Effects of Deficiency of FXR and LCN2 on Liver Injury in a High-Fat Diet-Induced Mouse NASH Model

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Farnesoid X receptor (FXR), known for maintaining bile acid homeostasis, regulates synthesis and transport. Studies show FXR activation is protective against liver inflammation and demonstrates FXR's role in adaptive and innate immunity during chronic inflammation. FXR knock-out (KO) mice are more susceptible to non-alcoholic steatohepatitis (NASH). NASH, an aggressive form of non-alcoholic fatty liver disease (NAFLD), is characterized by inflammation and steatosis. Around 30-40% of adults in the United States have NAFLD, and about 5-10% of those progress to NASH. This progression is not well understood. FXR is downregulated by inflammation, and expression is decreased in NASH patients. Recently, FXR has been shown to regulate acute phase proteins (APPs) that are mainly produced by hepatocytes. APPs are produced in response to acute phase response (APR), a systemic reaction to tissue injury or infection. Lipocalins are a family of proteins known to transport small hydrophobic molecules. Specifically, Lcn2 is defined as an APP that is up-regulated in response to cellular stress, including cell injury or inflammation. Lcn2 is overexpressed in livers of patients with NASH and may be protective against the progression of NASH. The aim of this study was to assess NAFLD and liver injury in mice lacking both hepatic FXR and Lcn2. In this study, we fed wild type (WT), FXRhep-/-, LCN2hep-/-, and LCN2/FXRhep-/- (DKO) mice a control diet (10% kCal) and high-fat diet (60% kCal) for 1, 3, and 6 months. DKO mice had worsened liver injury by 6 months revealed by elevated serum ALT (290.08 IU/L), total bile acid (94.462 µmol/L), and cholesterol levels (296.59 mg/dL). Mcp-1 expression increased ten-fold by 3 months in DKO mice; further showing the additive effect of FXR and APR in progression of liver injury. FXR and Lcn2 deletion worsened NASH phenotype; therefore, we propose that FXR and LCN2 are protective against NASH progression. Supported by NIH R25ES020721, R21ES029258, P30ES005022 and BX002741.