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Differential Expression Analysis Reveals that PSRC1 is Upregulated in Hepatocellular Carcinoma and Predicts Poor Prognosis

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Abstract

Hepatocellular carcinoma (HCC) poses a pressing global health challenge, ranking as the third leading cause of cancer-related mortality worldwide. However, the intricate molecular mechanisms underlying its onset remain elusive. The primary objective of this study is to identify novel genes associated with the disease progress of HCC. Using data from the GEO database, differential gene expression analysis was conducted using the online GEO2R tool, followed by functional enrichment analysis. A total of 1,729 upregulated and 1,131 downregulated genes were identified in HCC compared with the adjacent normal tissues. PSRC1 was selected for further analysis owing to few reports in liver cancer. PSRC1 was significantly upregulated in HCC, which was supported by either bulk or single cell RNA sequencing data. PSRC1 was mainly expressed in hepatocytes and tightly correlated to clinic staging and tumor grades. High expression of PSRC1 predicted poor prognosis. The current study provided new insight into the occurrence and development of HCC.

Keywords: Hepatocellular carcinoma, Differential expression gene, GEO database, PSRC1, HCC

1. Introduction

Liver cancer, a pressing global health issue, is classified into primary liver cancer and secondary metastatic liver cancer. Among primary liver cancers, hepatocellular carcinoma (HCC) stands out, accounting for 85-90% of cases and ranking as the third most lethal cancer worldwide (Chen & Zhang, 2011; El-Serag & Davila, 2011). More than 80% of HCC-related deaths occur in developing countries, with China having the highest incidence rate of liver cancer, accounting for over half of the global burden. Compared to other cancers, the incidence rate of HCC continued to rise at a faster pace, claiming the lives of more than 800,000 people each year since 2020. Therefore, finding effective treatment methods for HCC is urgent.

HCC can lead to liver function failure, causing the patients to experience symptoms such as jaundice, ascites (fluid buildup in the abdomen), fatigue, and a decline in overall health. The main causes of HCC can come from different forms of hepatitis and liver damage, including chronic infection with hepatitis C virus (HCV) or hepatitis B virus (HBV), excessive alcohol consumption or smoking, diabetes, obesity, or certain rare genetic disorders (Makarova-Rusher et al., 2016). During the developmental stages of HCC, several key molecular entities have been identified. While researchers have extensively studied and described the molecular pathogenesis of HCC, and certain molecules have emerged as potential early screening and treatment targets for HCC, the precise molecular mechanisms contributing to its occurrence remain elusive, a pressing research avenue (Wang & Deng, 2023).

Proline and serine rich coiled-coil 1 (PSRC1) is a proline-rich protein that is a target for regulation by the tumor suppressor protein p53. PSRC1 plays an important role in regulating the cell cycle, particularly during cell division (mitosis). By recruiting and regulating microtubule depolymerases, PSRC1 functions as a microtubule destabilizing

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protein that involves in the proper formation and function of the mitotic spindle, the structure that ensures chromosomes are accurately distributed to daughter cells when a cell divides. If PSRC1 is overexpressed or mutated, it can disrupt this process, leading to uncontrolled cell division, which is a hallmark of cancer development, including in HCC. The C-terminal domain of PSRC1 could bind to the mitotic spindle, while the regulatory N-terminal domain controls the C-terminal domain to bind to microtubules and determines the cellular activity of the PSRC1 protein (Jang & Fang, 2009). PSRC1 can influence cell proliferation process by promoting faster or abnormal cell division, which leads to an increase in tumor growth (Valente et al., 2009). Previous studies have shown that PSRC1 is overexpressed in several other cancers, such as colorectal cancer (Gylfe et al., 2013) and oral squamous cell carcinoma (Wang et al., 2015) and is therefore a potential biomarker and therapeutic target. In colorectal cancer, PSRC1 contains hot spot mutations and could potentially be used to develop personalized tumor analysis and therapy (Gylfe et al., 2013). The overexpression of PSRC1 is regulated by hypomethylation in the promoter region of the gene in cancer and therefore lead to cancer progress. PSRC1 is a prognostic predictor for oral squamous cell carcinoma without lymph node metastasis (Wang et al., 2015). However, there is less attention of PSRC1 in hepatocellular carcinoma. Although researchers are looking at whether targeting PSRC1 could be a therapeutic strategy to slow down or stop the growth of liver tumors, the relationship between PSRC1 and clinical staging, metastasis, and prognosis of liver cancer still necessitates investigation (Pan et al., 2023).

Therefore, this study aimed to identify novel genes associated with the disease progress of HCC. After the gene PSRC1 was identified, the correlation between PSRC1 expression, and clinicopathological features and prognosis of HCC were investigated to thus clarify the biological role of PSRC1 in HCC.

2. Materials and Methods

2.1 Datasets and Bulk Transcriptomic Data Analysis

The transcriptome refers to the complete set of RNA molecules (or transcripts) in a cell or a group of cells, including various types of RNA such as messenger RNAs (mRNAs), ribosomal (rRNAs) and transfer RNA (tRNAs), and regulatory non-coding RNAs. It is dynamic and specific to time, environment, tissue, and cell type. High-throughput transcriptomic approaches include microarray-based and sequencing-based methods. For researchers, transcriptome data must be submitted to public databases before their work is published. The Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/) is a public functional genomics data repository hosted by the National Center for Biotechnology Information (NCBI). It provides a platform for researchers to deposit, access, and analyze various types of high-throughput gene expression data, such as microarrays, next-generation sequencing, and other molecular profiling techniques (Clough et al., 2024).

Two GEO datasets with the accession numbers of GSE202069 (Li et al., 2024) and GSE149614 (Lu et al., 2022) (see below single-cell analysis) were used in this study and both datasets were derived from high throughput sequencing. The GSE202069 represents bulk RNA sequencing (RNA-seq) at tissue levels from 66 samples with 41 HCC tumor tissues and 25 adjacent non-tumor liver tissues. The online GEO2R tool, which is an R-based (programming language R based) web application based on GEO repository, was used for differential expression analysis. The results will be presented in a table including gene symbols, p-value and fold changes between tumor and normal (or non-tumor) tissues. Differentially expressed genes (DEGs) were obtained under a strict filter condition for the upregulated genes (log2 fold-change>1, Benjamini–Hochberg/BH adjusted P value < 0.01) and downregulated genes (log2 fold-change < -1, Benjamini-Hochberg adjusted P value < 0.01), respectively.

Besides the above GEO datasets, an additional independent cohort of HCC from The Cancer Genome Atlas (TCGA) was also used for analysis. TCGA was a landmark cancer genomics program, which molecularly characterized over 20,000 primary cancer and matched normal samples spanning 33 cancer types. The University of ALabama at Birmingham CANcer data analysis Portal (UALCAN, https://ualcan.path.uab.edu/analysis.html) web tool were used to query gene expression profiles in HCC and investigate expressional correlation with clinicopathological features, as well as survival analysis (Chandrashekar et al., 2022). TPM (transcripts per million) was used to measure gene expression levels.

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2.2 Single-Cell RNA Sequencing Data Analysis

Single-cell RNA sequencing (scRNA-seq) is an approach to measure the transcripts of genes at the level of individual cells, rather than a mass of mixed cells (Olsen & Baryawno, 2018). The GSE149614 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE149614) is from scRNA-seq data that comprise > 70,000 single-cell transcriptomes for 10 HCC patients from four relevant sites including primary tumor, portal vein tumor thrombus (PVTT), metastatic lymph node and non-tumor liver. A standard analysis pipeline using the R Seurat package (https://satijalab.org/seurat/) was performed to analyze the dataset. Cell types were annotated based on the labels directly from data submitters and confirmed by marker gene expression. Briefly, the downloaded raw UMI (unique molecular identifier) count data representing gene expression levels in each cell was first normalized to 10,000, and then the top 2,000 highly variable genes (HVGs) were selected. After the data were scaled and centered, principal component analysis (PCA) based on HVGs was conducted. For dimensionality reduction for single-cell cluster visualization, the uniform manifold approximation and projection (UMAP) method was used. UMAP takes the high-dimensional gene expression profiles of individual cells and maps them onto a 2D or 3D plot, making it easier to visualize patterns, clusters, and relationships between different cell types (Islam & Xing, 2023). Cell type labels were directly from the authors' annotation based on the downloaded metadata.

2.3 Functional Enrichment Analysis

Gene functional enrichment analysis is a process that involves identifying the biological functions, processes, pathways, or other functional annotations that are overrepresented in a set of genes that exhibit significant expression changes or are of interest in a specific context. This analysis helps researchers discern the biological significance and potential roles of genes within a particular biological context, such as a disease or experimental condition (Garcia-Moreno et al., 2022).

The R package 'clusterProfiler' (Wu et al., 2021) was used for functional annotation and enrichment analysis based on gene ontology (GO). The package provides a tidy interface to access, manipulate, and visualize enrichment results to help users achieve efficient data interpretation. Significant GO terms related biological processes were identified when the adjusted p-values ('BH' method) were less than or equal to 0.05.

3. Results

3.1 Identification of Differentially Expressed Genes (DEGs) in HCC

The GEO dataset 'GSE202069', which comprised 66 samples with 41 HCC tumor tissues and 25 non-tumor adjacent normal tissues, were selected, and the online tool GEO2R was used for differential expression analysis. A total of 1,729 upregulated and 1,131 downregulated DEGs were identified (Figure 1A). The most significantly upregulated genes including GPC3 (glypican 3), AKR1B10 (aldo-keto reductase family 1 member B10), STC2 (stanniocalcin 2), KPNA2 (karyopherin subunit alpha 2) and CAP2 (cyclase associated actin cytoskeleton regulatory protein 2), and so on (Table 1), whereas the most significantly downregulated genes including HAMP (hepcidin antimicrobial peptide), STAB2 (stabilin 2), PTH1R (parathyroid hormone 1 receptor), CFP (complement factor properdin) and ADAMTS13 (ADAM metallopeptidase with thrombospondin type 1 motif 13), and so on (Table 2).

Therefore, the results suggested that a large number of genes should be involved in the occurrence and development of hepatocellular carcinoma. To further explore the involved biological processes, functional enrichment analysis of these DEGs were conducted. It was found that upregulated genes were mainly involved in the cell cycle processes (Figure 1B), which accorded with the current knowledge about cancer, which is a group of diseases in which cells divide continuously and excessively (Matthews 2022). Interestingly, the downregulated genes were mainly involved in metabolic processes (Figure 1C), indicating that dysregulated metabolism should play an important role during oncogenesis of HCC.

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Table 1. A list of differentially expressed up-regulated genes in liver cancer tissues*.

Symbol	Description	Log2FC	P value	Adjusted p value	Direction
GPC3	glypican 3	5.87	4.73E-36	8.52E-32	up
AKR1B10	aldo-keto reductase family 1 member B10	6.01	6.96E-31	2.51E-27	up
STC2	stanniocalcin 2	4.62	1.54E-30	4.63E-27	up
KPNA2	karyopherin subunit alpha 2	2.26	8.51E-28	2.19E-24	up
CAP2	cyclase associated actin cytoskeleton regulatory protein 2	2.82	3.66E-27	6.60E-24	up
MELK	maternal embryonic leucine zipper kinase	4.25	5.72E-27	9.37E-24	up
RRM2	ribonucleotide reductase regulatory subunit M2	3.19	8.62E-27	1.19E-23	up
ESM1	endothelial cell specific molecule 1	4.71	8.40E-27	1.19E-23	up
IQGAP3	IQ motif containing GTPase activating protein 3	4.17	1.11E-26	1.43E-23	up
CTHRC1	collagen triple helix repeat containing 1	5.30	3.06E-26	3.44E-23	up
* Only the topmost 10 up-regulated genes are shown.					

Table 2. A list of differentially expressed down-regulated genes in liver cancer tissues*.

Symbol	Description	Log2FC	P value	Adjusted p value	Direction
HAMP	hepcidin antimicrobial peptide	-5.98	1.02E-35	9.17E-32	down
STAB2	stabilin 2	-3.67	9.67E-34	5.81E-30	down
PTH1R	parathyroid hormone 1 receptor	-3.61	5.77E-32	2.60E-28	down
CFP	complement factor properdin	-3.15	2.04E-27	4.59E-24	down
ADAMTS13	ADAM metallopeptidase with thrombospondin type 1 motif 13	-2.45	2.37E-27	4.75E-24	down
ADRA2B	adrenoceptor alpha 2B	-2.70	2.17E-26	2.61E-23	down
FCN3	ficolin 3	-4.12	3.61E-26	3.76E-23	down
IL13RA2	interleukin 13 receptor subunit alpha 2	-3.65	5.73E-24	3.04E-21	down
UICLM	up-regulated in colorectal cancer liver metastasis	-3.55	4.26E-23	1.75E-20	down
ZFP1	ZFP1 zinc finger protein	-2.12	8.41E-23	2.97E-20	down
* Only the topmost 10 down-regulated genes are shown.					

3.2 PSRC1 and HCC Clinicopathological Correlations

More attention was paid to the upregulated genes owning to their potential roles of targets by small molecule drugs. The highly enriched cell cycle related genes were surveyed, and that the gene PSRC1 had not yet received much attention in HCC had been found. Therefore, this molecule was the focus in the subsequent study.

PSRC1 was significantly upregulated in the tumor tissues of HCC than the adjacent normal tissues according to the dataset ‘GSE202069’ (Figure 2A). The upregulation was further confirmed by an independent cohort of liver cancer from TCGA and closely correlated to clinicopathological features (Figures 2 B&C). Stage refers to the extent of cancer, such as how large the tumor is and if it has spread. As shown in Figure 2B, with the increase of clinical stages, the expression level of PSRC1 also increased (Figure 2B). Tumor grade often describes how normal or abnormal cancer cells look under a microscope. The higher the grade number, the more abnormal the cells look and the more aggressive the cancer, and the faster it is likely to grow and spread. Analysis of PSRC1 in various liver cancer grades revealed its expression increased as the grading increased (Figure 2C).

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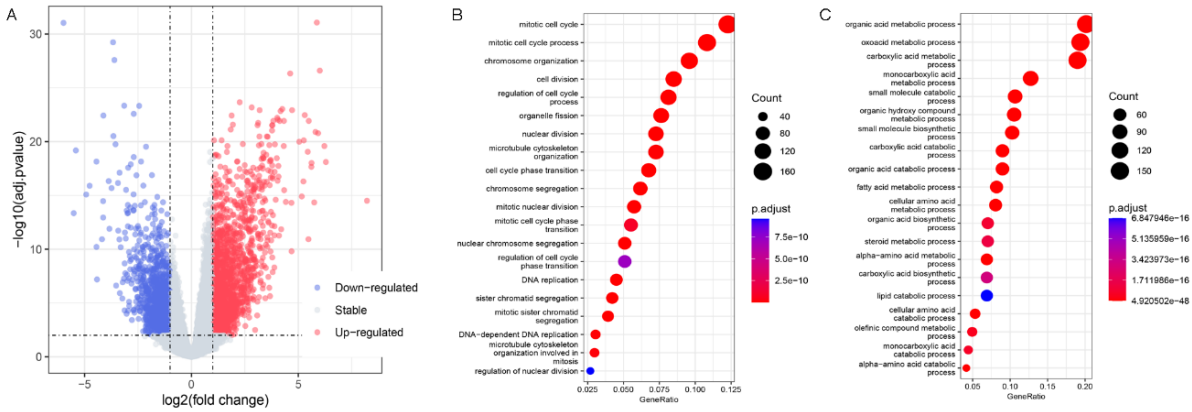

Figure 1. Visualization of DEGs in volcano plot and the results of functional enrichment analysis. A. The volcano plot shows DEGs in HCC. Each dot represents a gene. The red and blue dots indicate upregulated and downregulated DEGs, respectively, under the cutoffs shown in the Methods. B & C. The results of functional enrichment analysis for the upregulated (B) and downregulated (C) genes, respectively. The GeneRatio (B & C) represents a ratio of the gene count in the input list associated with the given GO term divided by the total number of input genes. P values are corrected for multiple testing using the Benjamini-Hochberg (BH) method.

However, PSRC1 showed no differential expression in liver cancers between male and female patients (Figure 2D). Therefore, this suggested that PSRC1 should be involved in the progression of liver cancer.

3.3 Single-Cell Transcriptomics of PSRC1

The above analyses were performed in cancer tissues, which were composed of many different cell types and states that dynamically interact. Therefore, the above analyzed bulk RNA sequencing (RNA-seq) data represented the averaged expressional signals from a mixture of cell types but not cell type-specific signals. In recent years, single-cell RNA sequencing (scRNA-seq) technologies have been greatly developed, which characterize the transcription state at single-cell resolution. Therefore, scRNA-seq data can be used to map the cell type-specific transcriptome landscape of cancer cells and their tumor microenvironment. This suggests that scRNA-seq data can uniquely identify which cells a gene is expressed in, which cell types of those cells belong to, and the expression levels in each cell type.

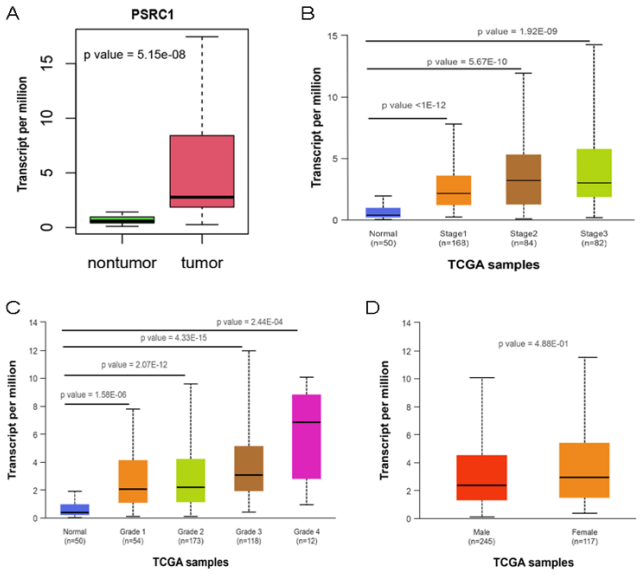

Figure 2. PSRC1 is upregulated in HCC shown in box plots and associated with clinicopathological features. PSRC1 is upregulated in HCC based on the dataset of GSE202069 (A). PSRC1 expression is tightly associated with liver cancer stages (B) and tumor grades (C), but shows no differential expression between male and female (D). The meaning of tumor grades is explained as following: Grade 1, well differentiated (low grade); Grade 2, moderately differentiated (intermediate grade); Grade 3, poorly differentiated (high grade); Grade 4, undifferentiated (high grade). The p-values are displayed between the compared groups, and $p < 0.05$ is considered statistically significant.

The single-cell dataset from GSE149614 was used to profile PSRC1 expression. The dataset comprised over 70,000 single-cell transcriptomes for 10 HCC patients from four relevant sites including primary tumor, portal vein tumor thrombus (PVTT), metastatic lymph node and non-tumor liver. These single cells were grouped into nine

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clusters including hepatocytes, myeloid cells, fibroblasts, endothelial cells, T/NK cells, B cells, plasma cells and two clusters of myeloid and T/NK cells corresponding to their proliferative states (Figure 3A). Therefore, gene expression in these cells from various tissue sources could be analyzed.

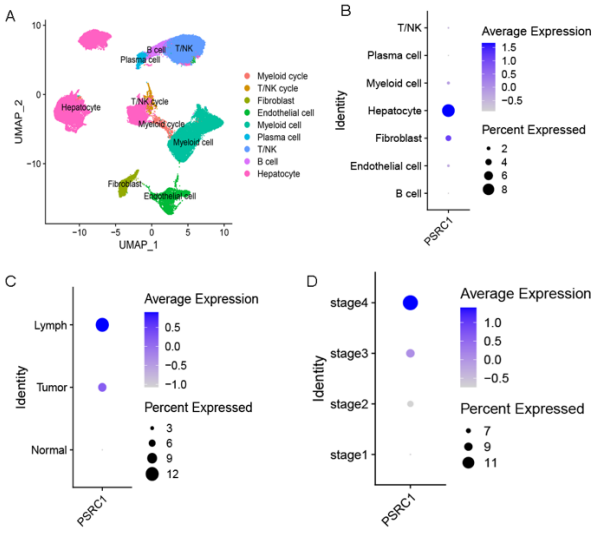

Figure 3. Single-cell analysis of PSRC1 expression in HCC. A. UMAP embedding of single-cell clusters indicated by different cell types. Each dot in the clusters represents one single cell. Uniform Manifold Approximation and Projection (UMAP) is a dimension reduction technique and is useful for visualizing high-dimensional scRNA-seq data in low-dimensional space (2-dimensions) shown on the x-axis (dimension 1/UMAP_1) and y-axis (dimension 2/UMAP_2), respectively. Cells with similar expression profiles cluster together and represent specific cell types, which are displayed in different colors. B-D. Dot plots show PSRC1 expression in various cell types (A), or in the hepatocytes from different tumor sites (B) and clinical stages (D), respectively. In a dot plot, the dot size represents the percentage of cells within each cell type (or cluster) that expresses the gene. The color of the dot represents the average gene expression, and the relative expression level ranges from low to high, indicated by the color bar from gray to blue. In B, proliferative myeloid and T/NK cells are grouped into the total myeloid and T/NK cells, respectively.

The results showed that PSRC1 was mainly expressed in hepatocytes and showed less expression levels in fibroblast (Figure 3B). PSRC1 showed far less expression in several immune cell types including T/NK cells, B cells and plasma cells (Figure 3B). Next, hepatocytes were extracted and a total of 20,782 hepatocytes were identified. Compared with the normal epithelial cells, PSRC1 showed increased expression in tumor cells, especially tumor cells that metastasized to lymph nodes (Figure 3C). Consistent with the result, as clinical staging increased, PSRC1 expression also increased, with the highest expression in the stage 4 (Figure 3D). These results based on scRNA-seq data confirmed the above results in the bulk RNA-seq data (Figure 2). Therefore, different data types and data sources of HCC supported that PSRC1 was tightly associated with clinicopathological features.

3.4 Survival Analysis of PSRC1

The above results suggested a close correlation between PSRC1 and the progression of HCC. The relationship between PSRC1 expression and patient survival were further explored using the TCGA data and found that patients with high expression of PSRC1 predicted poor prognosis (Figure 4). Therefore, this result suggested that PSRC1 could be one of the prognostic indicators for HCC.

4. Discussion

This study identified differentially expressed genes in HCC. A total of 1729 upregulated DEGs were identified by GEO2R. GPC3 is a cell surface proteoglycan involved in cell growth regulation and modulation of signaling pathways, such as Wnt signaling. It is often used as a diagnostic biomarker for HCC. Its overexpression is associated with tumor growth and poor prognosis (Zheng et al., 2022). AKR1B10 is a gene that makes an enzyme responsible for protecting cells from harmful chemicals that build up during metabolism. A recent study reported that its elevation is due to compensatory upregulation, aimed at protecting hepatocytes from oxidative stress during HCC development (Endo et al., 2021). STC2 is involved in cellular stress response, metabolism, and regulation of calcium and phosphate levels. It has high levels and is correlated with aggressive tumor behavior. In HCC, STC2 enhances tumor growth and metastasis by promoting cell proliferation and resistance to cell death (apoptosis) (Bu et al., 2023).

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This study focused on the functional role of PSRC1. *PSRC1* is located on chromosome 1. The functionality of the *PSRC1* gene primarily revolves around its potential impact on lipid metabolism and cholesterol regulation, and has an association with cardiovascular diseases (Wei el al., 2020). Recent studies have indicated that the variation rs599839 within the CELSR2-PSRC1-SORT1 gene cluster is associated with cardiovascular events (Al-Eitan et al., 2020; Castillo-Avila et al., 2023; Goettsch, 2018). While their primary focus has been on cardiovascular issues, cardiovascular diseases are also linked to non-alcoholic fatty liver disease, which may lead to HCC (Meroni et al., 2021). The involvement of the PSRC1 gene extends beyond lipid metabolism and cardiovascular health. PSRC1 is implicated in various cancers, showing elevated expression in multiple cancer types. Our work revealed that PSRC1 was highly expressed in liver cancer, particularly in relation to tumor metastasis, grading and prognosis, suggesting that it should be a potential target for liver cancer treatment.

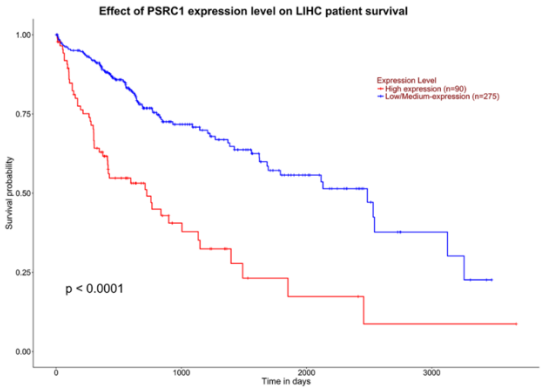

Figure 4. Survival analysis based on the TCGA samples reveals high PSRC1 expression predicts poor prognosis. The liver hepatocellular carcinoma (LIHC) data from the TCGA are used for the analysis.

Additionally, 1131 downregulated DEGs were found. HAMP is a key regulator of iron metabolism, responsible for controlling the release of iron from cells. It often leads to iron overload in liver cells, contributing to oxidative stress and promoting liver damage and cancer progression. Reduced levels of HAMP can fuel cancer cell proliferation and survival (Kouroumalis 2023). STAB2 is a receptor involved in clearing waste molecules and maintaining vascular and immune system function. Its loss may impair the liver's ability to remove damaged cells and waste (Harris & Baker, 2020; Du et al., 2020). PTH1R is involved in calcium and bone metabolism. Although PTH1R downregulation is not as well-studied in HCC, it is known to play a role in tumor suppression in other cancers by regulating cellular differentiation and growth (Martin, 2022).

However, some limitations should be acknowledged. Firstly, further functional experiments and validation studies should be needed to confirm the functional roles of PSRC1 in HCC. For example, at the cellular level, its impact on cell proliferation and migration can be verified through overexpression or gene knockdown experiments; at the animal level, the functional role in tumor occurrence and development through tumor models can be investigated. Moreover, this study primarily focused on upregulated genes, potentially overlooking important downregulated genes that could also play crucial roles in HCC development. Finally, while our findings suggest promising directions for diagnosis and prognosis, the translation of these discoveries into effective clinical applications would require more extensive research and rigorous testing in clinical settings. Therefore, a thorough investigation of the mechanisms of action of the gene will allow more precise and innovative solutions for the prevention, diagnosis, and treatment of HCC.

5. Conclusion

In summary, PSRC1 was upregulated in HCC and correlated to clinic staging and tumor grades. High expression of PSRC1 predicted poor prognosis. The distinct characteristics of PSRC1 provide rich starting points for future research. PSRC1 exhibits a unique regulatory pattern and function in the context of upregulation in HCC, further highlighting its potential roles in the pathogenesis of HCC. The association of PSRC1 with cardiovascular diseases offer new perspectives on HCC development. These traits unveil the diversity within HCC, prompting further in-depth molecular and cellular investigations to understand their exact roles in hepatocellular carcinoma. Furthermore, the findings have the potential to guide the development of novel therapeutic strategies. Given the challenges in HCC treatment, the search for new therapeutic avenues is particularly pressing. Building on the understanding of the regulatory patterns of PSRC1, future research should focus on innovative treatment methods targeting PSRC1, thus intervening more precisely in HCC progression. By utilizing PSRC1 as a target, researchers can explore therapeutic strategies targeting specific molecular pathways, thereby enhancing treatment efficacy and alleviating the health

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burden posed by HCC. A thorough investigation of the mechanisms of action of PSRC1 will allow more precise and innovative solutions for the prevention, diagnosis, and treatment of HCC.

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