Liver Cancer Progression in Chronic HBV Infection Is Driven by Sirtuin 2 Isoform 1 via AKT/GSK-3β/β-Catenin Signaling

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BACKGROUND

- **Liver cancer, particularly hepatocellular carcinoma (HCC), is a leading cause of cancer-related mortality worldwide and is strongly associated with chronic HBV infection.**
- **Among host factors influencing HBV-associated carcinogenesis, Sirtuin 2 (Sirt2)—a NAD^+-dependent deacetylase—is frequently overexpressed in HCC and modulates oncogenic signaling.**
- **Endogenous Sirt2 is upregulated in HBV WT-replicating cells, resulting in tubulin deacetylation, whereas replication-deficient or reverse-transcriptase-inhibited cells do not show this increase.**
- **Activated Sirt2 stimulates the AKT/GSK-3β/β-catenin pathway, promoting HBV replication and tumorigenic signaling.**
- **This study investigates how Sirt2 isoform 1 enhances HBV replication and drives hepatocarcinogenesis through AKT/β-catenin activation, independently of HBx.**

OBJECTIVES

- **To determine how endogenous and overexpressed Sirt2 affect HBV replication.**
- **To examine Sirt2-mediated activation of the AKT/GSK-3β/β-catenin pathway.To evaluate whether Sirt2 inhibition (AGK2) suppresses HBV replication and oncogenic signaling.**

METHODS

Cell Lines:

HepG2, HepG2.2.15, Huh7.

Techniques:

Co-immunoprecipitation (Co-IP)

Western Blotting (WB)

Northern & Southern blotting

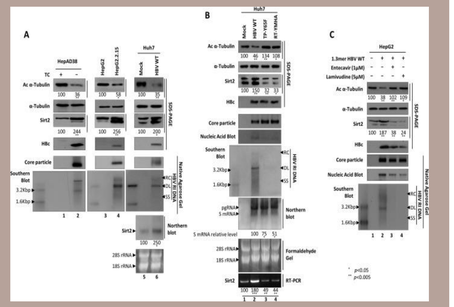
PCR analysis, cccDNA ChIP

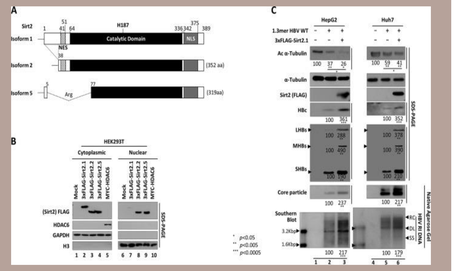
Treatments:

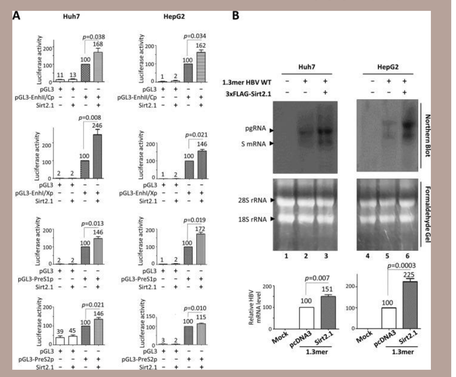
Sirtuin Inhibitors.

Readouts:

HBV RNA/DNA levels, AKT activation, β-catenin stabilization, tubulin acetylation status

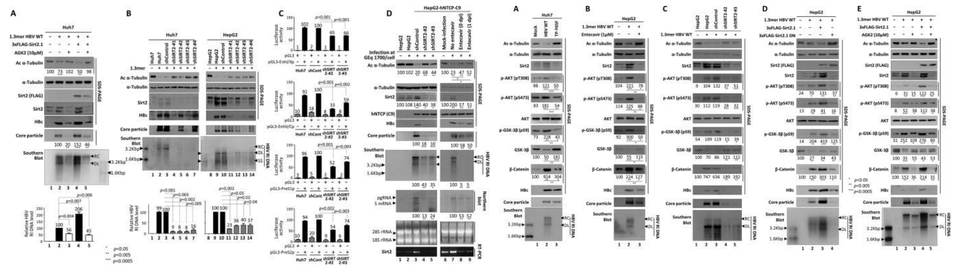


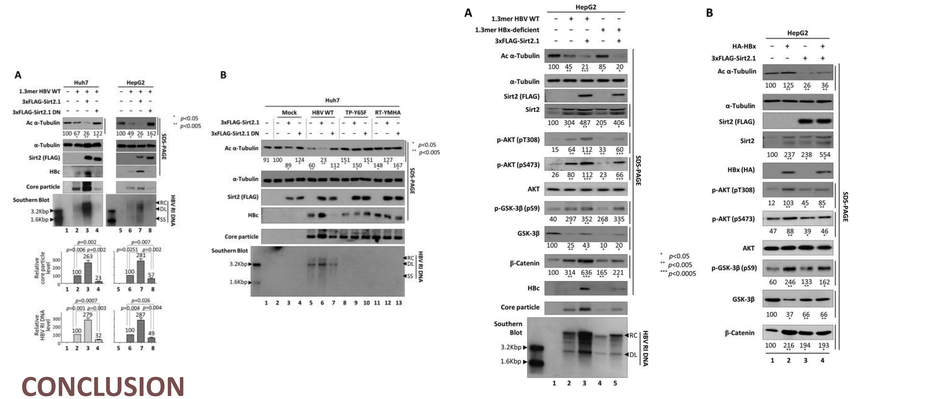




RESULTS & DISCUSSION

- **Sirt2 ↑ in HBV WT-replicating hepatocytes but not in replication-deficient or RT-inhibited cells. Elevated Sirt2 → tubulin deacetylation → AKT activation → GSK-3β suppression → β-catenin stabilization.**
- **Overexpression of Sirt2 isoform 1 enhanced HBV RNA transcription and DNA synthesis. Sirt2 knockdown / dominant-negative mutant / AGK2 treatment significantly reduced HBV replication, AKT activation, and β-catenin accumulation.**
- **These effects occurred independently of HBx, identifying Sirt2 as a direct modulator of HBV persistence and oncogenic signaling.**





CONCLUSION

- Sirt2 isoform 1 enhances HBV replication and promotes AKT/β-catenin-driven oncogenic signaling. These actions occur independently of HBx, defining Sirt2 as a host-driven amplifier of HBV persistence.
- AGK2 inhibition of Sirt2 attenuates HBV replication and β-catenin activation. Targeting Sirt2 offers a dual benefit — antiviral and anti-tumor — for preventing HCC progression in chronic HBV infection.