Liver Cancer Progression in Chronic HBV Infection Is Driven by Parvulin Proteins Par14/Par17 Through HBx Stabilization and cccDNA Activation

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BACKGROUND

- Chronic Hepatitis B Virus (HBV) infection remains a leading cause of hepatocellular carcinoma (HCC) globally.
- HBV cccDNA serves as a transcriptional template and persistence reservoir.
- The HBx protein acts as a transcriptional activator, essential for viral replication and oncogenesis.
- Parvulin family members (Par14 and Par17) are peptidyl-prolyl cis/trans isomerases involved in protein folding, chromatin remodeling, and cell cycle regulation.
- We investigated the interplay between Par14/Par17 and HBV proteins in driving liver cancer progression.

OBJECTIVES

- To determine whether Par14 and Par17 directly interact with HBx and HBc proteins.To evaluate the impact of Par14/Par17 on HBV replication and cccDNA activation.
- To assess the therapeutic potential of Parvulin inhibitors (Juglone and PiB) in suppressing HBV replication.

METHODS

Cell Lines:

HepG2, HepG2.2.15, Huh7.

Techniques:

Co-immunoprecipitation (Co-IP)

Western Blotting (WB)

Northern & Southern blotting

PCR analysis, cccDNA ChIP

Treatments:

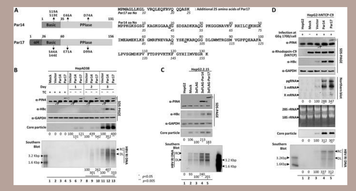
Juglone & PiB as Parvulin inhibitors.

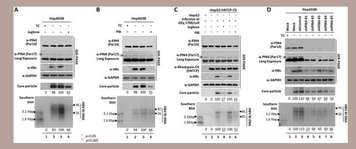
Readouts:

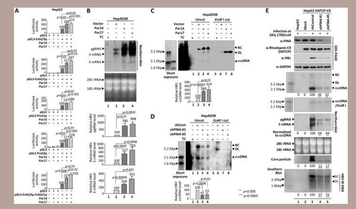
HBV RNA/DNA quantification

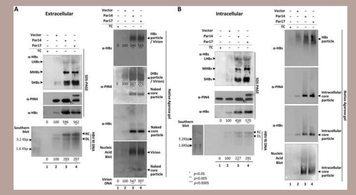
Par14/Par17 localization

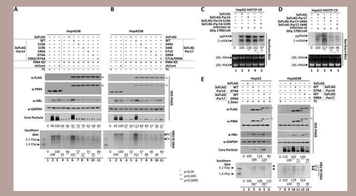
cccDNA chromatin modification

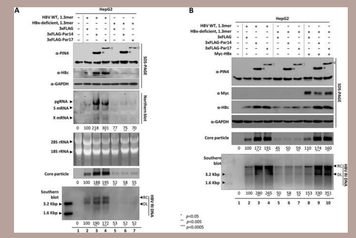






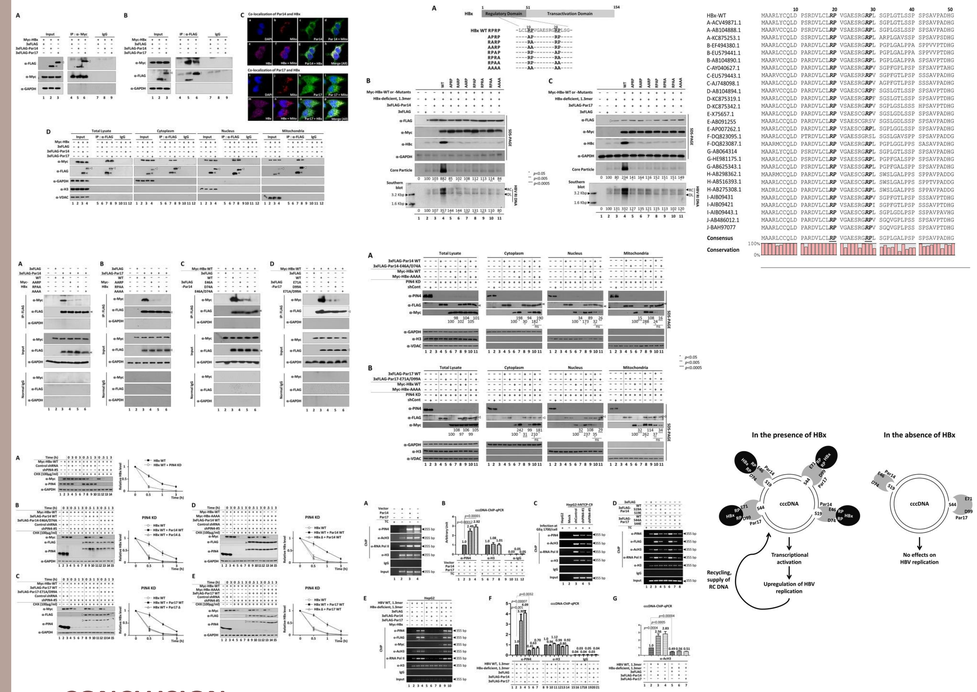






RESULTS & DISCUSSION

- Higher expression of PIN4 in several human hepatocellular carcinoma and HBV replicating cell lines
- 133RP134 motif conserved among human HBV genotypes and mammalian hepadnaviruses
- Parvulin inhibitors abrogate HBV replication
- Par14/17 bind to both outside and inside the core particle
- Model of Par14/17-HBc and core particle mediated HBV replication



CONCLUSION

- Par14 and Par17 stabilize HBx and activate cccDNA, promoting HBV persistence and liver cancer progression.
- Inhibition of Parvulins by Juglone or PiB effectively suppresses HBV replication.
- Targeting Par14/Par17 offers a novel therapeutic avenue for functional cure of chronic HBV infection and prevention of HCC.