**Supplementary Materials and Methods**

**Cell viability assay**

The Cell Counting Kit 8 assay (CCK8，Cat. no. C0005) (Topscience, Shanghai, China) was performed for cell viability detection.1 Briefly, cells were seeded into 96-well culture plates at a density of 3000 cells per well for 12 h with 3 replicate wells per group. After treatment with the corresponding different concentrations of PTX for 120 h, 10 μL of CCK-8 solution was added into each well respectively and incubated for 2 h. Next,the optical density (OD) value of each value at 450 nm was detected by a microplate reader (Bio-Tek Synergy HT).

**HBV virus particle collection and HepG2-NTCP cell HBV virus infection**

HBV virus particle was collected from HepAD38 cells as previously described.2 HepAD38 cells stably expressing HBV were cultured for 5-7 days without changing the solution. The supernatant of the cells was collected into a 50 mL tube and centrifuged at 4 ℃ and 2000 rpm for 5 min to remove the cellular debris, and then the supernatant was carefully transferred into an ultracentrifuge tube with 20% sucrose solution. The virus particles were purified by centrifugation at 120,000 g for 16 h at 4 ℃ in an ultracentrifuge. The final DNA copy of the virus particles was detected by fluorescence quantitative PCR. HepG2-NTCP cells were infected with HBV virus particle as described previously.3 2×105 HepG2-NTCP cells were inoculated into six-well plates, and after the cells were adhered to the wall, Williams E medium containing 10% FBS, 100 units/mL penicillin, 100 μg/mL streptomycin (HyClone, Logan, UT, USA), 2% DMSO, 1% glutamine was replaced, and the medium was changed after 24 hours. Infection was carried out by adding infection medium containing virus particles (about 1000-2000 copies per cell) with a final concentration of 5% PEG8000. After 24 h of infection, the medium was washed twice with PBS and changed to normal medium for further incubation. The virus particles were extracted 72 h after infection.

**Intracellular HBV DNA extraction**

HBV DNA levels were measured by qPCR using SYBR Green qPCR Master Mix (Bio-Rad). Intracellular HBV DNA was extracted as previously described.4 Cells or liver tissues were first lysed for 10 min at 37 ℃ in cell lysis buffer (10 mM Tris-HCl pH 8.0, 1 mM EDTA, 2% sucrose and 1% NP-40). The mixtures were then centrifuged at 14,000g for 3 minutes at room temperature to obtain the supernatant. In order to eliminate the residual DNA, the supernatant was treated with micrococcal nuclease (New England Biolabs, China) and 10 mM CaCl2 at 37 ℃ for 1 h. The reaction was terminated by adding 10 μL of 0.5 mM EDTA and centrifuged at 10,000 g for 1 min at 37 ℃. Then we use 0.5 mg/mL proteinase K (Cat. no. 3115879001; Roche Diagnostics GmbH, Mannheim, Germany) to digest viral DNAs which were precipitated with 35% PEG8000 at 45 ℃ for 12 h. Nucleic acids were purified by DNA extraction solution phenol:chloroform:isoamylalcohol (25:24:1), repeated three times and then precipitated with ethanol. The final extracted purified HBV DNA can be used for qPCR detection.

**Intracellular HBV cccDNA extraction**

Cells or liver tissues were lysed in Hirt lysis buffer (50 mM Tris-HCl pH 8.0, 10 mM EDTA, 150 mM NaCl, 1% SDS) for 20 min at 37 ℃.4 The mixture incubated at 4℃ with 5 M NaCl and the supernatant was extracted three times by phenol:chloroform:isoamylalcohol (25:24:1) after centrifugation at 14,000 g for 30 min at 4 ℃. The extracted DNA was precipitated with isopropanol. After washing with 75% ethanol, the DNA pellet was then dissolved in TE buffer. Extraction was treated with Plasmid-Safe ATP-Dependent DNase (Epicenter, Madison, WI, USA) to remove double-stranded DNA in the end.

**Measuremet of HBeAg and HBsAg**

The culture supernatants and mouse serum treated with the appropriate concentration of PTX were collected and assessed by the commercially available ELISA kits (Kehua Bioengineering, Shanghai, China) following the manufacturer’s instructions, while negative and positive controls were set at the same time. Finally, the absorbance was detected at 450 nm using a microplate reader.

CHIP-qPCR

CHIP-qPCR assay was performed as described.5 Different treated cells were fixed with 1% formaldehyde at room temperature for 10 min, followed by the addition of 5M glycine to terminate the crosslinking. The Cells were then resuspended in Chip lysis buffer (50 mM Hepes, 150 mM NaCl,1 mM EDTA, 0.1% SDS, 0.1% Sodium deoxycholate, 1% TritonX-100) containing 1% protein inhibitor cocktail. Subsequently, the DNA fragments were sonicated to a size range of 200 bp to 1000 bp. After ultrasonic crushing, the cell suspension was centrifuged at 13000 rpm at 4℃ for 15 min. Input was taken and the remaining cell suspension was incubated with 5 μg of primary antibody at 4°C overnight, followed by incubation with protein agarose beads at 4°C for 2-3 hours. To disrupt the cross-links between DNA and proteins, the DNA complexes were treated with 5 M NaCl in a water bath at 65℃ for 4 hours. Finally, the samples were purified and analyzed by qPCR using the sense primer P1(5′-CACCAGGTCTTGCCCAAGGTCTTAC-3′) and the antisense primer P2(5′-ACAAACAGTCTTTGAAGTATGCCTC-3′).

**References**

1. Chen J, Ge SJ, Feng HJ, Wu SZ, Ji R, Huang WR, *et al*. KRT17 Promotes the Activation of HSCs via EMT in Liver Fibrosis. J Clin Transl Hepatol 2022;10(2):207-218. doi: 10.14218/JCTH.2021.00101, PMID: 35528988.
2. Chen Y, Shen B, Zheng X, Long Q, Xia J, Huang Y, *et al*. DHX9 interacts with APOBEC3B and attenuates the anti-HBV effect of APOBEC3B. Emerg Microbes Infect 2020;9(1):366-377. doi: 10.1080/22221751.2020.1725398, PMID: 32056513.
3. Chen Y, Hu J, Cai X, Huang Y, Zhou X, Tu Z, *et al*. APOBEC3B edits HBV DNA and inhibits HBV replication during reverse transcription. Antiviral Res 2018;149:16-25. doi: 10.1016/j.antiviral.2017.11.006, PMID: 29129707.
4. Yang Y, Yan Y, Yin J, Hu J, Cai X, Hu J, *et al*. Structure-Based Discovery of N-Sulfonylpiperidine-3-Carboxamides as Novel Capsid Assembly Modulators for Potent Inhibition of HBV Replication. Viruses 2022;14(2):348. doi: 10.3390/v14020348, PMID: 35215939.
5. Wu G, Wang Q, Wang D, Xiong F, Liu W, Chen J, *et al*. Targeting polycomb repressor complex 2-mediated bivalent promoter epigenetic silencing of secreted frizzled-related protein 1 inhibits cholangiocarcinoma progression. Clin Transl Med 2023;13(12):e1502. doi: 10.1002/ctm2.1502, PMID: 38050190.