Investigating the Effects of the Nuclear Receptor PXR-KI in the Regulation of Bile Acid Homeostasis, Hepatic functions, and the Development of MASH in Mouse Models

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Metabolic-associated fatty liver disease (MAFLD) is the most common chronic liver disease characterized by hepatic steatosis. MAFLD can progress to metabolic associated steatohepatitis (MASH), fibrosis, cirrhosis, and even hepatocellular carcinoma. MAFLD affects 30% of the world's population, especially prevalent in countries like the United States. Pregnane X receptor (PXR) is a ligand activated transcription factor that is highly expressed in the liver and intestine of humans. PXR regulates the expression of genes involved in phase 1 and 2 drug metabolizing enzymes and transporters. PXR plays an important role in regulating glucose, lipid, cholesterol, and bile acid metabolism, making it an interesting target for therapeutics for MASH. PXR activation has been shown to induce lipid and triglyceride accumulation in mouse liver. We hypothesize that blocking of the phosphorylation site of PXR Serine 347 to Alanine (S347A KI) can modify PXR activity, increase bile acid activity, promote liver steatosis, and inflammation, potentially intensifying the development of MASH. To investigate the role of the Ser347 phosphorylation site in the development of MASH, six-week-old male wild-type (WT), and PXR-KI mice, both on the C57BL/6J genetic background, were fed either a chow diet, or HFD diet (40 Kcal% palm oil fat, 20 kcal% fructose, and 2% cholesterol) for 16 weeks. Samples from liver, intestine, blood, and gallbladder were collected to run qPCR to quantify gene expression. We found that PXR-KI mice on HFD demonstrated higher relative mRNA levels of hepatic metabolism-related genes such as Srebp-1c, Cd36, Fasn, and Cyp4a10. Similarly, the PXR-KI mice on HFD showed an increase in relative mRNA levels of hepatic inflammation- and fibrosis-related genes: Lcn2, Timp1, and Col1a1. In conclusion, the results suggest that blocking the Ser347 phosphorylation site of PXR in mice is associated with more liver damage during MASH development, indicating the importance of this site to regulate PXR functions in maintaining lipid and inflammation homeostasis. Moving forward with this project, other techniques will be used to confirm targets related to inflammation and steatosis in MASH. Funding: NIH R25ES20721 and the ASPET SURF Program.