Identification of BAK1 as a novel prognostic biomarker for liver cancer based on the mining of liver cancer pyroptosis-related genes

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Abstract

Hepatocellular carcinoma is a type of digestive tract cancer that has a high incidence and a poor prognosis. Pyroptosis, a newly discovered and proven method of pro-inflammatory programmed cell death, is linked to tumor development, patient prognosis, and response to therapy. In this study, the prognostic genes of liver cancer were obtained; their expressions were extracted from The Cancer Genome Atlas database; differential analysis, survival analysis, and clinical correlation analysis were performed; and a nomogram was constructed to predict the survival rate. Based on the expression of BAK1 gene, all samples were then divided into two groups: High expression and low expression. Enrichment analysis, immunological analysis, and drug susceptibility analysis of differential genes were subsequently performed in that order. BAK1 expression was found to be significantly higher in liver hepatocellular carcinoma (LIHC). High BAK1 expression levels were found to be linked to cancer development and poor prognosis. To assess the diagnostic value of BAK1 in LIHC, a receiver operating characteristic curve was drawn. In addition, there were significant differences in drug sensitivity between high and low BAK1 expression in 90 drugs. The BAK1 gene may be a good potential LIHC diagnostic marker, an oncogene in the occurrence and progression of liver cancer, a new prognostic biomarker, and a potential therapeutic target for liver cancer.

Keywords: BAK1; Liver cancer; Pan-cancer; Immunity; Biomarkers; Prognosis

1. Introduction

Hepatocellular carcinoma is a type of digestive tract cancer that has a high incidence and a poor prognosis. In recent years, the survival rate of liver cancer has improved due to the use of surgical resection as the primary treatment method and the development of immunotherapy[1]. Despite continuous advancements in medical technology, in the face of rising incidence, it is difficult to detect liver cancer in the early stages, and once it occurs, it metastasizes easily and has a poor prognosis[2]. Liver cancer is also one of the leading causes of cancer-related death, and the overall 5-year survival rate for patients with liver cancer remains <15%[3]. Therefore, novel diagnostic markers for liver cancer are urgently needed to improve the present therapeutic environment for liver cancer. Pyroptosis is a newly discovered and proven method of programmed cell death.
death with pro-inflammatory characteristics. It is classified into caspase-1-dependent classical pyroptotic pathway and caspase-4/5/11-dependent non-classical pyroptotic pathway. Pyroptosis is characterized by deoxyribonucleic acid (DNA) breakage, cell membrane rupture, and the release of pro-inflammatory proteins. According to research, the expression of caspase-1 is low in liver cancer tissue. Other research has demonstrated that hypoxia-induced caspase-1 activation and the subsequent generation of different inflammatory factors in liver cancer tissues and cell lines can promote cancer cell invasion and metastasis. Pyroptosis not only impedes tumor cell proliferation but also creates a microenvironment that promotes tumor cell development. Given the importance of pyroptosis in malignancies, the aim of this work was to identify HCC pyroptosis-related genes (PRGs) and investigate their implications in HCC prognosis.

To identify prognosis-related pyroptosis genes, the prognostic value of 52 PRGs in 115 HCC patients from the Gene Expression Omnibus (GEO, GSE 76427) cohort was examined. Following the selection of BAK1 target gene, its expression level was obtained from The Cancer Genome Atlas (TCGA) database. In addition to the construction of a nomogram, differential analysis, survival analysis, and clinical correlation analysis were carried out to predict the survival rate. Subsequently, all samples were separated into two groups based on BAK1 gene expression: High and low expression. Enrichment analysis, immunological analysis, and drug sensitivity analysis were performed on the differential genes. The role of BAK1 in predicting prognosis and immunotherapy response in patients with liver cancer was investigated.

2. Materials and method

2.1. Data sources

The clinically relevant data and gene expression of liver cancer were downloaded from TCGA database (https://portal.gdc.cancer.gov/). The GEO (https://www.ncbi.nlm.nih.gov/geo/) was also used in this work. For the following analysis, a GEO HCC cohort (GSE 76427) and a TCGA cohort were collected. Thereafter, the transcriptome and clinical data were combined and ID transformed. Fifty-two pyroptosis-related genes (REACTOME PYROPTOSIS) were obtained from previously published studies and the Molecular Signatures Database (MSigDB) (http://www.broad.mit.edu/gsea/msigdb/) [11,12]. TCGA and GEO data were integrated in R studio using “limma” and “sva” packages, and the expression of the PRGs was retrieved from the merged data. Finally, the survival analysis of pyroptotic genes was performed to obtain the prognosis-related pyroptotic genes.

2.2. Gene expression and survival prognostic analysis

Using the “Diff Exp” module on the Tumor Immunity Estimation Resource (TIMER) website (http://timer.cistrome.org/) and the R studio software, we investigated BAK1 expression in 33 human tumor and normal control tissues from the TCGA database. In LIHC, the packages “limma,” “ggplot2,” and “ggpubr” performed differential and pairwise differential analyses on BAK1. Kaplan–Meier curves created by the R studio programs “survival” and “survminer” were used to analyze the differences in survival between subtypes. Univariate and multivariate independent prognostic analyses were then carried out to determine if BAK1 could be used independently of other prognostic indicators.

2.3. Clinical correlation analysis and coexpression analysis

Clinical correlation analyses and heatmaps were created in R studio using “limma,” “ComplexHeatmap,” and “ggpubr” packages. Genes that share the same promoter as BAK1 were identified. A correlation coefficient larger than zero between the two indicates that the gene is positively regulated by BAK1, while a correlation coefficient lesser than zero indicates that the gene has a negative regulatory interaction with BAK1. The filter condition of the coefficient of correlation was corFilter = 0.6; the filter condition of the correlation test P-value was pFilter = 0.001, and the coexpression circle graph was drawn based on the coexpression results.

2.4. Gene enrichment analysis

The samples were separated into two groups with high and low BAK1 expression levels, respectively, using “limma” and “pheatmap” packages in R studio. A gene heat map with differences between the high and low expression groups was generated. The logFCfilter parameter was set to 1, the fdr filter condition was fdrFilter = 0.05, and the adjusted P-value was 0.05. We performed Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis of differential genes in R studio program using “org.Hs.eh.db,” “clusterProfiler,” and “enrichplot” packages to further investigate the enrichment of probable pathways of differential genes in different groups. To further explore the enrichment of potential pathways of differential genes in different groups, we performed KEGG and GSEA enrichment analysis.

2.4. Immune correlation analysis and drug sensitivity analysis

Through differential analysis of immune cells, immune cells with statistical significance between high and low BAK1 expression groups were discovered, and differential analysis
was performed on them. To assess the relationship between high and low BAK1 expression groups and immune cell infiltration content, the CIBERSORT algorithm was used, and the filter condition for immune cell infiltration findings was set to pFilter = 0.05. Immune checkpoint correlation analysis was then performed to investigate the relationship between immune checkpoint genes and BAK1, with the filter condition of correlation test P-value set to pFilter = 0.001. The immunoscores of liver cancer patients were gathered from http://tcia.at/, and immunotherapy analysis was performed in R studio program using “limma” and “ggpubr” packages. The immunohistochemical pictures of BAK1 protein in various cancer and normal tissues were obtained from http://www.proteinatlas.org/(Human Protein Atlas [HPA] database). We estimated the half maximal inhibitory concentrations (IC50s) of compounds collected from the Genomics of Drug Sensitivity in Cancer (GDSC) website in the TCGA project of the LIHC dataset to identify possible medications for clinical application in LIHC therapy. The IC50 of the chemical, acquired from the GDSC website, in LIHC patients was predicted using R studio’s “pRRophetic” package, with the filter condition for P-value set to pFilter = 0.001.

2.5. Building a nomogram scoring system

The clinical variables and risk scores were integrated to construct a predictive nomogram in R studio using “rms,” “survival,” and “regplot” packages. Each clinical feature and risk rating in the nomogram was assigned a score; the total score was calculated by summing the scores for all clinical features and risk ratings in each sample. The accuracy of anticipated 1-, 3-, and 5-year survival events was described using calibration plots.

2.6. Statistical analysis

R version 4 was used for all statistical studies. Statistical significance was defined as P < 0.05.

3. Results

3.1. Expression and survival analysis of BAK1

Table 1 lists the 33 cancers studied in this work. The HCC cohort (GSE76427) used has 115 patients in total. We analyzed the PRGs in 115 HCC patients using R studio packages “survival” and “limma.” P < 0.05 was deemed statistically significant for prognosis. Figure 1A depicts the gene coexpression relationship, revealing that GSDME, CHMP4B, CHMP3, BAK1, and NOD2 are high-risk genes that are strongly associated with prognosis. In view of the limited number of research on the prognosis and immunity of BAK1 expression in liver cancer, we chose BAK1 and used TIMER 2.0 database to investigate BAK1 expression in pan-cancer. Figure 1B shows that the expression of BAK1 was significantly upregulated in 11 cancer types (bladder urothelial carcinoma [BLCA], breast invasive carcinoma [BRCA], cholangiocarcinoma [CHOL], esophageal carcinoma [ESCA], glioblastoma multiforme [GBM], head-and-neck squamous cell carcinoma [HNSC], liver hepatocellular carcinoma [LIHC], lung adenocarcinoma [LUAD], lung squamous cell carcinoma [LUSC], stomach adenocarcinoma [STAD], and uterine corpus endometrial carcinoma [UCEC]; all P < 0.001), whereas it was

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Figure 1. (A) Pyroptosis-related genes interactions in liver cancer. (B) BAK1 expression levels in several cancer types and matching normal tissues. (C) BAK1 differential analysis in liver hepatocellular carcinoma (LIHC). (D) Pair-wise differential analysis of BAK1 in LIHC. (E) BAK1 survival analyses in LIHC. (F–G) Univariate and multivariate independent prognostic study of BAK1. *P < 0.05, **P < 0.01, ***P < 0.001.
significantly downregulated in two additional cancer types (colon adenocarcinoma [COAD] and kidney chromophobe [KICH]; all \( p < 0.001 \)). We then looked at how BAK1 differed between HCC and non-HCC tissues. Figures 1C and D reveal that BAK1 was expressed at a greater level in HCC tissues and that this level differs considerably from that of non-HCC tissues. We subsequently compared the prognosis of HCC patients with high and low BAK1 expression; the results revealed that the overall survival rate of HCC patients with high BAK1 expression was considerably lower than that of patients with low BAK1 expression (Figure 1E).

According to univariate and multivariate independent prognostic analyses (Figures 1F and G), BAK1 is associated with prognosis and can be a prognostic factor independent of other factors. In univariate Cox regression analysis, the hazard ratio (HR) was 1.262, and the 95% CI was 1.013 – 1.572 (\( p = 0.038 \)). In multivariate Cox regression analysis, the HR was 1.262, and the 95% CI was 1.013 – 1.572 (\( p = 0.038 \)).

3.2. Relationship between BAK1 expression and clinical features

A clinical correlation study was performed to determine if BAK1 expression differed between clinical groups. BAK1 exhibited significant differences in gender, tumor grade, tumor stage, and T stage. Figure 2A shows that BAK1 expression does not differ significantly with age. Figure 2B demonstrates that BAK1 expression is significantly higher in female HCC patients than in males. Figure 2C depicts BAK1 expression levels in various tumor stages, with substantial statistical differences between Stage 1 and Stage 2, as well as Stage 1 and Stage 3. Figure 2D shows a statistically significant difference in BAK1 expression among T1, T2, and T3, but no such difference was seen in the other T stages. The clinical correlation heatmap in Figure 2E shows that the three clinical parameters tumor grade, tumor stage, and T stage have substantial statistical differences between high and low BAK1 expression groups. Coexpression analysis revealed that BAK1 is positively regulated by SMARCD1, MFSID10, RCC2, CDK16, PKM, and MACROH2A1 but negatively regulated by GLYAT1, ALDH2, CDO1, DCXR, and SLC27A5 (Figure 2F). The diagnostic value of BAK1 in LIHC was assessed by drawing a receiver operating characteristic (ROC) curve (Figure 2G). We discovered that the area under the ROC curve was 0.694, 0.582, and 0.611 at 1, 3, and 5 years, indicating that this gene may be a good prospective LIHC diagnostic marker.

3.3. Analysis of differential genes and construction of nomogram

All samples were classified into high and low expression groups according to the expression of the target gene BAK1, and genes with differences in expression between the high and low expression groups were identified (Figure 3A). The differential genes were found to be involved in neuroactive ligand-receptor interaction, cytokine-cytokine receptor interaction, adenine 3’,5’-cyclic monophosphate (cAMP) signaling pathway, and hematopoietic cell lineage by KEGG enrichment analysis (Figure 3B). We then ran a GSEA, and the results in Figure 3C showed that the four functions HUMORAL IMMUNE RESPONSE MEDIATED BY CIRCULATING IMMUNC, IMMUNOGLOBULIN COMPLEX, IMMUNOGLOBULIN COMPLEX CIRCULATING, and IMMUNOGLOBULIN RECEPTOR BINDING were active in the high BAK1 expression group, and STEROID HYDROXYLASE ACTIVITY is active in the high and low expression group of BAK1. The five pathways FATTY ACID METABOLISM, GLYCINE SERINE AND THREONINE METABOLISM, PEROxisome, PRIMARY BILE ACID BIOSYNTHESIS, and RETINOL METABOLISM were all active in the low BAK1 expression group, as shown in Figure 3D. We constructed a nomogram using risk classes and clinical data to predict the 1-, 3-, and 5-year survival in LIHC patients, as shown in Figure 3E. Assuming a patient’s composite score is 394, the 1-year survival rate is 0.941, the 3-year survival rate is 0.882, and the 5-year survival rate is 0.839. Correlation plots revealed that the observed and expected rates of survival in LIHC patients at 1, 3, and 5 years were in perfect agreement (Figure 3F).

3.4. Expression of BAK1 and immunity and drug sensitivity

Figure 4A shows a differential study of immune cells, which revealed a statistically significant difference in dendritic cell activation between high and low BAK1 expression groups, suggesting that the activation is favorably regulated by BAK1. Figure 4B, we then examined the relationship between BAK1 and immunological checkpoint-related genes. BAK1 positively regulates CD276, CD86, CD80, TNFRSF8, TNFRSF15, LGALS9, TNFRSF18, PDCD1, VTCN1, and HAVCR2, while IDO2 and BAK1 have a skewed relationship. Unfortunately, no significant statistical difference was observed when receiving CTLA-4 and PD-1 treatment regardless of whether BAK1 expression was high or low (Figure 4C and D). Figure 4E and F illustrate the immunohistochemistry (IHC) status of BAK1 in normal and cancerous liver tissue, respectively. Representative IHC photos reveal that BAK1 protein is more abundant in tumors than in non-tumor tissues. We then identified drugs that showed substantial changes in their sensitivity in patients with high and low BAK1 expression. Ninety drugs were discovered. Figure 4G to Figure 4N, Fluorouracil, bosutinib, bleomycin, cyclopamine, and other drugs were
Figure 2. (A–D) BAK1 correlation analysis by age, gender, tumor grade, and tumor stage. (E) Heatmap of BAK1 and clinical feature correlations. (F) Genes with BAK1 coexpression relationship. (G) Receiver operating characteristic (ROC) curves used in GSE 76427 to predict 1-, 3-, and 5-year ROC curves.
**Figure 3.** (A) Differential gene analysis in groups with high and low BAK1 expression. (B) Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis of differential genes. (C and D) Gene Set Enrichment Analysis (GSEA) of differential genes. (E) A nomogram to predict the 1-, 3-, and 5-year survival in LIHC patients. (F) Calibration curves for the nomogram used in GSE 76427 to predict the 1-, 3-, and 5-year survival.
Figure 4. (A) BAK1 and immune cell correlation diagram. (B) BAK1 association with immune checkpoint-related genes. (C and D) BAK1 and immunotherapy correlation study. (E and F) Immunohistochemical pictures of BAK1 protein in normal and malignant liver tissues. (G–N) Drugs with significant differences in drug sensitivity in high and low BAK1 expression.
found to be more sensitive to BAK1 expression in patients. Patients with reduced BAK1 expression are more sensitive to all-trans retinoic acid (ATRA), erlotinib, temsirolimus, vorinostat, and other drugs.

4. Discussion
One of the most prevalent primary malignant tumors worldwide is HCC. HCC is often diagnosed at an advanced stage in the majority of patients due to the disease's gradual onset; the early diagnosis of HCC poses a challenge. Certain physiological activities can alter the changes to its indicators due to the poor sensitivity and specificity of early screening, such as serum alpha-fetoprotein (AFP)\textsuperscript{[13]}. Therefore, identifying molecular biomarkers that fully reflect the biological characteristics of liver cancer is a critical link in the early diagnosis and treatment of patients with liver cancer\textsuperscript{[14,15]}. Previous research has looked at the role of pyroptosis-related genes in anti-tumor activity\textsuperscript{[16]}; thus, we set out to investigate the role of pyroptosis-related genes in the prognosis of patients with liver cancer. By examining the predictive value of PRG in 115 HCC patients in the HCC cohort (GSE76427), we discovered that GSDME, CHMP4B, CHMP3, BAK1, and NOD2 are all high-risk genes, which are closely associated with the prognosis of patients. We chose BAK1 as the target gene for this investigation due to the lack of prior research on the prognosis and immunity of BAK1 expression in liver cancer. The BAK1 (BCL2-antagonist/killer1) gene is found on the outer mitochondrial model and belongs to the B-cell lymphoma/leukemia-2 (BCL2) gene family\textsuperscript{[17,18]}. The previous research has found BAK1 to be a prognostic biomarker in women with lung adenocarcinoma\textsuperscript{[19]} as well as a prognostic marker in individuals with colon cancer\textsuperscript{[20]}. It reduces apoptosis and enhances cisplatin resistance in non-small cell lung cancer when combined with cancer-associated fibroblast (CAF)-derived exosomal miR-103a-3p\textsuperscript{[21]}. It has also been shown that BAK1 is a tumor suppressor gene that regulates cell cycle through microRNA in patients with endometrial cancer\textsuperscript{[22]}. However, there are several studies that have linked BAK1 to HCC diagnosis and prognosis.

The expression of BAK1 in pan-cancer was investigated using the TIMER database. The expression of BAK1 was shown to be highly upregulated in 11 cancer types (\textit{i.e.}, BLCA, BRCA, CHOL, ESCA, GBM, HNSC, LIHC, LUAD, LUSC, STAD, and UCEC), but significantly downregulated in two cancer types (\textit{i.e.}, COAD and KICH). We then looked at the differences in BAK1 expression between HCC and non-HCC tissues; we discovered that BAK1 was expressed at a greater level in HCC tissues than in non-HCC tissues. The predictive analysis of high and low BAK1 expression groups revealed that patients with high BAK1 expression had a considerably poorer overall survival rate than patients with low BAK1 expression. According to univariate and multivariate independent prognostic analyses, BAK1 is associated with prognosis and can be independent of other factors. These findings show that BAK1 could become one of the diagnostic indicators for HCC prognosis. We also constructed a nomogram containing risk classes and clinical characteristics to predict the 1-, 3-, and 5-year survival in LIHC patients, thus making practical application easier. Assuming a patient's comprehensive score is 394, the 1-year survival rate is 0.941, the 3-year survival rate is 0.882, and the 5-year survival rate is 0.839, indicating that it has good prediction ability. The ROC curve was used to assess the diagnostic value of BAK1 in LIHC, and the area under the ROC curve was 0.694, 0.582, and 0.611 at 1, 3, and 5 years, respectively. According to the findings, the BAK1 gene may be a good potential LIHC diagnostic marker. Furthermore, we discovered a link between clinical phase features and BAK1 expression. The findings revealed that BAK1 expression differed significantly by gender, tumor grade, tumor stage, and T stage, with BAK1 being more evident in female patients. BAK1 expression increased with tumor grade in females, and there were significant statistical differences between the other groups except for the expression between G3 and G4. There were statistically significant variations in BAK1 expression between Stage 1 and Stage 2, as well as Stage 1 and Stage 3. In addition, there was a statistically significant difference in BAK1 expression among T1, T2, and T3. According to coexpression study, BAK1 was found to be positively regulated by SMARCD1, MFSD10, RCC2, CDK16, PKM, and MACRO2H1, but negatively regulated by GLYAT1, ALDH2, CDO1, DCXR, and SLC27A5. The finding of these genes may bring new ideas for multi-biomarker diagnosis in the future.

The differential study of immune cells showed that the difference between dendritic cells activated in groups with high and low BAK1 expression was statistically significant and exhibited a positive regulatory interaction with BAK1. The immune checkpoint-related gene HAVCR2 is upregulated, while IDO2 and BAK1 are downregulated. The finding of these immune checkpoint-related genes may provide specific ideas and directions for the later use of BAK1 in liver cancer immunological research. Subsequently, we identified drugs that showed substantial changes in sensitivity with high and low BAK1 expression, of which 90 drugs were discovered. Fluorouracil, bosutinib, bleomycin, cyclophamine, and other drugs were found to be more sensitive to BAK1 expression. Patients with reduced BAK1 expression are more sensitive to ATRA, erlotinib, temsirolimus, and other drugs. The discovery of these medications may provide more alternatives for the treatment
BAK1 as a novel prognostic biomarker

of liver cancer in the future, as well as new directions for clinical use and drug development. Our current study, inevitably, has certain limitations. First, our work is based on RNA-sequencing data, derived from public dataset (TCGA), and lacks clinical trials; thus, the predictive ability of all pyroptosis-related prognostic indicators and nomograms needs to be further studied in multicenter clinical trials and prospective investigations. Furthermore, the prognostic role of BAK1 in hepatocellular carcinoma also needs to be further investigated, as does the underlying mechanism.

5. Conclusion

Our data demonstrate that BAK1 expression is greatly enhanced in LIHC and that high levels of BAK1 expression are associated with cancer progression and poor prognosis. These findings suggest that BAK1 may be an oncogene for HCC pathogenesis and progression, as well as a novel prognostic biomarker and potential therapeutic target for HCC.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Author contributions

Conceptualization: Yiyang Chen and Xi Ou
Formal analysis: Yiyang Chen and Yiju Gong
Writing – original draft: Yiyang Chen and Wanbang Zhou
Writing – review & editing: Yiyang Chen

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Peking University Shenzhen Hospital.

Consent for publication

Not applicable.

Availability of data

The datasets presented in this study can be found in online repositories. The names of the repository and accession number(s) can be found in the article.

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BAK1 as a novel prognostic biomarker

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