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RESEARCH ARTICLE
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THE UP-REGULATED CUL7 GENE IS ASSOCIATED WITH PATHOGENESIS, METASTASIS, AND LOW SURVIVAL RATES IN LIVER HEPATOCELLULAR CARCINOMA PATIENTS

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Abstract

The investigation focused on exploring the role of CUL7 genes in Liver Hepatocellular Carcinoma (LIHC) development and progression. Utilizing the UALCAN database, a significant up-regulation of CUL7 expression was observed in LIHC tissues, suggesting its potential involvement in the development of LIHC. Subsequent analysis across various clinical parameters revealed consistent up-regulation of CUL7 expression in LIHC, regardless of cancer stage, patient gender, age, or racial

background. Furthermore, promoter methylation analysis indicated hypermethylation of the CUL7 promoter in LIHC samples compared to normal controls, implying potential epigenetic dysregulation of CUL7 in LIHC pathogenesis. Notably, differences in promoter methylation levels were observed across different cancer stages, patient genders, ages, and racial groups, highlighting the complex relationship between CUL7 promoter methylation and various clinical parameters in LIHC. Additionally, survival analysis demonstrated a significant association between CUL7 expression levels and patient overall survival, with high CUL7 expression correlating with shorter survival rates in LIHC patients. However, mutational analysis using the cBioPortal platform did not reveal significant mutations in CUL7 in LIHC samples. Overall, these findings shed light on the potential role of CUL7 as a biomarker and therapeutic target in LIHC management, emphasizing its clinical significance in prognostic assessment and personalized treatment strategies.

Keywords: CUL7, LIHC, Metastasis: Prognosis

Introduction

The growth of cancer is widely acknowledged as being rooted in genomic alterations, with recent advancements in sequencing and informatics solidifying genomics as a cornerstone of cancer research [1]. This has played a pivotal role in unraveling the molecular complexities of cancer [1-4]. Liver cancer stands out as a prevalent malignancy within the digestive system on a global scale [5]. Liver Hepatocellular Carcinoma (LIHC), also known as Hepatocellular Carcinoma (HCC), ranks as the fifth most common malignancy and represents a significant contributor to cancer-related mortality, with nearly 788,000 deaths reported worldwide in 2020 [6-8]. HCC is the predominant form of primary liver cancer, accounting for 85% to 90% of cases. LIHC/HCC typically arises from chronic liver injury, such as ongoing viral hepatitis B or hepatitis C, or cirrhosis resulting from long-term alcohol consumption [9]. The dismal prognosis associated with LIHC primarily stems from its low survival rate, with only 18% of patients surviving beyond five years [10-14]. Hepatic resection remains the primary treatment modality for LIHC, followed by other interventions such as ablation, radiotherapy, immunotherapy, liver transplantation, chemotherapy, and targeted therapy [15-17]. However, the recurrence rate following hepatic resection is notably high, reaching approximately 70% [18]. Consequently, achieving a complete cure for LIHC remains challenging, underscoring the critical need for the identification of sensitive diagnostic and prognostic markers [19, 20]. Tumor biomarkers hold promise as potential therapeutic targets for inhibiting tumor progression [21-24].

The CUL7 gene encodes the cullin-7 protein, also known as KIAA0076, p193, or p185. Comprising 26 exons, CUL7 codes for a protein crucial in cellular processes [25]. As an E3 ligase, CUL7 facilitates protein degradation via the proteasome pathway [25]. Regulating cellular functions such as senescence, apoptosis, and cellular transformation, CUL7 is tightly linked with the activity of cellular protein D1 [26]. Moreover, CUL7 exhibits significant expression in various cancers including breast, lung, hepatic, and ovarian malignancies, playing a role in their development and progression [27]. Wang and his colleagues discovered that the CUL7/Fbxw8f ubiquitin ligase plays a pivotal role in pancreatic cancer development by inhibiting the degradation of HPK1 [28]. Despite numerous studies investigating the involvement of CUL7 in cancer, the comprehensive mechanism of CUL7 in LIHC remains to be fully elucidated. Therefore, exploring the variant expression of the CUL7 gene in LIHC holds significant therapeutic implications, highlighting the importance of further research in this area.

Material and methods

Expression analysis of CUL7 in LIHC

The UALCAN dataset emerges as a robust, user-friendly tool for cancer researchers, providing easy access to comprehensive cancer transcriptome, proteomics, and patient survival data [29, 30]. Its online interface facilitates the exploration and dissemination of such critical information within the cancer research community. Leveraging data sourced from The Cancer Genome Atlas (TCGA)

project, UALCAN enables users to evaluate protein-coding gene expression and its impact on patient survival across 33 cancer types. In our study, we conducted an analysis of CUL7 expression in both normal and LIHC samples by utilizing data from the TCGA platform. Additionally, we explored CUL7 expression patterns in relation to various demographic parameters such as patient age, gender, and race, utilizing the extensive capabilities of the UALCAN dataset.

Promoter methylation analysis of CUL7

For our analysis of the promoter methylation level of CUL7 in LIHC, we utilized the UALCAN database. This approach allowed us to gain a deeper understanding of the epigenetic regulation of CUL7 in LIHC and its potential implications for progression and patient outcomes.

Survival analysis of CUL7

The Kaplan Meier (KM) plotter stands out as a crucial tool in the realm of survival analysis [31]. This web-based platform leverages extensive clinical data to assess the impact of specific genes on patient survival across various cancer types. Through its intuitive interface, the KM Plotter provides Kaplan-Meier survival curves, offering insights into how gene expression correlates with patient outcomes. In our study, we utilized the KM plotter tool to analyze the effect of CUL7 dysregulation on the overall survival (OS) of cancer patients. This enabled us to elucidate the potential prognostic significance of CUL7 expression in different malignancies, providing valuable insights for clinical decision-making and patient management.

Mutational analysis of CUL7

cBioPortal serves as a vital resource for cancer genomics research [32]. With its user-friendly visualization tools, it streamlines the analysis of complex genomic data, making it accessible to a wide range of researchers. In the current study, we utilized this dataset to conduct a mutational analysis of CUL7 across various cancers. By leveraging the comprehensive data available on cBioPortal, we were able to gain valuable insights into the genetic alterations and potential implications of CUL7 mutations in different cancer types, enhancing our understanding of its role in oncogenesis and tumor progression.

Results

Expression analysis of CUL7 in LIHC and normal control samples

Our primary focus was to investigate the expression of the CUL7 gene across both normal and malignant tissues utilizing the UALCAN database (Figure 1). Our comprehensive analysis revealed a significant up-regulation of CUL7 expression in cancerous cells compared to normal controls. This pronounced up-regulation suggests a potential association between CUL7 expression and the proliferation of LIHC cells. These findings shed light on the intricate molecular mechanisms underlying LIHC progression, implicating CUL7 as a likely regulator in the pathogenesis of this disease.

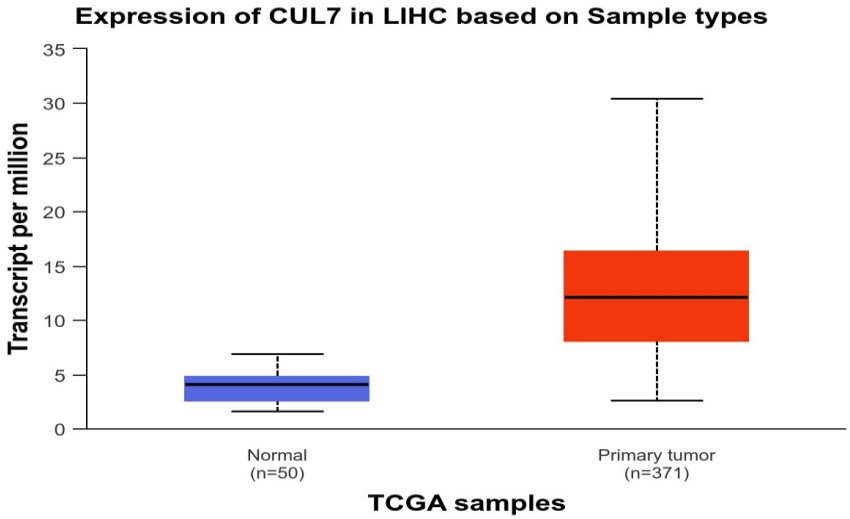

Figure 1: Expression pattern of CUL7 in LIHC and paired control samples. P-value < 0.05

Expression analysis of CUL7 in LIHC samples divided by different parameters

Concurrently, we conducted an examination of CUL7 expression in LIHC samples across different clinical parameters, including cancer stages, patient race, gender, and age (Figure 2). Initially, we evaluated CUL7 expression across various cancer stages and observed a significant up-regulation of CUL7 in LIHC across all stages compared to normal samples (Figure 2A). Furthermore, we analyzed CUL7 expression in LIHC patients stratified by gender, revealing a substantial up-regulation of CUL7 in both male and female patients compared to normal samples (Figure 2B). Subsequently, we investigated the association between CUL7 expression and patient age in LIHC. Our analysis unveiled up-regulation of CUL7 expression across different age groups among LIHC patients (Figure 2C). Finally, we examined CUL7 expression in LIHC patients of diverse racial backgrounds, uncovering consistent up-regulation of CUL7 across various racial groups relative to normal samples (Figure 2D).

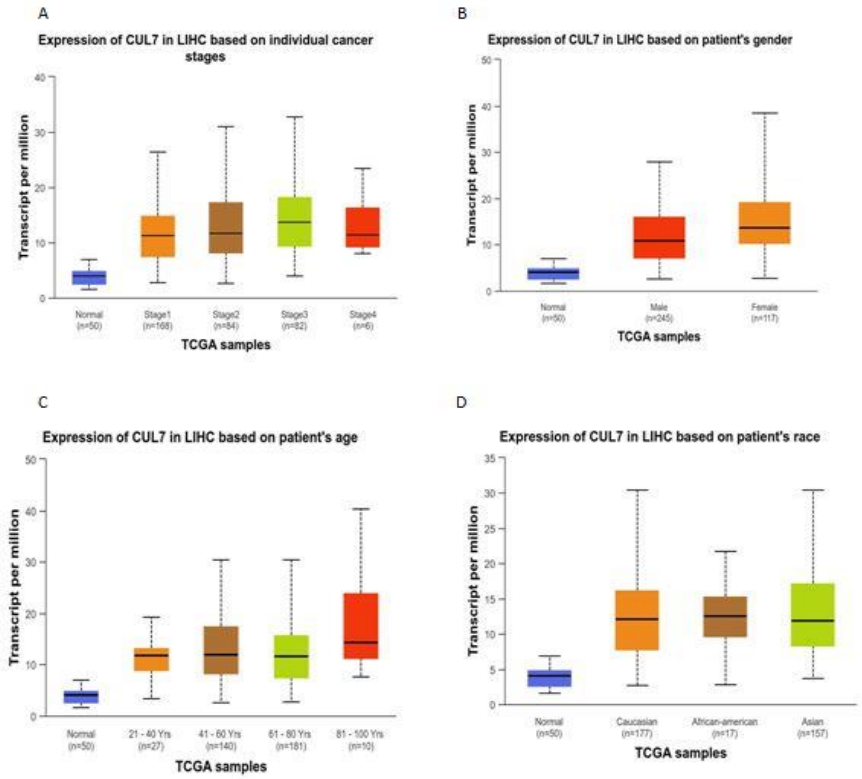

Figure 2: Expression of CUL7 across different clinical variables of LIHC. P-value < 0.05

Promoter methylation of CUL7 in LIHC and normal control samples

Subsequently, we investigated the difference in promoter methylation of CUL7 in LIHC samples compared to normal control samples using the UALCAN dataset (Figure 3). Our analysis revealed significant variability, particularly hypermethylation, in the promoter methylation status of CUL7 in LIHC compared to normal control samples. This observation suggests potential epigenetic dysregulation of CUL7, highlighting its involvement in LIHC pathogenesis. Such findings contribute to our understanding of the molecular mechanisms underlying LIHC development and provide insights into the role of CUL7 as a potential biomarker or therapeutic target in LIHC management.

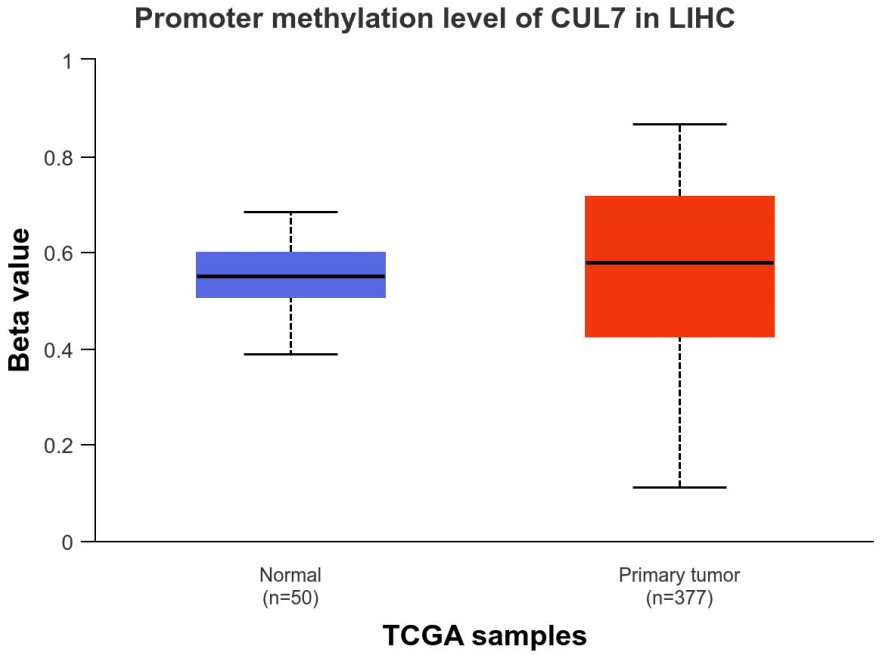

Figure 3: Promoter methylation pattern of CUL7 in LIHC and normal control samples. P-value < 0.05

Promoter methylation of CUL7 in LIHC samples divided by different parameters

We conducted an analysis of various parameters to dissect the promoter methylation of CUL7 in LIHC (Figure 4). Initially, we examined CUL7 promoter methylation across different LIHC stages compared to normal samples. Our findings revealed variations among stages, with all four phases displaying hypermethylation (Figure 4A). Subsequently, an investigation of CUL7 promoter methylation according to patient gender unveiled gender-specific differences, with both females and males exhibiting hypermethylation (Figure 4B). Furthermore, we explored CUL7 promoter methylation in relation to patient age, uncovering varying methylation levels across different age groups (Figure 4C). Finally, we examined CUL7 promoter methylation based on the race of LIHC patients. Interestingly, we observed hypermethylation in CUL7 promoter regions across races except in African-American patients, where notable hypomethylation was observed (Figure 4D). These comprehensive analyses highlight the complex relationship between CUL7 promoter methylation and various clinical parameters in LIHC, providing insight into the multi-layered mechanisms underlying CUL7 expression regulation in LIHC pathogenesis.

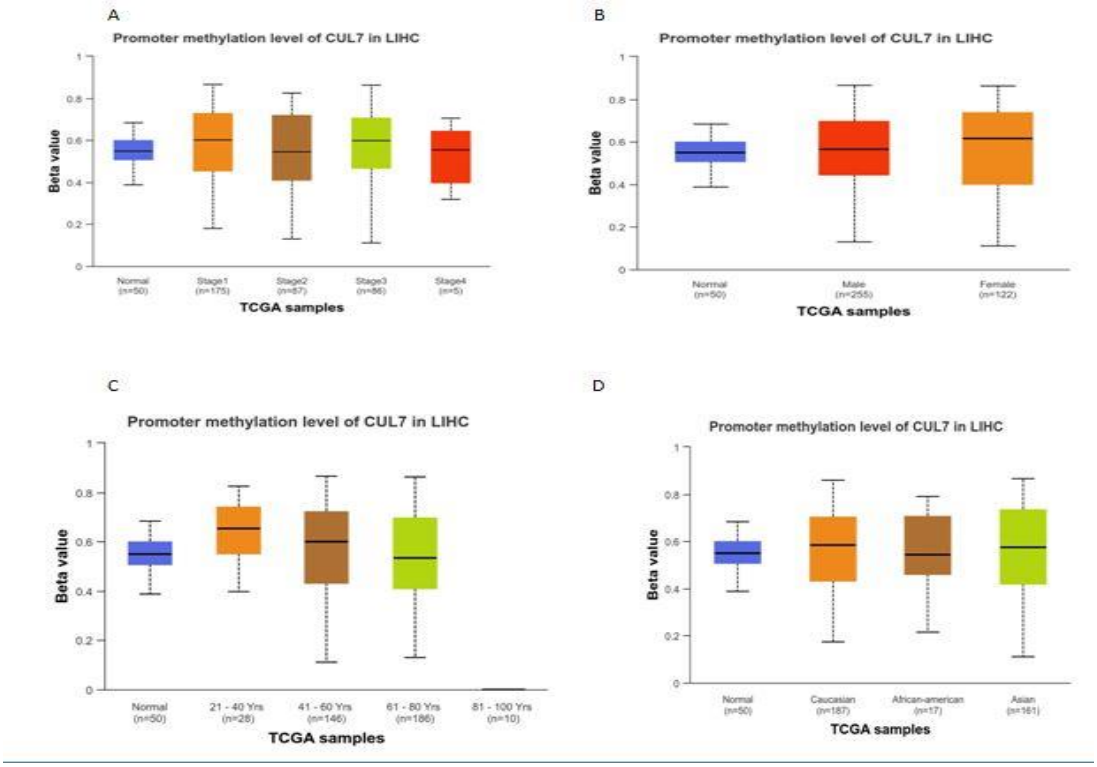

Figure 4: CUL7 promoter methylation pattern across different clinical variables of LIHC. P-value < 0.05

3.5 Survival analysis of CUL7

Using the KM plotter tool, we conducted an analysis to assess the overall survival (OS) of patients based on CUL7 gene expression in LIHC. Our analysis revealed a significant correlation between CUL7 gene expression levels and patient survival outcomes. Specifically, LIHC patients with low CUL7 expression demonstrated markedly higher overall survival rates compared to those with high CUL7 expression (Figure 5). These findings underscore the pivotal role of CUL7 in influencing the survival outcomes of LIHC patients, highlighting its potential clinical significance as a prognostic marker in LIHC management.

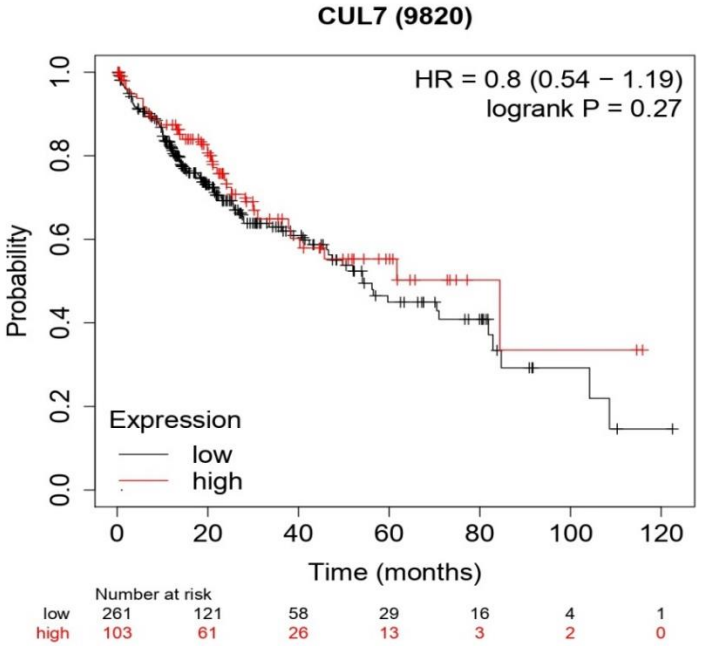

Figure 5: KM survival curve of CUL7 in LIHC patients.

Mutational analysis of CUL7 in LIHC

Using the cBioPortal platform, we performed a thorough mutational analysis of the CUL7 gene in LIHC. Our study revealed that no significant mutations were detected in CUL7 among the LIHC samples analyzed.

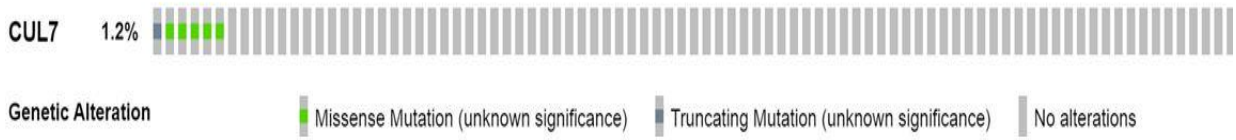

Figure 6: Oncoplot of CUL7 in LIHC samples from TCGA.

Discussion

Liver Hepatocellular Carcinoma (LIHC) is one of the most prevalent and aggressive types of liver cancer globally, characterized by its high mortality rate and limited treatment options [33, 34]. The molecular mechanisms underlying LIHC development and progression remain incompletely understood. Dysregulation of various genes and pathways plays a critical role in LIHC pathogenesis, including aberrant expression of Cullin 7 (CUL7), a key component of the Cullin-RING E3 ubiquitin ligase complex [35]. While CUL7 dysregulation has been implicated in several cancers [36-38], its specific role in LIHC remains unclear. In this study, we investigated the dysregulation status of CUL7 in LIHC and explored its potential implications in cancer progression.

CUL7 is a scaffolding protein that forms the backbone of the Cullin-RING E3 ubiquitin ligase complex, which plays a crucial role in the ubiquitin-proteasome system-mediated protein degradation pathway [39]. Dysregulation of CUL7 has been implicated in various cancers, including breast cancer, ovarian cancer, and lung cancer [36-38]. In these contexts, aberrant CUL7 expression has been associated with tumor growth, metastasis, and poor prognosis, highlighting its potential as a therapeutic target and prognostic marker [36].

Our findings reveal a significant dysregulation of CUL7 in LIHC, with elevated expression levels observed in tumor tissues compared to adjacent normal liver tissues. This up-regulation of CUL7 suggests its potential involvement in LIHC pathogenesis and progression. Interestingly, CUL7 dysregulation in LIHC appears to correlate with clinicopathological parameters such as tumor stage, grade, and patient survival outcomes. These observations underscore the clinical significance of CUL7 as a potential biomarker for LIHC diagnosis, prognosis, and therapeutic targeting. The dysregulation of CUL7 in LIHC implies its involvement in key molecular pathways driving hepatocarcinogenesis. CUL7 may contribute to LIHC development by promoting cell proliferation, inhibiting apoptosis, and enhancing tumor invasion and metastasis through its regulatory effects on downstream signaling molecules and pathways [40]. Moreover, CUL7 dysregulation may influence the tumor microenvironment, immune evasion mechanisms, and response to therapy in LIHC, thereby shaping the disease phenotype and clinical outcomes [41].

Targeting CUL7 and its associated pathways may represent a promising therapeutic strategy for LIHC treatment. Small molecule inhibitors, RNA interference-based approaches, and immunotherapeutic interventions aimed at modulating CUL7 expression or activity could potentially attenuate LIHC progression and improve patient outcomes. Future studies elucidating the molecular mechanisms underlying CUL7 dysregulation in LIHC, its interactions with other oncogenic factors, and its functional significance in tumor biology are warranted. Additionally, clinical investigations exploring the prognostic value of CUL7 expression and its predictive potential for therapeutic response in LIHC are needed to validate its utility as a biomarker and therapeutic target in clinical practice.

Conclusion

In conclusion, our study provides novel insights into the dysregulation status of CUL7 in LIHC and its potential implications for cancer progression. Dysregulated expression of CUL7 in LIHC suggests its involvement in hepatocarcinogenesis and highlights its clinical significance as a

potential biomarker and therapeutic target. Further research aimed at elucidating the molecular mechanisms underlying CUL7-mediated tumorigenesis in LIHC and evaluating its therapeutic potential is warranted to advance our understanding and management of this aggressive malignancy.

Conflict of interest
None

Acknowledgement
None

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