Effect of HCV infection on the mRNA expression of drug transporters and cytochrome P450 enzymes in chimeric mice with humanized liver

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Purpose.
Hepatitis C virus (HCV) infection is the leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma. Chimeric mice with humanized liver, including PXB mice, are a readily available model which is permissive to the in vivo infection of HCV. The mRNA expression of pharmacokinetics-related genes, i.e. transporters and enzymes, has not been described in these mice under HCV-infected conditions. The aim of the present study is to investigate the effect of HCV infection on the mRNA expression of drug transporters and metabolizing enzymes in the liver of PXB mice.

Methods.
PXB mice were infected with HCV genotype 1b. A separate group of non-infected mice served as controls. HCV serum titers were measured four weeks post infection, and the livers harvested at 17-19 weeks of age. Total RNA was isolated, and the mRNA expression of human ABC transporters (P-gp, MDR3, BSEP, MRP1-4, and BCRP), SLC transporters (NTCP, OCT1, OAT2, OATP1B1, OATP1B3, and OATP2B1), and cytochrome P450 enzymes (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5), as well as key genes associated with the interferon-signaling pathways (IRF9, MX1, OAS1-3, OASL, STAT1, and TLR3), were determined by TaqMan analysis. The expression was normalized to GAPDH expression, and statistically compared between two groups.

Results.
The HCV titer in infected mice was $4.26 \times 10^7 \pm 1.08 \times 10^7$, which confirmed the successful infection of HCV in PXB mice. MX1, OAS2, OAS3, OASL, and STAT1 showed an increase in expression in HCV-infected mice when compared to controls, suggesting that the interferon-signaling pathways were activated in these animals, which is similar to the observation in HCV-infected patients. There was little marked difference in the mRNA expression of drug transporters and cytochrome enzymes between the HCV-infected and non-infected groups with the exception of statistically significantly higher expression of MRP4 and OATP2B1 and lower expression of OCT1 and CYP2D6 in infected mice.

Conclusion.
The mRNA expression of pharmacokinetics-related genes was in general unaffected by HCV infection in PXB mice. These data suggest that in PXB mice the potential for HCV infection to alter the pharmacokinetics of small molecule antiviral therapies is small.