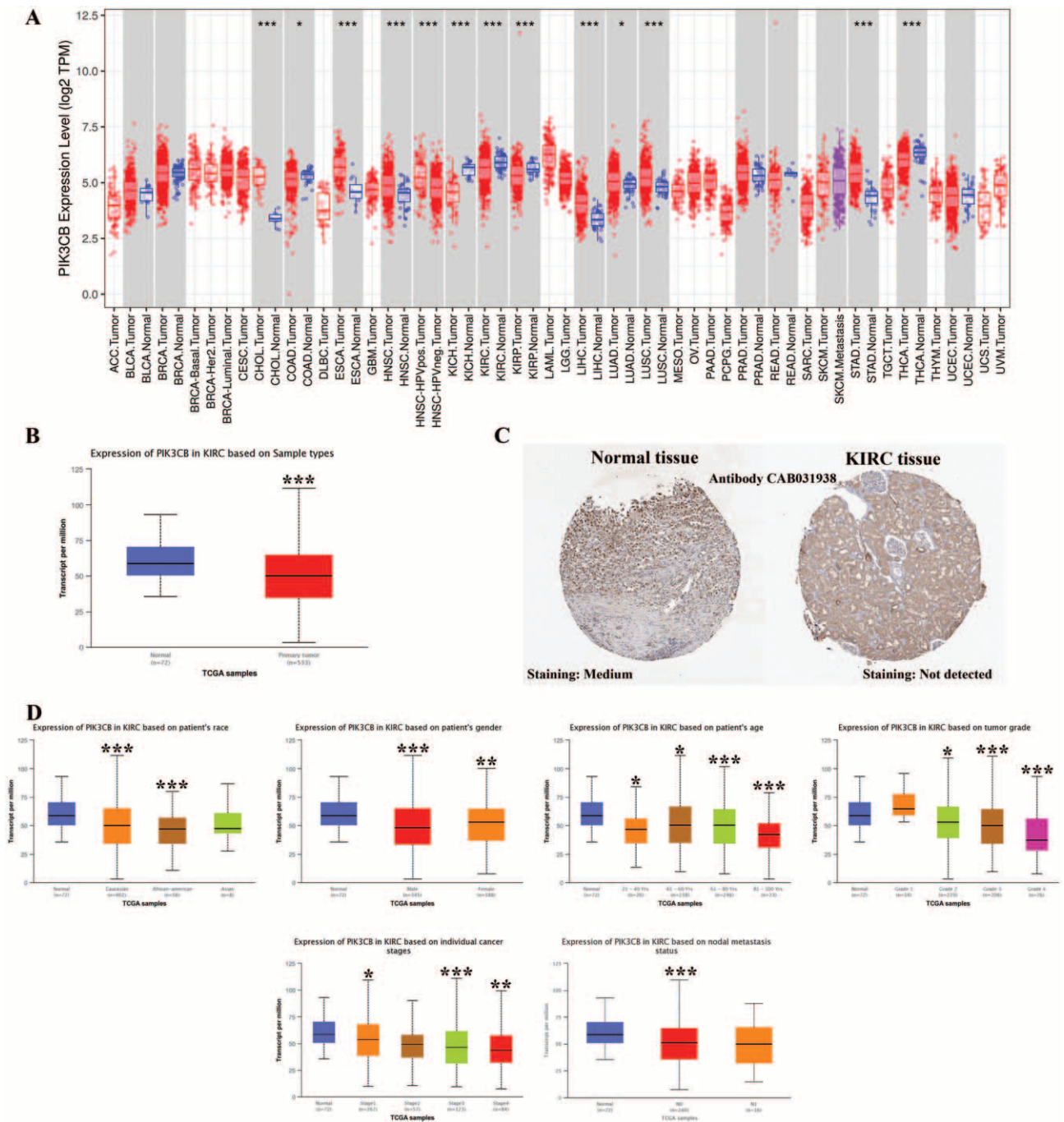


Figure 1. The expression of PIK3CB in KIRC. (A) Upregulation or downregulation PIK3CB in different type of cancers. (B) TCGA KIRC dataset revealing PIK3CB expression in KIRC and normal tissue. (C) Immunohistochemical staining revealing the protein level of PIK3CB in KIRC and normal tissue. (D) The level of PIK3CB in subgroups of patients with KIRC. *, $P < .05$; **, $P < .01$; ***, $P < .001$. KIRC = kidney renal clear cell carcinoma, TCGA = The Cancer Genome Atlas.

in KIRC using the Human Protein Atlas, which suggested a downregulation of PIK3CB protein level in KIRC tissues (Fig. 1C). Figure 1D showed the PIK3CB mRNA expression in sub-group of KIRC patients. As expected, downregulation of PIK3CB mRNA levels was found in KIRC patients vs normal controls in a sub-group analyses based on race, gender, age, tumor grade, cancer stages, and nodal metastasis status, suggested a significant function of PIK3CB in the detection of KIRC.

3.2. PIK3CB acted a prognostic biomarker in KIRC

KIRC patients with high PIK3CB expression had a better overall survival ($P = 2.19 \times 10^{-5}$), progression free survival ($P = .00092$), and disease-free survival ($P = 3.86 \times 10^{-5}$) with 5-year AUC of 0.643, 0.629, and 0.644, respectively (Fig. 2A–C), suggesting PIK3CB as a potential prognostic marker in KIRC. As shown in Figure 2D and E, univariate and multivariate analysis demonstrated PIK3CB, age, pTNM stage, and tumor grade were independent prognosis factors for KIRC. Considering these independent prognosis

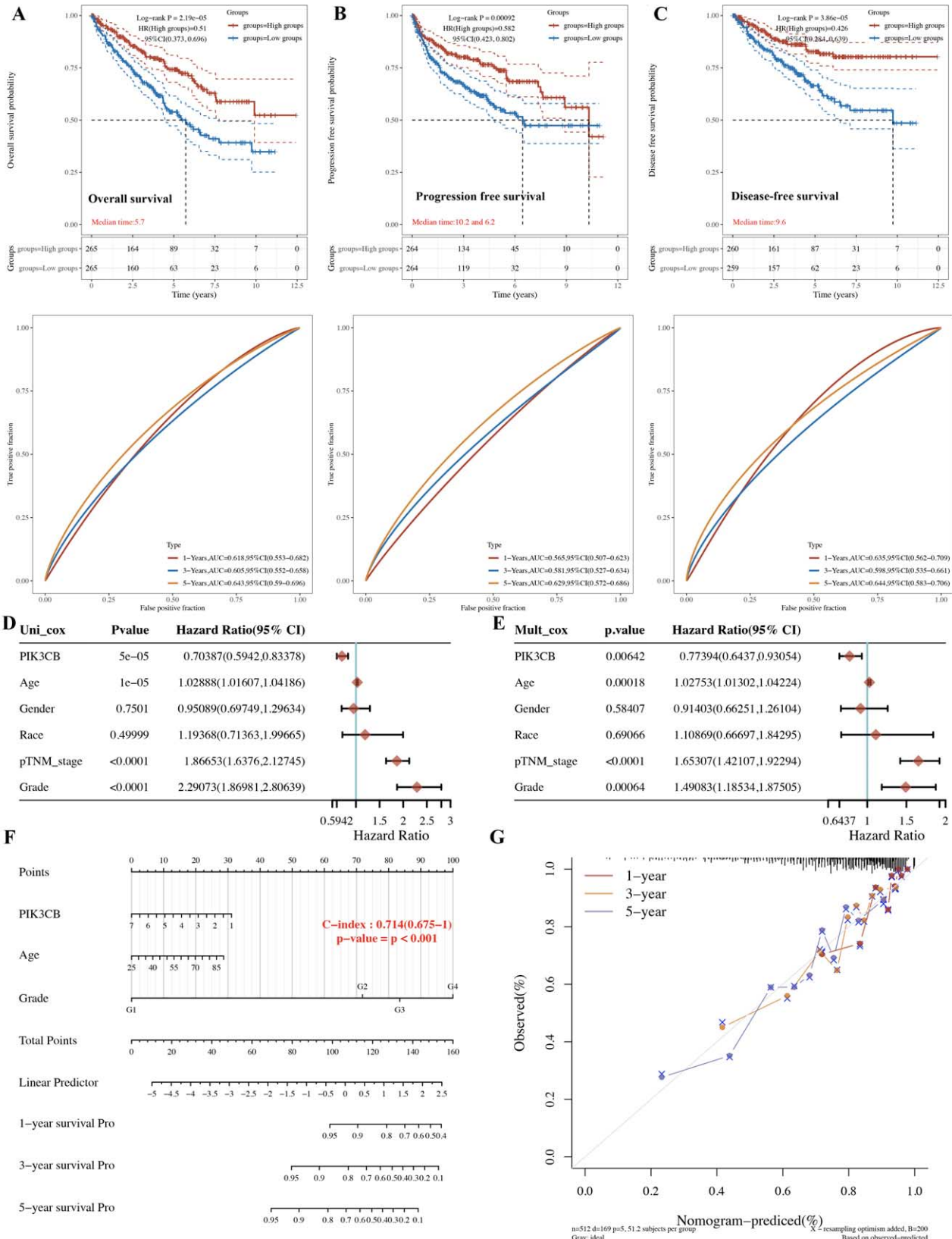


Figure 2. PIK3CB served a prognostic biomarker in KIRC. KIRC patients with high PIK3CB expression had a better overall survival rate (A), progression free survival rate (B), and disease-free survival rate (C) in KIRC and the receiver operating characteristic curve in predicting the prognosis of KIRC patients. (D-E) Univariate and multivariate cox regression considering clinical parameters and PIK3CB in KIRC. (F-G) The predictive nomogram to predict the 1-year, 3-year, and 5-year overall survival of KIRC patients. KIRC = kidney renal clear cell carcinoma.

factors, we constructed a predictive nomogram to predict the 1-year overall survival (OS), 3-year OS, and 5-year OS rates using the Cox regression algorithm and the result demonstrated that the predicted calibration plots for 1-year, 3-year, and 5-year OS probabilities showed good agreement compared with the actual OS of KIRC patients (Fig. 2F–G).

3.3. Validation of the expression and prognostic value of PIK3CB in KIRC

qRT-PCR was performed to verify the expression and prognostic value of PIK3CB in KIRC using the clinical tissues. As shown in Figure 3A, PIK3CB was down-regulated in KIRC versus normal tissues ($P < .001$). Moreover, OS analysis suggested a better prognosis in KIRC patients with high PIK3CB expression ($P = .016$, Fig. 3B). As shown in Figure 3C–D, univariate and multivariate analysis also demonstrated PIK3CB as an independent prognosis factor for KIRC. These data further confirmed previous results.

3.4. PIK3CB expression correlated with immune infiltration and drug resistance in KIRC

The correlation between PIK3CB expression and immune cells and biomarker sets in KIRC was explored with TIMER. As expected, we obtained a distinct correlation between PIK3CB expression and immune infiltration of B cells ($Cor = 0.327$), CD8 + T cells ($Cor = 0.148$), CD4+ T cells ($Cor = 0.204$), macrophage ($Cor = 0.391$), neutrophils ($Cor = 0.362$), and dendritic cells ($Cor = 0.276$) (Fig. 4A, all $P < .05$). To develop cancer therapy target, an important way is to assess the correlation between

target gene and existed drug targets. In our study, we found that PIK3CB was correlated with the drug resistance of 30 small molecules or drugs, suggesting PIK3CB as a promising biomarker for drug screening (Fig. 4B).

3.5. Genetic alterations and PI3K/AKT pathway related genes in KIRC

We then determined genetic alterations of PIK3CB in KIRC. Thirty-seven of 537 (7%) of TCGA KIRC patients had a PIK3CB genetic alteration. mRNA low was the most common type genetic alteration followed by mRNA low and amplification in KIRC (Fig. 4C). Moreover, after isolated the genes correlated with PI3K/AKT pathway, we performed GO and KEGG pathway analysis using these gene. Results indicated that these genes were mainly involved in cellular response to insulin stimulus, phosphorylation, cellular response to peptide, wnt signalosome, threonine kinase activity, and protein kinase A binding in GO functions (Fig. 5A). Moreover, KEGG pathway analysis revealed that these genes were mainly involved in mTOR signaling pathway, chemokine signaling pathway, P13K-AKT signaling pathway, and PD-L1 and PD-1 checkpoint pathway in cancer (Fig. 5B).

3.6. GO and KEGG pathway analyses of co-expression genes correlated with PIK3CB in KIRC.

We submitted PIK3CB to LinkedOmics and performed Pearson correlation analysis, which indicated 7238 genes (dark red dots) positively correlated with PIK3CB and 6987 genes (dark green

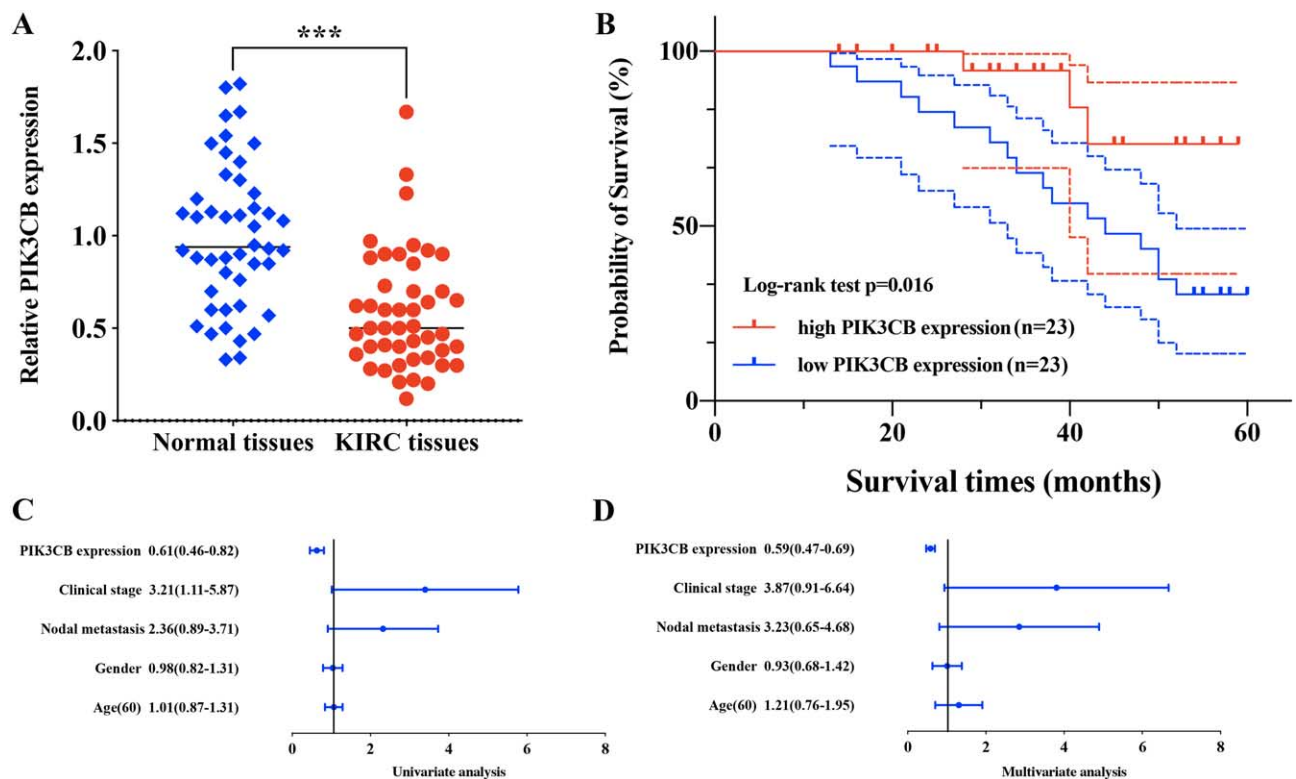


Figure 3. The expression and prognosis value of PIK3CB in KIRC. (A) The relative expression of PIK3CB in KIRC vs normal tissues. (B) Overall survival curve in high and low PIK3CB expression group in KIRC. (C–D) Univariate and multivariate analysis considering clinical parameters and PIK3CB in KIRC. KIRC = kidney renal clear cell carcinoma.

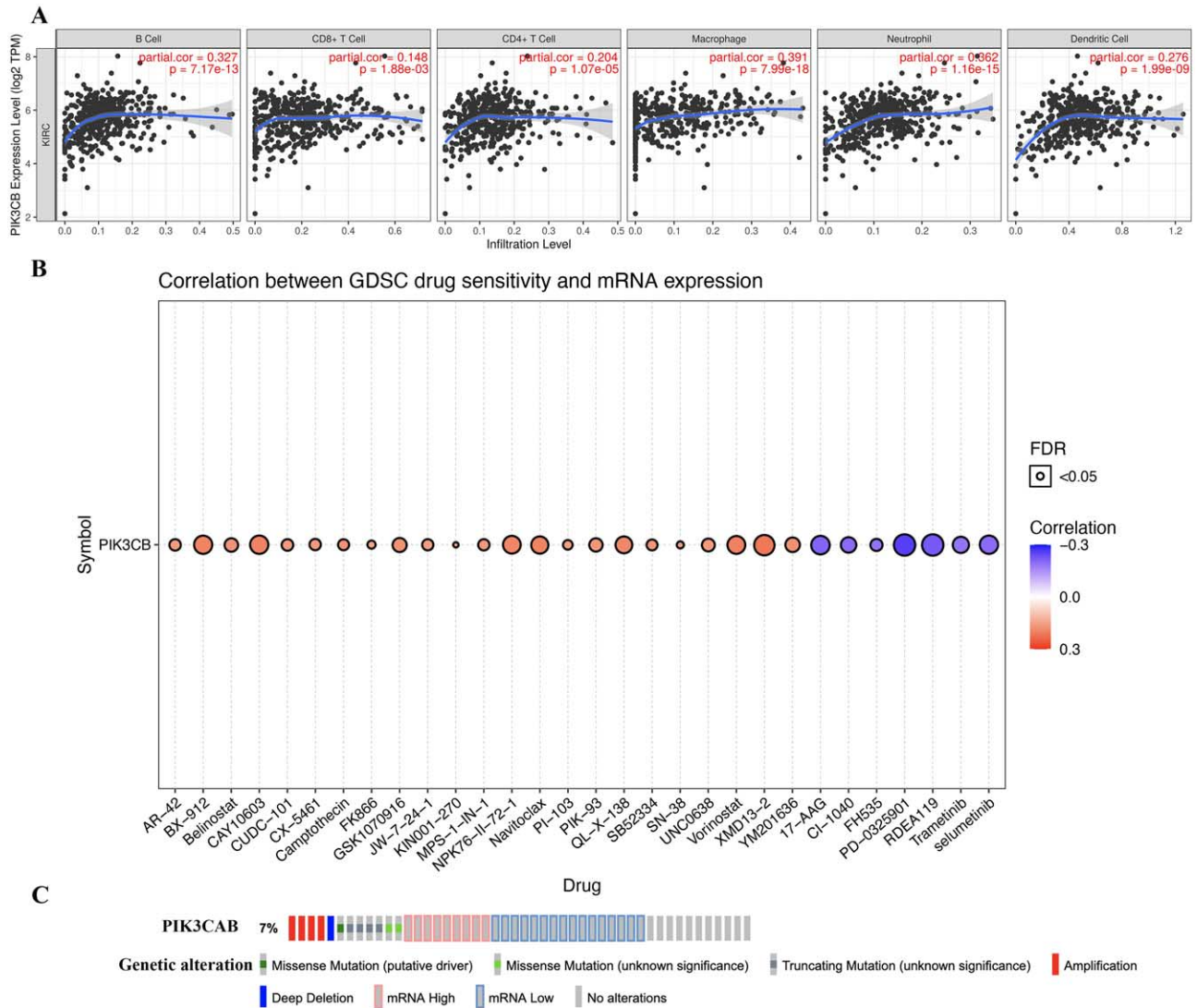


Figure 4. Immune infiltration analysis, drug sensitivity, and genetic alteration of PIK3CB in KIRC. (A) PIK3CB expression showed positive correlation with immune cell infiltration in KIRC. (B) The correlation between PIK3CB and drug sensitivity in KIRC. (C) PIK3CB genetic alteration in KIRC. KIRC = kidney renal clear cell carcinoma.

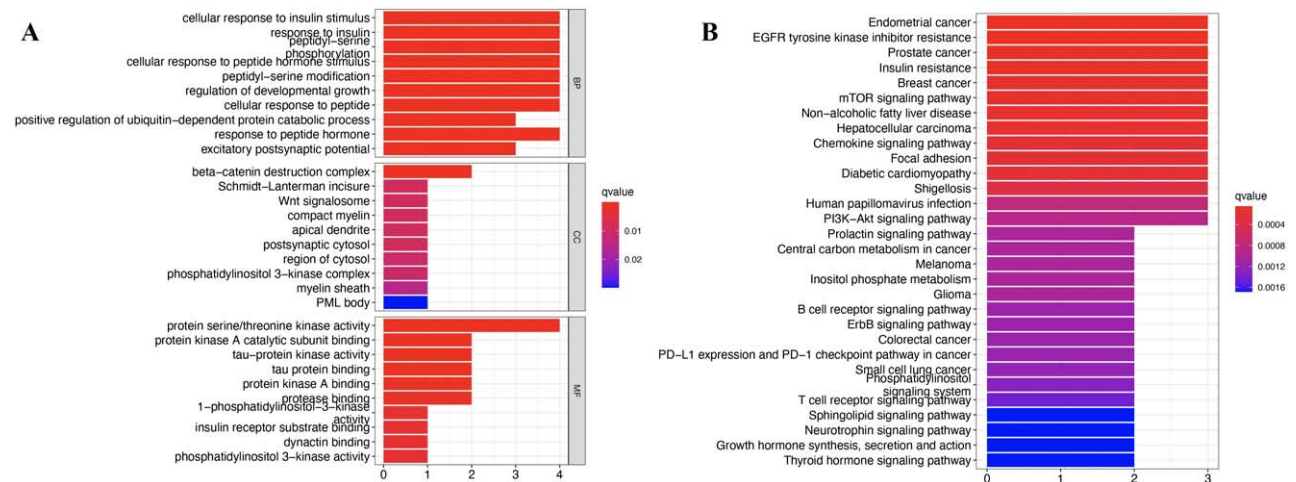


Figure 5. Enrichment analysis of PI3K/AKT pathway related genes. (A) The enriched items in Gene Ontology analysis (B) The enriched items in Kyoto Encyclopedia of Genes and Genomes pathway analysis. BP = biological processes, CC = cellular components, MF = molecular functions, PI3K = phosphatidylinositol 3-kinase.

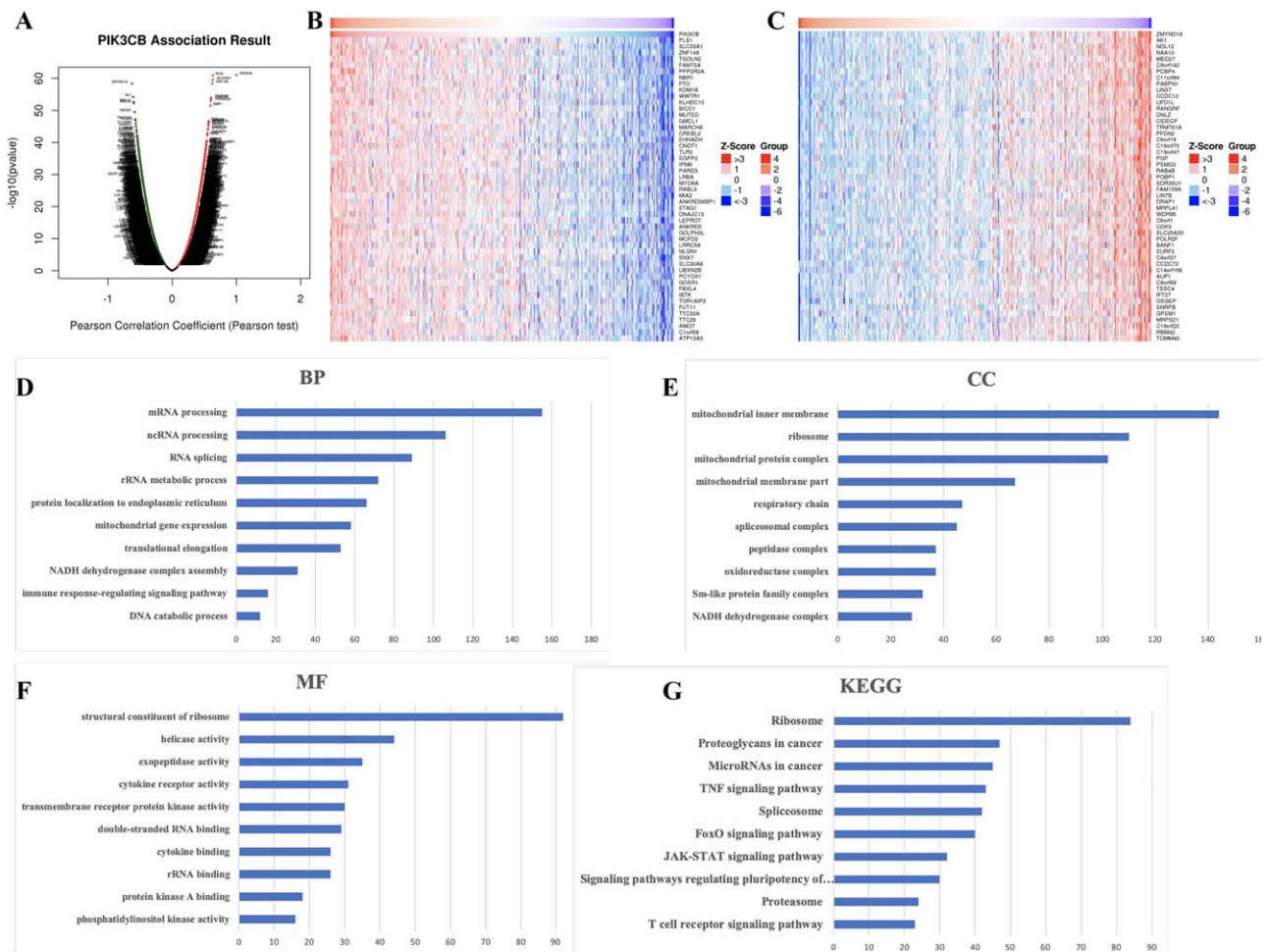


Figure 6. Correlated genes, GO and KEGG pathways analysis of PIK3CB in KIRC. (A) PIK3CB association result in KIRC. (B–C) Heat maps of the most significant 50 genes positively and negatively correlated with PIK3CB in KIRC. (D) BP analysis. (E) CC analysis. (F) MF analysis. (G) KEGG pathway analysis. BP = biological processes, GO = Gene Ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes, KIRC = kidney renal clear cell carcinoma, MF = molecular functions.

dots) negatively correlated with PIK3CB (Fig. 6A). Figure 6B–C showed the top 50 genes that were most positively and negatively associated with PIK3CB in KIRC. We then performed GO and KEGG pathway analyses with these positively correlated genes. GO results in Figure 6D–F suggested that the PIK3CB-associated genes are involved in mRNA processing, RNA splicing, rRNA metabolic process, ribosome, helicase activity, cytokine binding. Moreover, KEGG pathway analysis suggest that PIK3CB-associated genes were enriched in ribosome, proteoglycans in cancer, microRNAs in cancer, TNF signaling pathway, spliceosome, JAK-STAT signaling pathway (Fig. 6G). Furthermore, result of Open Targets also suggest that PIK3CB was involved in cell proliferation disorder, integumentary system disease, respiratory disease, gastrointestinal disease, immune system disease, endocrine system disease, and urinary system disease (Fig. 7).

3.7. PIK3CB networks of kinase and miRNA targets in KIRC

To explore the potential mechanism of PIK3CB in KIRC, we then detected kinase and miRNA targets of PIK3CB using LinkedOmics. As shown in Table 1, the data suggested MAPK3,

E2F1, MAPK1, EGFR, and HCK as the top 5 most significant kinase targets. We also constructed a PPI network based on the genes correlated with kinases MAPK3 target network, indicating enrichment in myeloid cell differentiation, gene silencing by miRNA, posttranscriptional gene silencing (Fig. 8). The top 5 most significant miRNA targets were MIR-381 (CTTGTAT), MIR-448 (ATATGCA), MIR-202 (ATAGGAA), MIR-302C (ATGTAA), and MIR-369-3P (GTATTAT) (Table 1). The PPI network based on the target network of miR-381 suggested their functions in regulation of translation, ubiquitin-protein transferase activity, translational initiation (Figure S1B, Supplemental Digital Content, <http://links.lww.com/MD2/B5>).

4. Discussion

PI3K signaling pathway is crucial for tumor cell migration, growth, metastasis, and survival.^[17] Increasing evidences revealed that PIK3CB could regulate the growth and metastasis of cancer.^[18] PIK3CB acted as a prognosis biomarker in cancer progression and regulated biological process.^[7,10] However, the role of PIK3CB in KIRC was still a mystery. Thus, our study was performed to identify the significance of PIK3CB in KIRC.

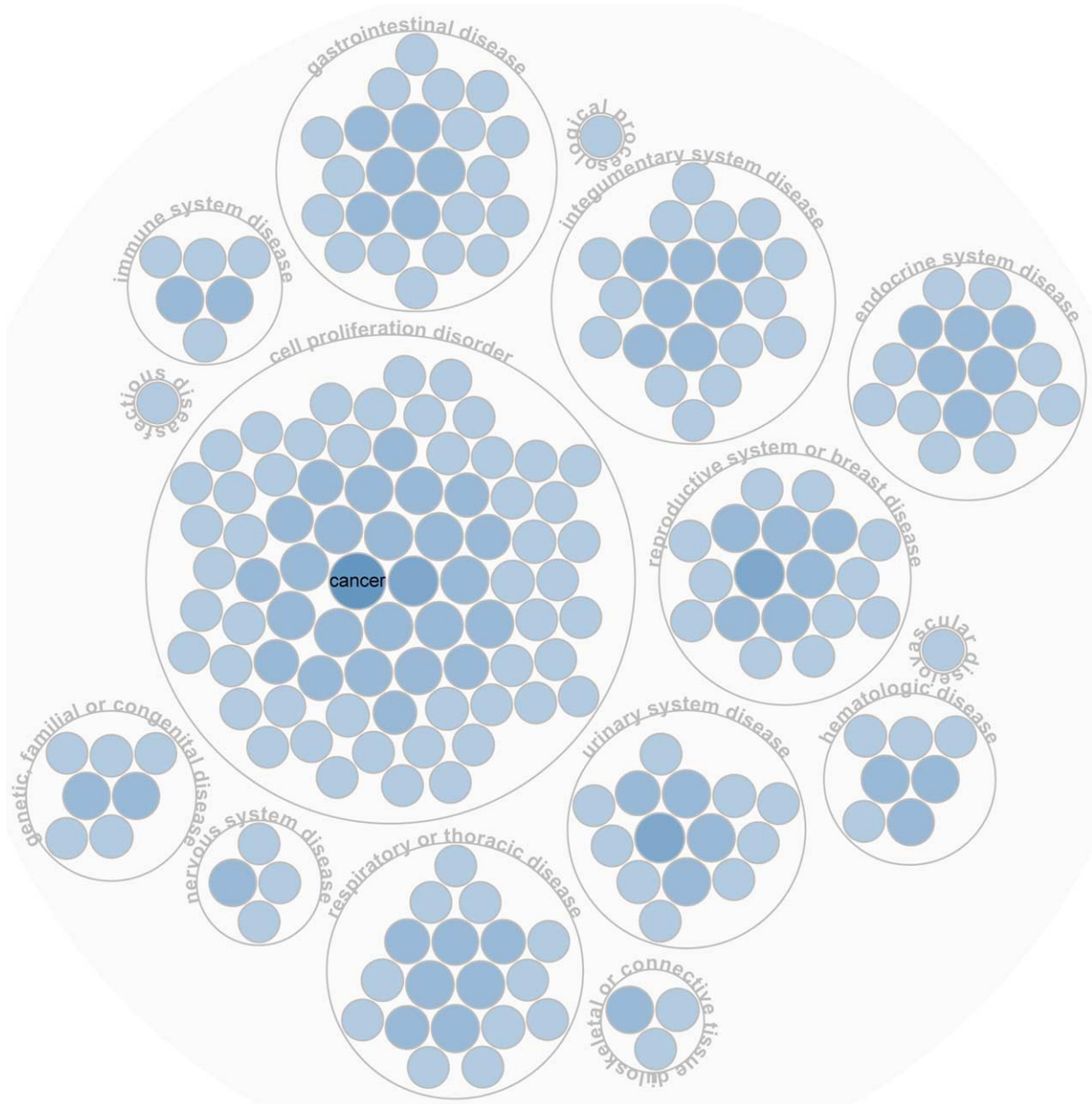


Figure 7. Bubble map revealing the diseases associated with PIK3CB.

Table 1			
The kinase and miRNA of PIK3CB in KIRC (LinkedOmics).			
Enriched category	Geneset	LeadingEdgeNum	P value
Kinase target	Kinase_MAPK3	68	0
	Kinase_E2F1	99	0
	Kinase_MAPK1	87	0
	Kinase_EGFR	54	0
	Kinase_HCK	32	0
miRNA target	CTGTAT, MIR-381	68	0
	ATATGCA, MIR-448	94	0
	ATAGGAA, MIR-202	49	0
	ATGTTAA, MIR-302C	83	0
	GTATTAT, MIR-369-3P	75	0

KIRC = kidney renal clear cell carcinoma.

We initially explored the expression of PIK3CB in KIRC, suggesting the downregulation of the mRNA and protein levels of PIK3CB in tumor tissues versus normal tissues. Moreover, further prognosis analysis demonstrated that PIK3CB acted as a prognostic biomarker in KIRC, predicting a better overall survival, progression free survival, and disease-free survival in KIRC. Actually, the study about the prognosis of PIK3CB in cancer was limited. Kevin et al^[19] suggested PIK3CB as a selective prognosis biomarker for glioblastoma.

Our study also revealed a significant association between PIK3CB expression and immune cell infiltration, including B cells, CD8+ T cells, CD4+ T cells, macrophage, neutrophils, and dendritic cells. CD8+ T cells and CD4+ T cells played a vital role in tumor progression.^[20] Moreover, dendritic cells, one of vital parts of tumor microenvironment, can infiltrate into tumors,

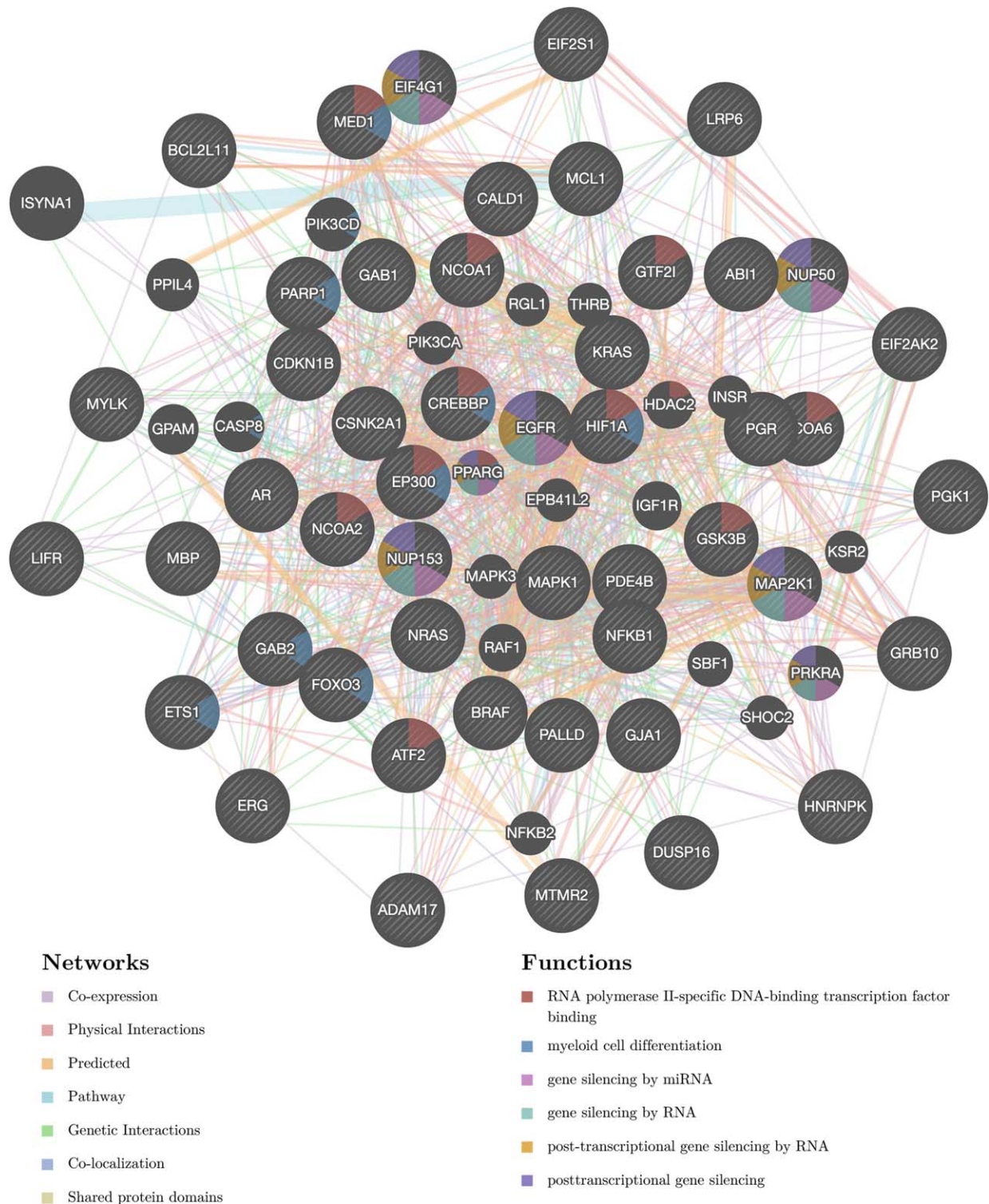


Figure 8. PPI network of kinase MAPK3 networks. PPI network and functional analysis of the gene sets of kinase MAPK3 networks. The different colors for the network nodes indicate the biological functions of the set of enrichment genes.

which could activate immune response and recruit disease-fighting immune effector cells and pathways.^[21] PIK3CB may also be involved in immune infiltration of KIRC and PIK3CB may be a therapy target for KIRC. Interestingly, we found that PIK3CB was correlated with the drug resistance of 30 small molecules or drugs, suggesting PIK3CB as a promising

biomarker for drug screening. Previous study revealed that the combined detection of PIK3CB was a prognosis biomarker and optimal therapy target in colorectal carcinoma.^[22] Sunitinib is the only widely approved drug for KIRC treatment. However, no significant correlation was obtained between PIK3CB and sunitinib and further study should be conducted to study this.

Moreover, our study revealed that PIK3CB-associated genes are associated with mRNA processing, RNA splicing, rRNA metabolic process, microRNAs in cancer, TNF signaling pathway, spliceosome, JAK-STAT signaling pathway. Interestingly, the processes and signaling pathway were involved in the tumorigenesis and cancer progression. Accumulating evidence revealed that aberrant JAK/STAT signaling is crucial for tumor progression and metastatic development.^[23] Many members of JAK/STAT signaling were suggested as a prognosis biomarker for KIRC.^[24]

The current study also identified some miRNA targets of PIK3CB in KIRC, such as MIR-381, MIR-448, MIR-202, MIR-302C, and MIR-369-3P. Actually, these miRNAs were play a vital role in KIRC.

Downregulation of miRNA-381 could accelerate tumor growth and chemoresistance in KIRC.^[25] Moreover, miRNA-381-3p acted as a dual suppressor of apoptosis and necroptosis and promoted cell proliferation in KIRC.^[26] Another study revealed that miRNA-302c could suppress cell proliferation via Gab2 in KIRC.^[27]

Some limitations could be found in our study. Another database should be applied to verify our result. Moreover, further in vivo and in vitro experiments should be performed to validate our results.

5. Conclusions

All in all, our study suggested that PIK3CB was a prognostic biomarker that associated with immune cell infiltration, providing additional data for further study of the functions of PIK3CB in KIRC carcinogenesis.

Author contributions

Conception: Tao Zeng.

Interpretation or analysis of data: Jianzhong Ye.

Preparation of the manuscript: Jianzhong Ye.

Revision for important intellectual content: Jianzhong Ye.

Supervision: Tao Zeng.

Formal analysis: Tao Zeng.

Funding acquisition: Tao Zeng.

Investigation: Jianzhong Ye, Tao Zeng.

Methodology: Jianzhong Ye, Tao Zeng.

Project administration: Tao Zeng.

Resources: Tao Zeng.

Supervision: Tao Zeng.

Validation: Tao Zeng.

Visualization: Jianzhong Ye.

Writing – original draft: Jianzhong Ye.

Writing – review & editing: Jianzhong Ye, Tao Zeng.

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