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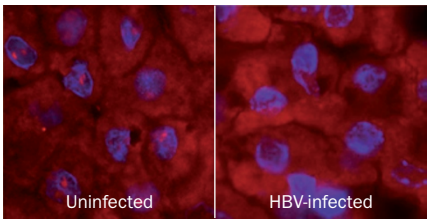
HEPATITIS

# HBV infection alters bile acid metabolism gene profile

The effect of HBV infection on hepatocyte function remains unclear because of the narrow host range for HBV and the existence of few robust *in vitro* systems. A new study in *Hepatology* sidesteps this issue by using a human liver–chimeric mouse model. HBV infection in these mice altered the expression of genes involved in lipid and bile acid metabolism, most notably *CYP7A1*, which encodes a key enzyme involved in bile acid synthesis. Moreover, the researchers pinpoint binding of the preS1-domain of the HBV envelope to hepatocytes as a potential key trigger of these changes.

Human hepatocytes were injected into uPA/SCID mice; 40–70% of the mouse liver was reconstituted by human cells, enabling HBV infection. HBV-infected and uninfected mice were then used to study the viral effects on metabolic gene expression.

*CYP7A1* expression was increased in the HBV-infected chimeric mice. Compared with controls, farnesoid X receptor (*FXR*) nuclear translocation decreased and the expression of its transcriptional target, small heterodimer partner (*SHP*) was reduced in the HBV-infected group. SHP is a transcriptional repressor of CYP7A1 and its decrease could explain CYP7A1 induction. Similar gene expression patterns were observed in biopsy samples from patients with chronic HBV infection, leading the authors to speculate that the alterations in these genes might be an adaptive response to maintain intracellular cholesterol and bile acid homeostasis.




Reduced nuclear FXR (red dots) staining in HBV infected human hepatocytes. Image courtesy of M. Dandri.

"After observing a dramatic enhancement of CYP7A1 expression both in human and to our great surprise mouse hepatocytes, we thought that circulating viral factors rather than intracellular viral replication may be responsible," says author Maura Dandri. Crucially, when uninfected mice were treated with an HBV entry inhibitor derived from preS1—which binds and suppresses the activity of the bile acid transporter NTCP—a similar induction of CYP7A1 occurred. This virus–host interaction might thus be the cause of changes in expression of metabolic genes.

Dandri goes on to say that, as NTCP is involved in drug uptake, decreased NTCP function might limit the response to certain drugs in the setting of HBV infection. The group will focus on the pharmacodynamic effect of HBV infection and the effect of reduced nuclear FXR on other signalling pathways in future studies.

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