Activation of Hepatitis B Virus Transcription by CRTC1 Coactivator and PRMT5 Protein Arginine Methyltransferase

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Background/Objective
Chronic infection of hepatitis B virus (HBV) occurs in 350 million people worldwide, causing severe liver diseases such as hepatocellular carcinoma in 15-40% of them. High level of HBV DNA has been singled out as one major and independent risk factor for disease progression. Transcription of pregenomic RNA (pgRNA) from cccDNA is a rate-limiting step in HBV replication. Identification and characterization of cellular cofactors and regulators of cccDNA transcription could reveal new strategies for disease intervention. Whereas transcriptional coactivator CRTC1 is a key regulator of liver metabolism, protein arginine methyltransferase PRMT5 dimethylates arginine residues symmetrically in its substrates and is known to stimulate the activation of gluconeogenic genes by CREB and CRTC1.

Method
HBV infection of HepG2-NTCP cells or transfection with HBV molecular clone pHBV1.3D. Viral and cellular DNA, RNA and proteins were analyzed using standard molecular assays.

Result
In this study, we demonstrated the activation of cccDNA transcription by CRTC1 and PRMT5. The steady-state levels of CRTC1 and PRMT5 mRNA and protein were elevated in HBV-infected hepatocytes and liver tissues. The amounts of pgRNA, cccDNA and secreted HBsAg in HBV-infected hepatocytes were boosted when CRTC1 or PRMT5 was overexpressed, but significantly decreased when either CRTC1 or PRMT5 was knocked down by siRNA. CRTC1 and PRMT5 interacted with each other and they augmented the transcriptional activity of HBV preS2/S promoter by affecting the recruitment of CREB. In addition, HBV transactivator HBx and CRTC1 mutually stabilized each other. Finally, CRTC1 inhibitor metformin and PRMT5 inhibitor AMI-1 suppressed the production of pgRNA, cccDNA and secreted HBsAg in HBV-infected hepatocytes.

Conclusion
Our findings revealed a new stimulatory role of CRTC1 and PRMT5 in HBV transcription. Pharmaceutical agonists of CRTC1 and PRMT5 might be developed as new anti-HBV agents.

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