UKE Paper of the Month June 2011

Gastroenterology, 2011, Jun; 140(7):2074-2083 (PMID:21376046)

Hepatitis B virus limits response of human hepatocytes to interferon-α in chimeric mice

Lütgehetmann M, Bornscheuer T, Volz T, Allweiss L, Bockmann J-H, Pollok JM, Lohse AW, Petersen J, Dandri M

Abstract: Background & Aims: Interferon (IFN)-alpha therapy is not effective for most patients with chronic hepatitis B virus (HBV) infection, for unclear reasons. We investigated whether HBV infection reduced IFN-alpha–mediated induction of antiviral defence mechanisms in human hepatocytes. Methods: Human hepatocytes were injected into severe combined immune deficient mice (SCID/beige) that expressed transgenic urokinase plasminogen activator under control of the albumin promoter. Some mice were infected with HBV; infected and uninfected mice were given injections of human IFN-alpha. Changes in viral DNA and expression of human interferon-stimulated genes (ISGs) were measured by real-time PCR, using human-specific primers, and by immunohistochemistry. Results: Median HBV viremia (0.8log) and intrahepatic loads of HBV RNA decreased 3-fold by 8 and 12 h after each injection of IFN-alpha, but then increased within 24 h. IFN-alpha activated expression of human ISGs and nuclear translocation of STAT-1 in human hepatocytes that repopulated the livers of uninfected mice. Although baseline levels of human ISGs were slightly increased in HBV-infected mice, compared with uninfected mice, IFN-alpha failed to increase expression of the ISGs OAS-1, MxA, MyD88, and TAP-1 (which regulates antigen presentation) in HBV-infected mice. Remarkably, IFN-alpha did not induce nuclear translocation of STAT-1 in HBV-infected human hepatocytes. Administration of the nucleoside analogue entecavir (for 20 days) suppressed HBV replication but did not restore responsiveness to IFN-alpha. Conclusions: HBV prevents induction of IFN-alpha signaling by inhibiting nuclear translocation of STAT-1; this can interfere with transcription of ISGs in human hepatocytes. These effects of HBV might contribute to the limited effectiveness of endogenous and therapeutic IFN-alpha in patients and promote viral persistence.

Statement: Mice harbouring livers partially reconstituted with human hepatocytes offer unique possibilities to perform infection studies with hepatitis viruses. Using this system we could show for the first time that hepatitis B virus is able to interfere with pathways of the innate immune response by blocking the induction of specific interferon regulated genes as well as genes involved in the antigen presentation process. Our work reveals new aspects of the virus-host interactions, which have important implications for the understanding of the molecular mechanisms of HBV persistence and limited responsiveness to interferon treatment.

This work was performed at the I. Department of Internal Medicine in the group of PD Dr. Maura Dandri (Viral Hepatitis) and was supported by DFG grants (SFB841) to MD. Dr. Lütgehetmann and T. Bornscheuer contributed equally to this work, which was also part of the Doctoral thesis of Med. Stud. T.B., who attended the research training group (GRK-Inflammation & Regeneration). The work is also the result of fruitful collaborations within the UKE, in particular with the Department of Hepatobiliary Surgery. Maura Dandri´s group is interested in the molecular mechanisms responsible for the persistence of HBV infection.