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Original Article

Thyroid hormone suppresses cell growth by regulating CDK2 and cyclin E1 expression via Hepsin

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Abstract: Thyroid hormone (T3) and its receptor (TR) play crucial roles in regulating cell proliferation and cancer progression, including hepatocellular carcinoma (HCC). However, the specific mechanisms underlying HCC development mediated by T3/TR remain unclear. This study aimed to identify differentially expressed target genes influenced by T3/TR in HCC progression. Microarray profiling analysis revealed hepsin (HPN) as a potential target gene regulated by T3/TR. Quantitative reverse transcription-PCR (qRT-PCR) confirmed that T3/TR upregulates HPN expression. Promoter assays and chromatin immunoprecipitation (ChIP) analysis further demonstrated that TR directly binds to the HPN promoter region (+506/+523), activating its transcription. Functional studies showed that ectopic expression of HPN significantly inhibited cell proliferation. Furthermore, HPN was found to be involved in T3/TR-mediated suppression of cell growth by modulating the expression of CDK2 and cyclin E1. Clinically, HPN expression levels were inversely correlated with CDK2 and cyclin E1 in HCC tissues. These findings establish a novel regulatory relationship among T3/TR, HPN, CDK2, and cyclin E1, highlighting their potential role in controlling liver cancer cell proliferation.

Keywords: Thyroid hormone, hepatocellular carcinoma, gene expression, hepsin, cell growth

Introduction

Hepatocellular carcinoma (HCC) is one of the major types of liver cancer globally and is linked to a high death rate [1]. While antiviral treatments, including the hepatitis B virus (HBV) vaccine and nucleotide analogs, have successfully reduced HCC incidence in HBV-infected patients, HCC remains a significant global health burden [2]. Elucidating its underlying mechanisms is essential for devising more effective therapeutic strategies.

Thyroid hormone (T3) is essential for various physiological processes, including cell differentiation, metabolism, and growth, by regulating its nuclear receptors, thyroid hormone receptor α1 (TRα1) and β1 (TRβ1) [3, 4]. In the absence of T3, TR binds to thyroid hormone response elements (TREs), which lead to suppressing gene repression. TR leads to a conformational change in T3 binding and activates target genes. Clinical studies showed that hypothyroid women had a high risk of developing [5]. In addition, animal model studies have shown that T3 decreases the number and burden of HCC tumors [6]. In line with these findings, our data have clearly demonstrated that T3 treatment suppresses cell growth and inhibits sphere formation, which is consistent with the proposed tumor suppressor function of T3 during the initiation of HCC [7, 8].

Hepsin (HPN) is a transmembrane serine protease that functions as a glycoprotein, as evidenced by in vitro assays [9, 10]. HPN is expressed in various tissues, including the liver, lungs, kidneys, thyroid, breast, stomach, and adipose tissue [11]. Studies have shown that ectopic HPN expression in a mouse model led to prostate cancer progression and metastasis [12]. Similarly, HPN overexpression in ovarian

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cancer promoted tumor growth [13]. These tumor-promoting effects require the catalytic domain of HPN. In colorectal cancer patients, elevated HPN levels correlate with poor prognosis [14], suggesting an oncogenic role. Conversely, higher HPN expression is linked to better prognosis in breast cancer patients [15]. Notably, HPN expression is lower in HCC tissues than adjacent normal tissues, with reduced HPN levels associated with poorer prognosis [16].

The physiological role of HPN and its significance in different cancers remains controversial. To date, limited research has explored the T3/TR/HPN axis in liver cancer. This study found that T3/TR positively regulates HPN expression. Upon T3 treatment, TR directly binds to the HPN promoter, enhancing its expression. Functionally, HPN suppresses cell growth-related markers such as CDK2 and cyclin E1. Furthermore, in HCC tissues, HPN expression negatively correlates with CDK2 and cyclin E1 levels, suggesting its role in inhibiting cell proliferation.

Materials and methods

Cell line and reagent

The liver cancer cell lines used in this study were HepG2 (RRID: CVCL_0027), Hep3B (RRID: CVCL_0326), Huh7 (RRID: CVCL_0336), J7 (RRID: CVCL_4Z69, a gift from Dr. C.S. Yang, National Taiwan University) [17], and Mahlavu (RRID: CVCL_0405). All parental cell lines were cultured in DMEM with 10% FBS, 100 μg/mL streptomycin sulfate and 100 IU/mL penicillin G. HepG2-neo, HepG2-TRα1 and HepG2-TRβ1 cells were maintained in DMEM supplemented with 10% FBS, 100 μg/mL streptomycin sulfate, 100 IU/mL penicillin G and 800 μg/mL neomycin. The T3 was obtained from Sigma-Aldrich (St. Louis, MO, USA). All cell lines were routinely screened to confirm the absence of mycoplasma contamination prior to the experimentation, using the TOOLS mycoplasma detection kit (BIOTOOLS, New Taipei City, Taiwan, TTB-GBC8).

Quantitative reverse transcription PCR (qRT-PCR)

Total RNA was extracted from the cells by Trizol reagent (Life Technologies Inc., Carlsbad, CA, USA) and subsequently converted to complementary DNA (cDNA) by reverse transcriptase (Thermo Fisher Scientific, Waltham, MA, USA). HPN expression was measured by the use of qRT-PCR with SYBR Green Master Mix (Applied Biosystems, Carlsbad, CA, USA) and specific primers. β-actin was used as the internal control. Primers sequences used were: HPN forward primer: 5'-CAGCAATGATGTCTGCAATGG-3', reverse primer: 5'-CGTGGCGTCCGAGAGATG-3'; β-actin forward primer: 5'-AGAGCTACGAGCTGCCTGAC-3', reverse primer: 5'-AGCACTGTGTTGGCGTACAG-3.

Animal model of thyroidectomy

Rat models were induced to be euthyroid, hypothyroid and hyperthyroid based on previously published studies [18, 19]. All animal experiments were performed in accordance with Chang Gung Institutional Animal Care (IACUC: CGU11-015).

Western blot analysis

The detailed protocols for western blot analysis were previously described [20]. Antibodies used in this study were anti-HPN (Cayman Chemical, Ann Arbor, Michigan, USA, No. 100022), anti-CDK2 (Santa Cruz Biotechnology, Inc., Dallas, Texas, USA, sc-6248), anti-cyclin E1 (Santa Cruz, sc-481), and anti-β-actin (Sigma, A5441). Signal intensities were quantified using Image Gauge software, and target gene expression levels were normalized to β-actin.

Establishment of HPN-stable cell lines

For HPN overexpression, the full length of the HPN sequence was amplified and cloned into the expression plasmid, such as pcDNA3. The integrity of the HPN sequences was confirmed via Sanger sequencing. The construct was transfected into hepatoma cells by using TurboFectTM (Thermo Fisher Scientific, Waltham, MA, USA, R0531). After 48 hours of transfection, the culture medium was replaced with a fresh medium containing 800 μg/mL neomycin to select for stable expression. For HPN knockdown, shRNA targeting HPN was sourced from the National RNA Interference Core Facility (Academia Sinica, Taiwan). Stable knockdown cell lines were cultured in DME supplemented with 10% FBS and 0.5 μg/mL puromycin. Knockdown and overexpression efficiency were confirmed by Western blot analysis.

Promoter assay

To prepare HPN gene promoter fragments (I-VII), their sequences were amplified and cloned in the pA3TK plasmid. Further, a TRE-deleted promoter fragments (VIII) were constructed. To evaluate the effect of T3 on HPN promoter activity, these constructs and a β-galactosidase expression vector were transfected into HepG2-TRα1 cells by TurboFect™ (Thermo Fisher Scientific). T3 was added 24 h after transfection, and luciferase activity was measured 24 hours after T3 treatment. β-galactosidase was used as the transfection efficiency control in the promoter assay. Luciferase activity was expressed relative to vector control cells not treated with T3.

Chromatin immunoprecipitation (ChIP) assay

Using our previously described protocols, ChIP assays were assayed to characterize TR binding to the HPN promoter [20]. Cells were treated with T3 (10 nM) for 24 hours, cross-linked with 1% formaldehyde, and this reaction was stopped with 0.125 M glycine. Cells were lysed, and chromatin was shared by sonication using a Misonix Sonicator 3000 Homogenizer (Mandel Scientific Company Inc., Guelph, ON, Canada). To minimize non-specific binding, samples were pre-cleared with protein A/G (GE Healthcare Life Sciences). Following pre-clearance, samples were incubated overnight with TR antibody (Santa Cruz, sc-739) or IgG control (Cell Signaling, #2729) at 4°C. TR-bound DNA was purified by QIAquick PCR purification kit (QIAGEN, Cat. No. 8106) and PCR-amplified with the following primers: Hepsin ChIP forward primer: 5'-TATCTGGGGCAAGCAGCC-3', Hepsin ChIP reverse primer: 5'-ATAACACACTGTCCCG-CC-3'; Furin ChIP forward primer: 5'-CTCCAAA-GACCCACTGCG-3', Furin ChIP reverse primer: 5'-CCACTTGTCCTCAGGCCTAG-3'; GAPDH ChIP forward primer: 5'-TACTAGCGGTTTTACGGGCG-3', GAPDH ChIP reverse primer: 5'-TCGAACAG-GAGCAGAGAGCGA-3'.

Cell proliferation

Cells (2×10^5, as specified in the figure legends) were plated in 6 cm dishes and proliferation was evaluated with a cell counter after Trypan blue (0.4%) staining at different time points (24-120 hours).

Data analysis

Data are shown as the means with ± standard deviation (SD) from a minimum of three independent experiments. IBM SPSS Statistics software (version 20; SPSS Inc., Chicago, IL, USA) and GraphPad Prism 8 software were used for statistical analyses. Student's t-test or the Mann-Whitney test was used for pairwise comparisons, while one-way ANOVA with Tukey's post-hoc test was used to compare among multiple groups. Survival analysis (overall and disease-free survival) was performed with the GEPIA database (http://gepia.cancer-pku.cn/). Statistical significance was defined as P value < 0.05.

Results

HPN is upregulated by T3/TR

To begin, HepG2 cell lines overexpressing TRα1 and TRβ1 and vector control (HepG2-neo) were established. The expression levels of TRα1 and TRβ1 in these cell lines were confirmed via western blot analysis (**Figure 1A**). To determine whether HPN is a direct target gene of T3/TR, qRT-PCR and western blot analyses were performed on HepG2-neo and HepG2-TR-overexpressing cell lines treated with or without T3. The results demonstrated that T3 treatment significantly induced HPN mRNA expression in a time-dependent manner in HepG2-TRα1 and HepG2-TRβ1 cell lines (**Figure 1B**). In contrast, no such regulation was observed in the HepG2-neo control cells (**Figure 1B**). As expected, the protein levels of HPN were also upregulated by T3/TR in HepG2-TRα1 and HepG2-TRβ1 cells (**Figure 1C**). To further validate this regulation *in vivo*, qRT-PCR analysis was performed to assess HPN expression in thyroidectomized rats under different thyroid conditions: euthyroid (sham), hypothyroid (Tx), and hyperthyroid (Tx + T3). Consistently, HPN expression was significantly induced by T3 treatment compared to the sham and Tx groups (**Figure 1D**). These *in vitro* and *in vivo* findings collectively support that HPN is a target gene of T3/TR in liver cancer cells.

T3/TR binds to the promoter region of HPN and drives its expression

TRs that can directly bind to DNA through thyroid hormone response elements (TREs), which

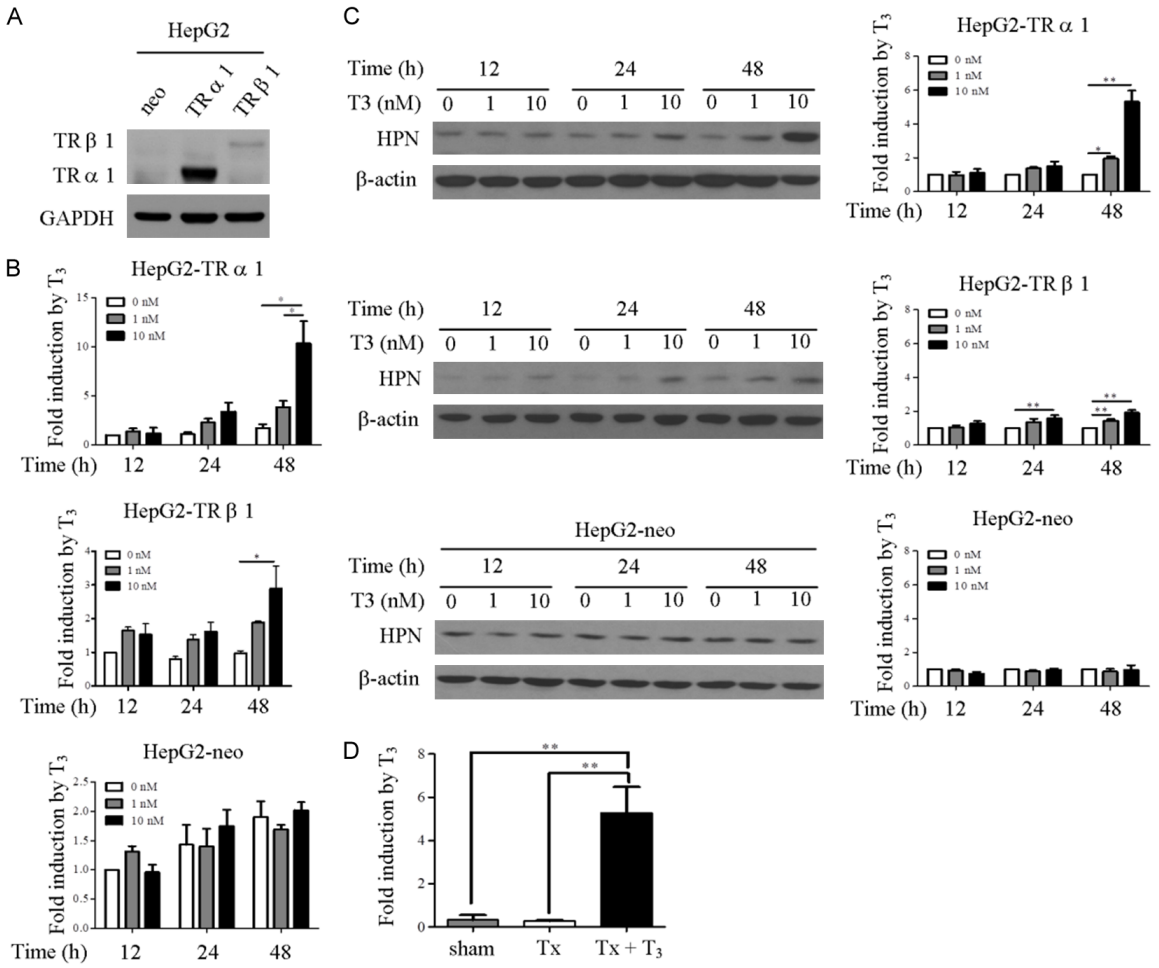

Figure 1. T3 upregulates HPN expression in HepG2-TRα1 and HepG2-TRβ1 cell lines. A. Western blot analysis of TRα1 and TRβ1 expression in HepG2-neo, HepG2-TRα1 and HepG2-TRβ1. β-actin served as a loading control. B. Quantitative RT-PCR analysis of HPN mRNA expression in HepG2-TRα1, HepG2-TRβ1, and HepG2-neo cell lines following treatment with T3 (0, 1, and 10 nM) for 12, 24, and 48 hours. Data are presented as fold change relative to the untreated control. β-actin served as a loading control. *P < 0.05. C. Western blot analysis of HPN protein expression in HepG2-TRα1, HepG2-TRβ1, and HepG2-neo cell lines treated with T3 (0, 1, and 10 nM) for 12, 24, and 48 hours. β-actin was used as a loading control. Quantification of protein expression levels is shown. **P < 0.01, *P < 0.05. D. qRT-PCR analysis of HPN mRNA levels in thyroidectomized rats under different thyroid conditions: euthyroid (sham), hypothyroid (Tx), and hyperthyroid (Tx + T3). β-actin was used as a loading control.

contain the consensus sequence AGGTCA arranged in various configurations, including direct repeats separated by four nucleotides (DR4), inverted repeats separated by six nucleotides (IR6), and palindromic sequences [21]. To investigate the mechanism by which T3/TR upregulates HPN expression in liver cancer cell lines, TREs within the HPN promoter region were predicted using Vector NTI software. Seven TREs (direct repeat and inverted repeat) were identified within the promoter region (**Figure 2A**). The wild-type HPN promoter fragments (I-VII) and a mutated promoter fragment (VIII) were amplified by PCR, cloned into the pA3TK plasmid, and analyzed using a reporter assay. The results demonstrated that the full-length promoter fragment (fragment I) and fragment VII were significantly activated by T3 treatment (**Figure 2A**). In contrast, fragments II-VI showed no response to T3 (**Figure 2A**). Notably, deleting a specific TRE (fragment VIII) abolished T3-induced reporter activity (**Figure 2A**), suggesting its essential role in HPN transcriptional regulation. To further confirm whether TR directly binds to fragment VIII, a chromatin immunoprecipitation (ChIP) assay was per-

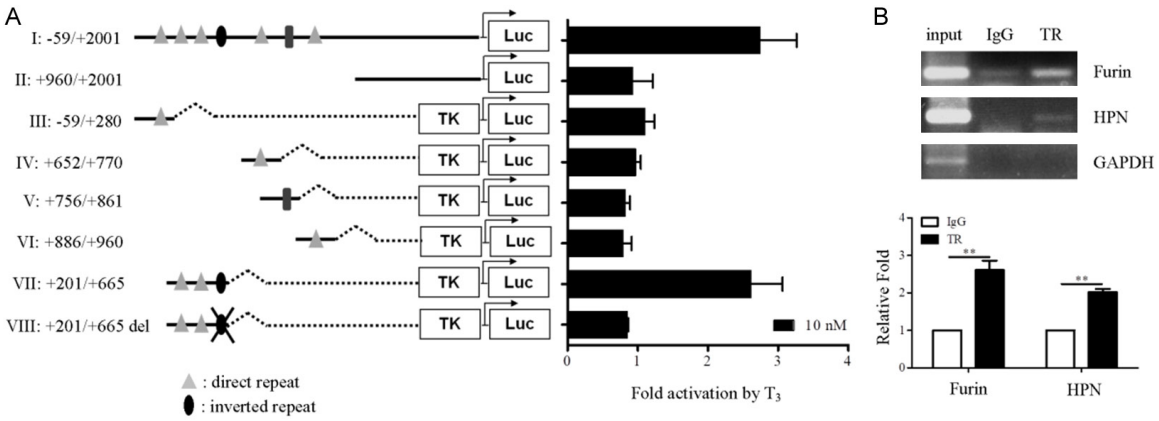

Figure 2. T3 induces HPN expression via direct TR binding to the HPN promoter. A. Luciferase reporter assay analyzing the effects of T3 on different HPN promoter fragments. Various HPN promoter constructs (fragments I-VIII) were cloned into the pA3TK-Luc plasmid and transfected into HepG2-TRα1 cells. Following treatment with 10 nM T3 for 24 hours, luciferase activity was measured. Data are presented as fold activation by T3 relative to the untreated control. B. ChIP assay confirming direct TR binding to the HPN promoter. HepG2-TRα1 cells were treated with T3, and chromatin was immunoprecipitated using an anti-TR antibody. PCR analysis was performed to detect HPN promoter fragments. Furin and GAPDH served as positive and negative controls, respectively.

formed. The results revealed a direct interaction between TR and fragment VIII, with Furin and GAPDH as positive and negative controls, respectively (**Figure 2B**). These findings collectively demonstrate that T3 upregulates HPN expression by facilitating TR binding to the promoter region (+506/+523) of HPN, thereby driving its transcription.

Ectopic expression of HPN suppresses hepatoma cell growth

To investigate the functional role of HPN in liver cancer, its protein expression levels were assessed in various hepatoma cell lines using western blot analysis. The results revealed that HPN expression was low in HepG2, Huh7, and SK-Hep1 cells, whereas it was highly expressed in Hep3B, J7, and Mahlavu cell lines (**Figure 3A**). These findings generated stable HPN-overexpressing and HPN-knockdown cell lines in Huh7 and Mahlavu cells, respectively (**Figure 3B**). Cell proliferation assays demonstrated that HPN overexpression significantly suppressed cell growth (**Figure 3C**, left panel), while HPN depletion enhanced proliferation (**Figure 3C**, right panel). Furthermore, T3 treatment in HepG2-TRα1 and HepG2-TRβ1 cells markedly inhibited cell growth compared to the control group (**Figure 3D**). Western blot analysis further revealed that HPN knockdown upregulated cyclin E1 and CDK2 expression (**Figure 3E**), whereas HPN overexpression led to their downregulation (**Figure 3F**). To further validate the role of HPN in T3-mediated suppression of cell growth, HPN-depleted HepG2-TRβ1 cell lines were generated. Cell proliferation assays were performed in both sh-luc control and HPN-knockdown HepG2-TRβ1 cells, with or without T3 treatment. As shown in **Figure 3G**, T3 markedly inhibited cell proliferation in the sh-luc control group. This growth-inhibitory effect was reversed upon HPN knockdown. Furthermore, the downregulation of cyclin E1 expression by T3 was restored in HPN-depleted HepG2-TRβ1 cells (**Figure 3G**). These findings suggest that HPN plays a critical role in T3-mediated suppression of cell proliferation by regulating cyclin E1 and CDK2 expression.

HPN is downregulated in HCC, and its elevated expression correlated with a favorable prognosis

To investigate the clinical significance of HPN in hepatocellular carcinoma (HCC), publicly available datasets (GSE14520 [22] and TCGA) were analyzed. The results demonstrated that HPN expression was significantly lower in HCC tissues than in adjacent normal tissues (**Figure 4A** and **4B**). Furthermore, Kaplan-Meier survival analysis revealed that higher HPN expression was associated with improved overall survival in HCC patients (**Figure 4C**). These findings suggest that HPN plays a clinically relevant role in HCC. Pearson correlation analysis was performed to examine further the clinical associa-

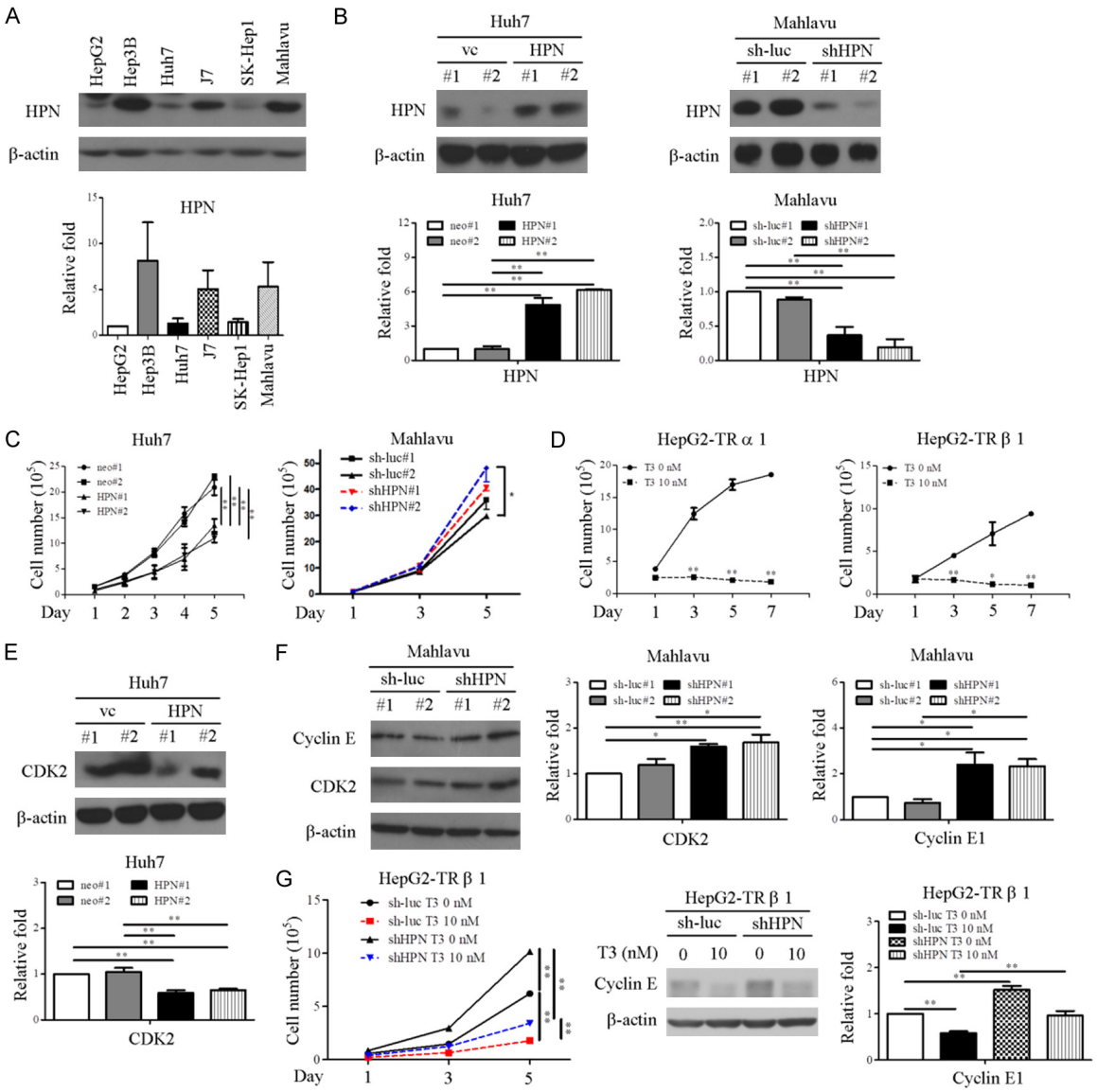

Figure 3. HPN inhibits cell proliferation in hepatoma cells. A. Western blot analysis of HPN protein expression in various hepatoma cell lines. β-actin was used as a loading control. B. Generation of stable HPN-overexpressing Huh7 cells and HPN-knockdown Mahlavu cells via transfection/infection. Western blot analysis confirmed HPN overexpression in Huh7 cells and HPN knockdown in Mahlavu cells. β-actin served as a loading control. C. Cell proliferation assay assessing the effects of HPN on cell growth. The left panel shows the proliferation of HPN-overexpressing Huh7 cells, while the right panel shows the proliferation of HPN-knockdown Mahlavu cells. Cell counts were recorded over five days. Data are presented as mean ± SD (n = 3). *P < 0.05, **P < 0.01. D. Effect of T3 on cell proliferation in HepG2-TRα1 and HepG2-TRβ1 cells. Cells were treated with 10 nM T3, and cell counts were measured over seven days. Data are shown as mean ± SD (n = 3). **P < 0.01. E. Western blot analysis of CDK2 expression in HPN-overexpressing Huh7 cells. β-actin served as a loading control. F. Western blot analysis of cyclin E and CDK2 expression in HPN-knockdown Mahlavu cells. β-actin was used as a loading control. G. Cell growth was conducted in HepG2-TRβ1-sh-luc and HepG2-TRβ1-shHPN cell lines with or without T3 treatment. Cell numbers were detected and presented. Data are presented as mean ± SD (n = 3). Western blot analysis evaluated cyclin E expression in the same cell lines under T3-treated and untreated conditions. β-actin was used as a loading control.

tion between HPN, CDK2, and cyclin E1 in HCC specimens. The results revealed a negative correlation between HPN, CDK2, and cyclin E1 (**Figure 4D**). These findings indicate that CDK2 and cyclin E1 may serve as downstream targets of HPN in both *in vitro* and *in vivo* models.

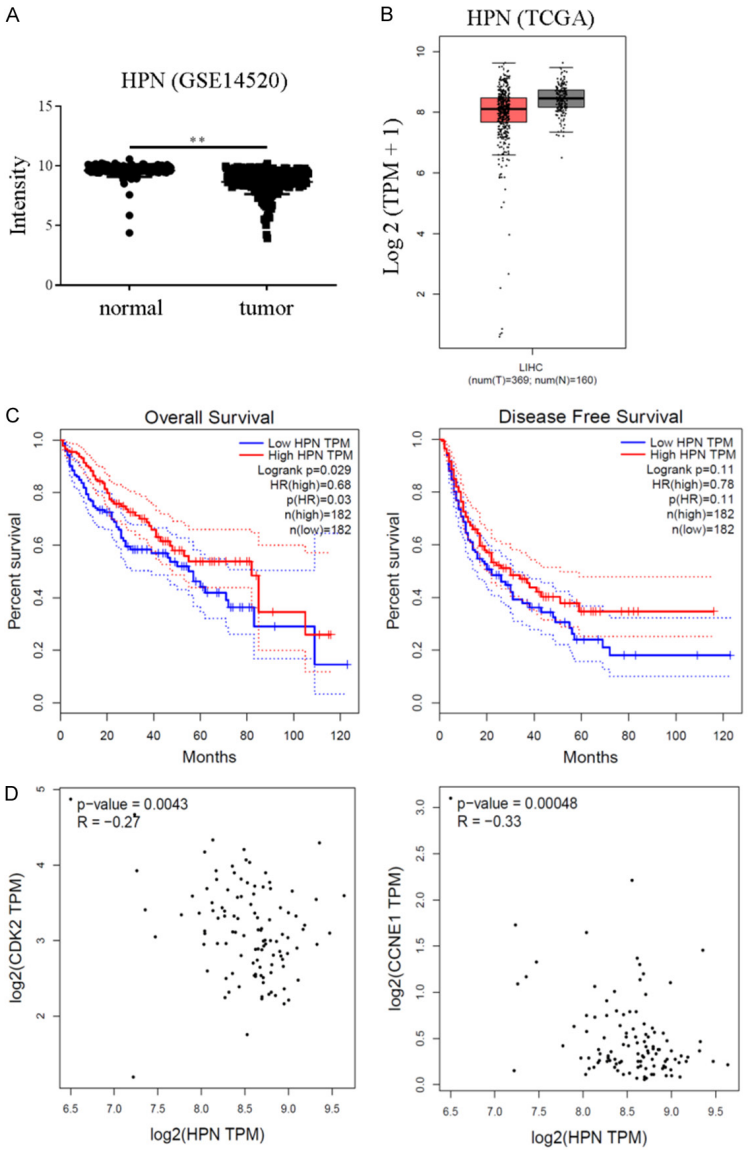

Figure 4. HPN expression and its prognostic significance in liver cancer. A. Comparison of HPN expression levels between adjacent normal (N) and tumor (T) tissues using the publicly available GSE14520 dataset. Data were collected until October 2023. **P < 0.01 indicates statistical significance. B. Boxplot analysis of HPN expression levels in HCC samples from the TCGA dataset, comparing tumor (T, red) and normal (N, gray) tissues. C. Kaplan-Meier survival curves depicting overall survival (left) and disease-free survival (right) based on high and low HPN expression levels, with median values used as the cutoff. Log-rank *p* values and hazard ratios (HR) are displayed. D. Pearson correlation analysis showing the relationships between HPN, CDK2, and cyclin E1 expression in HCC samples. Pearson correlation coefficients are presented.

Discussion

The specific biological roles of HPN in liver cancer cell lines remain unclear. In this study, we characterized the functional role of HPN in hepatoma cells, demonstrating that ectopic expression of HPN inhibited cell growth by downregulating cyclin E1 and CDK2 expression. Additionally, T3 treatment negatively regulated cyclin E1 and CDK2 in HepG2-TR cell lines. Clinical analysis revealed a negative correlation between HPN expression and cyclin E1 and CDK2. Based on these findings, we conclude that T3/TR inhibits cell growth in an HPN-dependent manner.

Previous studies have reported conflicting results regarding the role of HPN in cancer. For instance, treatment with an anti-hepsin antibody or transfection with HPN-targeted antisense oligonucleotides suppressed cell growth in PLC/PRF/5 cells [23]. This observation contrasts with our findings, possibly due to differences in cell line characteristics, as PLC/PRF/5 cells uniquely produce hepatitis B surface antigens, unlike Huh7 and Mahlavu cells. Similarly, in breast cancer cell lines (MCF-10A), hepsin overexpression enhanced tumor growth by regulating the TGFβ and EGFR pathways [24]. In contrast, Nakamura et al. reported that HPN overexpression in endometrial cancer cell lines significantly inhibited cell proliferation and anchorage-independent growth [25]. Mechanistically, HPN was shown to upregulate tumor suppressors such as p53, 14-3-3σ, Bak, and Bax, while downregulating cyclin B, cyclin A, Bcl-xL, and Bcl-2. Furthermore, HPN has been identified as a tumor suppressor in prostate cancer cell lines, where increased HPN levels inhibited cell proliferation, colony formation in soft agar, and invasion [26]. These findings suggest that HPN plays diverse roles in cancer progression, and in our study, it appears to function as a tumor suppressor in hepatoma cell lines.

Both *in vitro* and *in vivo* studies have demonstrated that T3 treatment inhibits cell proliferation and tumor growth [6, 8]. T3 was found to suppress HBx-promoted hepatocarcinogenesis by reducing reactive oxygen species (ROS) formation, thereby mitigating DNA damage [27]. This effect was mediated through PTEN-induced kinase 1 (PINK1)/parkin modulation, which influenced HBx-associated mitochondrial ubiquitination and activated selective mitophagy. These animal models provide strong evidence supporting the tumor-suppressive role of T3 in liver cancer. Our previous research indicated that T3 downregulates CDK2 and cyclin E1 expression [28]. In this study, we further identified HPN as a key mediator of T3-induced suppression of CDK2 and cyclin E1.

In conclusion, we identify HPN as a novel target gene of T3/TR. This study is the first to reveal that HPN negatively regulates cyclin E1 and CDK2 expression in hepatoma cell lines. *In vitro* assays support that T3/TR-mediated suppression of cell proliferation occurs through HPN, further reinforcing its role as a tumor suppressor in liver cancer.

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Disclosure of conflict of interest

None.

Abbreviations

T3, thyroid hormone; TR, thyroid hormone receptor; HCC, hepatocellular carcinoma; HPN, hepsin; HBV, hepatitis B virus; TRα1, thyroid hormone receptor α1; TRβ1, thyroid hormone receptor β1; qRT-PCR, quantitative reverse transcription PCR; ChIP, chromatin immunoprecipitation; TRE, TR response elements; SD, standard deviation; PINK1, PTEN-induced kinase 1.

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