A RHESUS MACAQUE MODEL OF CHRONIC HBV INFECTION FOR CURE RESEARCH

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BACKGROUND

Chronic HBV infection (CHB) is a major global health concern, affecting 247 million individuals worldwide and causing 887,000 deaths annually. CHB induces various degrees of liver damage and is strongly associated with the development of liver cirrhosis and hepatocellular carcinoma. Chimpanzees were the gold standard for primate HBV research, but are no longer available. Indeed, one of the major obstacles to the discovery of an HBV cure is the lack of a physiologically-relevant primate model. Based on our previous work showing that expression of the HBV receptor, human Na^+-taurocholate co-transporting polypeptide (hNTCP), on rhesus macaque (RM) hepatocytes facilitates *in vitro* and *in vivo* HBV infection, we hypothesized that RM can be chronically infected with HBV.

METHODS

We treated three infant RM (<1-year-old) with an immunosuppression regimen consisting of daily tacrolimus and semi-monthly belatacept injections. Following initiation of this immunosuppression, we intravenously administered high-dose adenovirus expressing hNTCP. Seven days later we challenged all three RM intravenously with HBV (1 x 10^9 virions). Immunosuppression was tapered after 18 weeks of HBV infection. We have followed HBV infection in the blood and liver in these RM by qPCR, ELISA, and immunofluorescent microscopy over the course of 42 weeks.

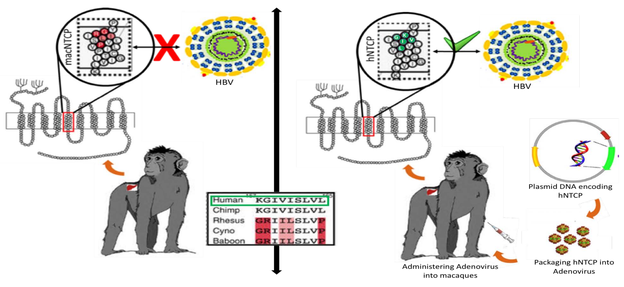


Figure 1. Human NTCP expression on RM hepatocytes allows for HBV binding and replication.

Rhesus macaques are a model of chronic HBV infection.

RESULTS

We found persistently high levels of HBV plasma viremia (>1 x 10^5 copies/ml) accompanied by high levels of HBV surface (HBsAg) and envelope (HBeAg) antigens in blood for more than six months, the clinical definition of chronic HBV infection. In addition, high frequencies of HBV core antigen (HBcAg)- and HBsAg-positive hepatocytes were detected longitudinally in liver biopsies. Following immunosuppression tapering, two of the three animals maintained ongoing viral replication, indicating HBV immunotolerance. The set point HBV loads in these two animals correlated with the level of hNTCP expression in the liver by qPCR, indicating that hepatocyte target availability is the restricting factor in this model.

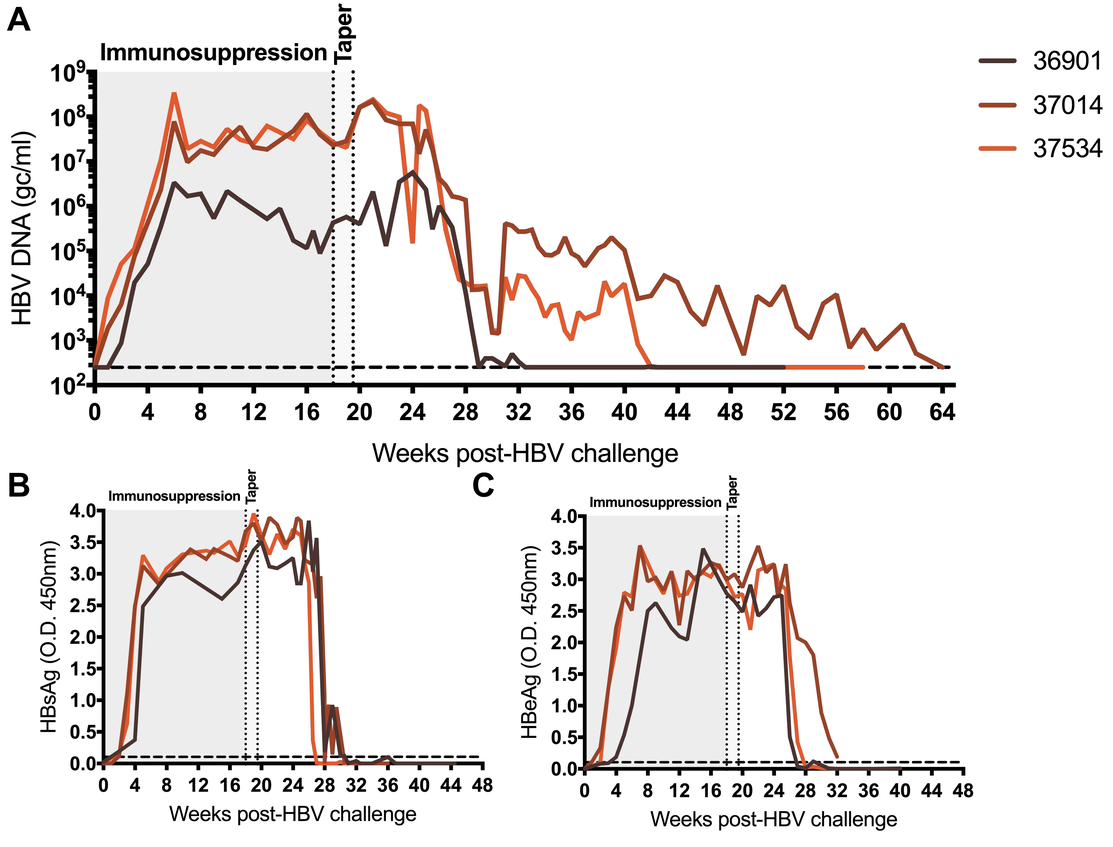


Figure 2. Sustained HBV replication in RM. A) HBV DNA levels in serum, B) HBsAg levels in serum, C) HBeAg levels in serum.

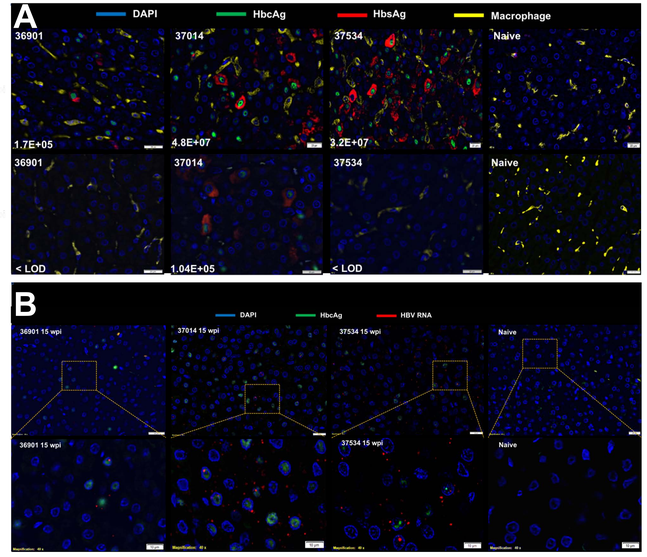


Figure 3. HBV replication in RM hepatocytes *in vivo*. A) Assessment of HBV core and surface expression in RM livers, B) HBV RNA detection by RNAScope.

CONCLUSIONS

Our data indicate that RM can be chronically infected with HBV and represent a promising model for the testing of emerging HBV curative therapies.

ADDITIONAL KEY INFORMATION

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