Determining the Tissue-Specific Role of FXR in Inflammation Using Diet-Induced NASH Mouse Models

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Non-alcoholic fatty liver disease (NAFLD) is a spectrum of diseases featured with over-accumulation of fat (steatosis) in the liver and it is estimated that over one third of the US population is affected by this disease. Non-alcoholic Steatohepatitis (NASH) is a more serious form of NAFLD, consisting of steatosis, inflammation, and fibrosis. Currently, there exists no FDA-approved treatment for NASH. The farnesoid X receptor (FXR) has been identified as a therapeutic target for NASH due to its ability to decrease steatosis, inflammation, and fibrosis. Synthetic ligands of FXR have been developed for therapeutic purposes but showed severe side effects as they are whole-body FXR activators; therefore, it is important to understand the tissue-specific functions of FXR in the development of NASH to design efficacious and safe therapeutics. To understand the underlying mechanisms of FXR tissue-specificity, 6-8 week old female mice in 4 genotypes: wild-type (WT, C57BL/6J, Fxr+/+), liver FXR knockout (KO) ((Fxrfloxed/floxed, Albumin Cre (+), FXR LKO), intestinal FXR KO (Fxrfloxed/floxed, Villin Cre (+), FXR IKO), and whole-body FXR KO (WB FXR KO, Fxr-/-), were fed either a low-fat control diet (CTL) or a NASH “Fast Food” (FF) diet (Western diet with 21% milk fat, 1.25% cholesterol, and 34% sucrose) for 16 weeks. Liver samples were collected for histology and sections were stained with F4/80, a macrophage marker to indirectly measure inflammation, to distinguish differences in macrophage abundance among groups. The FXR LKO mice fed the FF diet displayed significantly increased F4/80 staining compared to the FXR IKO group. The FXR LKO on the CTL diet showed a trending increase compared to the FXR IKO. Both the FXR KO and FXR IKO groups displayed positive staining for F4/80 at levels comparable to the WT regardless of the diet. These data suggest that FXR LKO is more critical to suppressing hepatic inflammation compared to FXR IKO. As a result, targeting hepatic FXR opposed to intestinal FXR may be more beneficial to treat liver inflammation present during NASH. Funding: ASPET SURF Program, NIH R01GM135258-01A1S1, GM135258, ES029258, DK122725 and the VA BX002741.