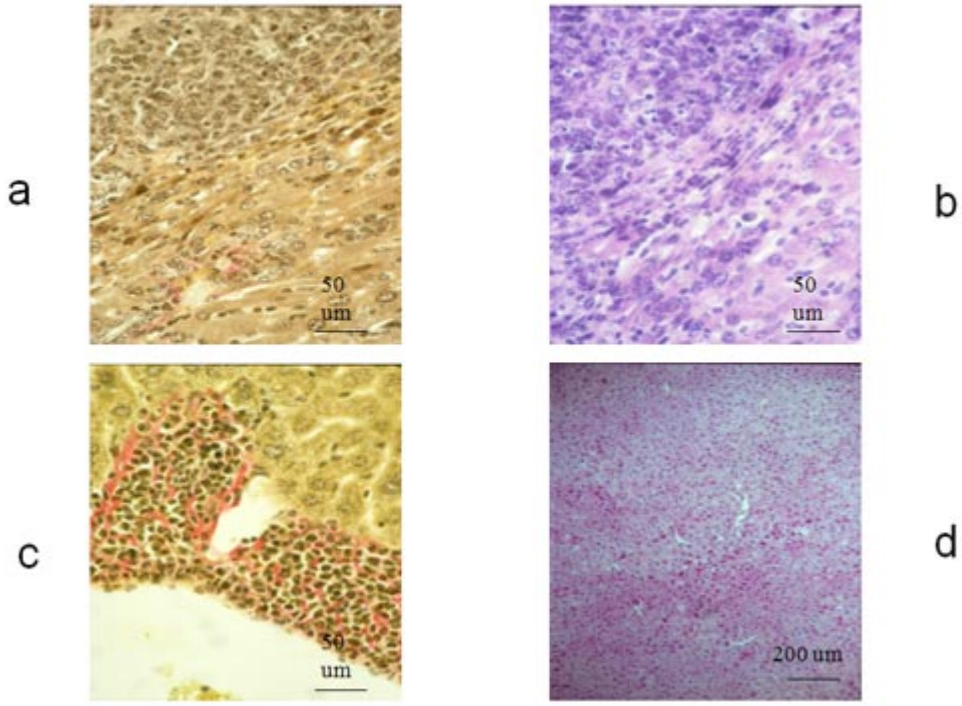
Virus-associated pathogenesis

Both HBV and HCV can cause chronic inflammation of the liver, cirrhosis, and hepatocellular carcinoma (HCC). A variety of different factors contribute to the development of HBV- and HCV-associated HCC. Interestingly, deregulation of intracellular signal transduction cascades might be one the factors that can be causative for virus-associated carcinogenesis.
The HBV genome encodes two types of proteins that can be regulators of intracellular signal transduction pathways: The HBx protein and the PreS2 activators LHBs and MHBst1. Recently, we could demonstrate that both PreS2 activators bind to and activate PKCa/b resulting in the subsequent activation of the c-Raf/MEK/Erk signal transduction cascade. Further experiments based on transgenic mice that express the PreS2 activator MHBst1 in the liver demonstrated that the HBV regulatory proteins exert a tumor promoter-like function.



Increased incidence of liver tumors in transgenics producing the HBV-derived regulatory protein (PreS2/MHBst76) Van Gieson-stained (a, c) and HE-stained (b, d) sections of liver tissue from 15 month old transgenic mice (a-c) or a 4 month old transgenic mouse (d) Source: PEI
With respect to HCV, we recently identified c-Raf as a novel binding partner of NS5A. Consequently, c-Raf is an integral part of the replicon complex. Furthermore, we could demonstrate that inhibition of c-Raf blocks HCV replication. Currently, the underlying mechanism that eventually mediates the inhibition of HCV replication is being studied. Specifically, we are investigating the effects of c-Raf inhibition on the phosphorylation pattern of NS5A, on the composition of the replicon complex, the formation of lipid droplets and on viral morphogenesis. Regarding the morphogenesis, we could recently identify via proteome analyses two proteins that are associated with intracellular vesicle transport to be deregulated in HCV replicating cells. In this context we are aiming at characterizing the specific role of these proteins in HCV morphogenesis and secretion.
In addition, HBV is able to activate the transcription factor Nrf2 (Schaedler et al., 2010). Nrf2 is involved in the control of a variety of cytoprotective genes harboring an ARE (antioxidative response element) in their promoter region. Among these are the genes encoding for NQO1, GPx, HO-1, and subunits of the immune proteasome. Moreover, Nrf2 plays a crucial role during liver regeneration (Beyer et al., 2008). Against this backdrop, we are aiming at characterizing

the specific mechanism of HBV-dependent activation of Nrf2 and the relevance of the Nrf2 target genes for virus-associated pathogenesis. In particular, the relevance of a potential HBV-dependent modulation of the antigen-processing activity of the immune proteasome by Nrf2, and thus for HBV-associated “immune pathogenesis”, is being studied.
With respect to HCV, the viral core protein and the nonstructural protein 5A (NS5A) are known to act as regulators of intracellular signal transduction cascades. We could recently demonstrate that NS5A binds to c-Raf, resulting in an impaired signal transduction to MEK (Burckstummer et al., 2006, Himmelsbach et al., 2009; Sauter et al., 2009). Moreover, NS5A can interfere with interferon α/β-dependent signal transduction cascades. From that background, we are studying the relevance of NS5A for virus-associated pathogenesis using a NS5A transgenic mouse model developed in our lab (Kriegs et al., 2009). In particular, we are analyzing the effects of NS5A on liver regeneration. Moreover, the effect of NS5A on antigen processing and on the innate and adaptive immune response and the underlying molecular mechanisms is currently being investigated.
In parallel to our work on HBV we are investigating the interaction of HCV with Nrf2 (Carvajal-Yepes et al., 2011). Here we focus on the identification of signal cascades that mediate the interference of HCV with Nrf2 and we are studying the relevance of the deregulation of ARE-dependent genes for HCV-associated pathogenesis.