**Additional file 2: Supplementary methods**

**Cell culture**

HCCLM3, MHCC97H, MHCC97L, YY8103, Huh7, HepG2, and Hep3B cell lines were obtained from the Key Laboratory of Liver Transplantation, Chinese Academy of Medical Sciences (Nanjing, China). The normal hepatic cell line QSG-7701 and mouse HCC cell line Hepa1-6 were purchased from American Type Culture Collection (Rockville, MD, USA). All cells were cultured in Dulbecco’s Modified Eagle’s Medium (DMEM; Gibco, Carlsbad, CA, USA) containing 10% fetal bovine serum (Gibco) and 1% penicillin/streptomycin (Gibco) at 37℃ in a humidified atmosphere of 5% CO2.

**RNA stability assay**

HCCLM3 and HepG2 cells were treated with actinomycin D for 0 h, 4 h, 8 h, 12 h, and 24 h. Total RNA was isolated, and RT-qPCR was performed to quantify the relative levels of circRHBDD1 and RHBDD1 mRNA.

**Nuclear and cytoplasmic separation**

The PARISTM Kit (Invitrogen, Carlsbad, CA, USA) was applied to extract nuclear and cytoplasmic RNA in cells according to the manufacturer’s protocols. The relative expression of circRHBDD1 in the nuclear and cytoplasmic fractions was detected by RT-qPCR.

**Immunohistochemistry (IHC)**

Tissue specimens were fixed in 4% paraformaldehyde and embedded in paraffin sections. The primary antibodies against GLUT1 (ab115730, Abcam, Cambridge, UK), ASCT2 (ab237704, Abcam), Ki-67 (#9027, Cell Signaling Technology, Beverly, MA, USA), PIK3R1 (ab86714, Abcam), and p-AKT (#4060, Cell Signaling Technology) were used for IHC staining. The sections were scanned under a microscope (Nikon Corporation).

**Lentivirus transfection and stable cell line construction**

Lentiviruses overexpressing circRHBDD1 and lentiviral-based small hairpin RNAs (shRNAs) targeting circRHBDD1 were designed and purchased from RiboBio (Guangzhou, China). Lentivirus transfection and stable cell line construction were performed as previously described [1].

**Plasmids and siRNAs transfection**

The plasmids overexpressing YTHDF1, PIK3R1, or EIF4A3, and siRNAs targeting YTHDF1 or EIF4A3 were designed and synthesized by GenePharma (Shanghai, China). For transient transfection, cells were seeded into 6-well plates to 60-70% confluence and transfected with plasmids or siRNAs using Lipofectamine 3000 (Invitrogen) according to the manufacturer’s protocols. The siRNA sequences were as follows: si-YTHDF1#1: 5′-GATACAGTTCATGACAATGA-3′, si-YTHDF1#2: 5′-GAAACGTCCAGCCTAATTCT-3′; si-EIF4A3#1: 5′-GCAUCUUGGUGAAACGUGATT-3′, si-EIF4A3#2: 5′-CCGAGUGCUUAUUUCUACATT-3′.

**Cell Counting Kit-8 (CCK-8) assay**

Cells were seeded into 96-well plates at a density of 1 × 103 cells/well. Then, 10 μl of CCK-8 solution reagent (Dojindo, Kumamoto, Japan) was added to each well at the appointed time. After incubation in dark for 2 h, the absorbance at the wavelength of 450 nm was measured by an automatic microplate reader (Bio-Tek Elx 800; Bio-Tek Instruments, Winooski, VT, USA).

**Colony formation assay**

Cells were seeded into 6-well plates at a density of 5 × 102 cells/well. After incubated for 14 days, the colonies on the plates were fixed in 4% paraformaldehyde and stained with 1% crystal violet.

**5-ethynyl-2’-deoxyuridine (EdU) incorporation assay**

EdU assay was performed with Cell-Light™ EdU Apollo488 *In Vitro* Imaging Kit (RiboBio). Cells (5 × 104 cells/well) were seeded into 24-well plates and cultured overnight. After incubated with EdU for 2h, the cells were fixed in 4% paraformaldehyde, permeabilization in PBS with 0.5% Triton X-100, and stained with Apollo Dye Solution for 30 min. Hoechst 33342 was used to stain the nuclei. Images were taken using a fluorescence microscope (Leica Microsystems, Mannheim, Germany).

**RNA sequencing (RNA-seq) analysis**

Total RNA was isolated from sh-NC (*n* = 3) and sh-circRHBDD1#1 (*n* = 3) HCCLM3 cells. RNA samples were subjected to high-throughput sequencing by BGI (Shenzhen, China). Briefly, BGISEQ-500 platform was used to sequence the samples. Clean data was obtained by removing reads with low quality from raw data. Differential mRNA abundance analysis between sh-NC and sh-circRHBDD1#1 groups was carried out with DESeq2 based on fold change > 2.0 and *P* < 0.001. Analysis of signaling pathway was subsequently performed using KEGG databases (http://www.genome.jp/kegg).

**Western blotting**

Cells were dissolved in RIPA lysis buffer, and the total protein concentrations were determined using a bicinchoninic acid Protein Assay Kit (Beyotime, Jiangsu, China). Cell lysates were resolved by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (Beyotime) and transferred onto polyvinylidene difluoride membranes (Millipore, Billerica, MA, USA). The immunocomplexes were detected by Super ECL Detection Reagent (Yeasen, Shanghai, China) and visualized using Image Lab software (Bio-Rad, Hercules, CA, USA). The following antibodies were used: GLUT1 (ab115730, Abcam), HK2 (#2106, Cell Signaling Technology), ASCT2 (ab237704, Abcam), GLS1 (#56750, Cell Signaling Technology), p-AKT (#4060, Cell Signaling Technology), AKT (#4691, Cell Signaling Technology), YTHDF1 (#86463, Cell Signaling Technology), PIK3R1 (ab86714, Abcam), EIF4A3 (ab32485, Abcam), β-tubulin (#2146, Cell Signaling Technology), HRP-linked anti-rabbit IgG (#7074, Cell Signaling Technology), and HRP-linked anti-mouse IgG (#7076, Cell Signaling Technology).

**Polysome profiling**

Polysome profiling was performed as previously described [2]. In brief, cells were incubated with cycloheximide for 15 min, lysed by polysome buffer on ice for 15 min, and centrifuged (14,000 rpm) for 15 min. Then the supernatant was layered onto a 5 to 50 % sucrose gradient. After centrifugation, the polysome bound fractions were collected using a Density Gradient Fractionation System (Teledyne ISCO, Lincoln, NE, USA) and analyzed by RT-qPCR.

**Immunoprecipitation (IP)**

Cells were harvested to extract the total proteins. Protein aliquots were pre-cleared by incubating with protein A/G-agarose beads. The pre-cleared samples were then immunoprecipitated with EIF4A3 antibody (ab32485, Abcam) according to the manufacturer’s instructions. The immunoprecipitated proteins were then subjected to western blotting assay.

***In vivo* anti-PD-1 experiments**

For *in vivo*anti-PD-1 experiments, a total of 5 × 106 circRHBDD1-silenced Hepa1-6 cells or control cells were injected into the right flank of C57BL/6 mice to generate subcutaneous tumors. Then the tumor-bearing mice were randomly divided into two subgroups and administered 100 μg anti-PD-1 antibody (Clone 29F.1A12, BioXCell, West Lebanon, NH, USA) or IgG (Clone 2A3, BioXCell) via intraperitoneal injection on day 9, 12, 15, and 18 post tumor injection. Tumor volume was calculated as (length × width2)/2.

**References**

1. Zuo X, Chen Z, Cai J, Gao W, Zhang Y, Han G, et al. 5-hydroxytryptamine receptor 1D aggravates hepatocellular carcinoma progression through FoxO6 in AKT-dependent and independent Manners. Hepatology. 2019;69(5):2031-2047.

2. Song P, Feng L, Li J, Dai D, Zhu L, Wang C, et al. β-catenin represses miR455-3p to stimulate m6A modification of HSF1 mRNA and promote its translation in colorectal cancer. Mol Cancer. 2020;19(1):129.