

Characterization of Liver and Lung Injury and Inflammation in a High Fat Diet Mouse Model of Non-alcoholic Steatohepatitis

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Non-alcoholic fatty liver disease (NAFLD) is a chronic liver condition that affects millions of individuals in the United States, of which ~20% of cases progress to non-alcoholic steatohepatitis (NASH). NASH is characterized by macrovascular steatosis and persistent inflammation, which can lead to fibrosis. Emerging evidence suggests potential effects of NAFLD and NASH on the development of pulmonary pathologies, but the interplay between the liver and the lung remains largely unexplored. In the current study, we assessed the impact of NASH on lung inflammation and fibrosis using a genetically modified mouse model lacking hepatic farnesoid X-receptor (FXR), a nuclear receptor involved in bile acid and lipid homeostasis, and lipocalin-2 (Lcn2), an acute phase protein upregulated in response to stress. Both FXR and Lcn2 are also involved in regulating innate immune responses. Wild type (WT) and Lcn2 hep^{-/-}/Fxrhep^{-/-} (DKO) mice were fed control (10% kCal) or high-fat (HFD) (60% kCal) diets. Liver, lung, serum, and bronchoalveolar lavage (BAL) fluid were collected after 6 months of feeding. Histopathologic evaluation of livers and elevated liver enzymes (ALT, AST, & ALP) from HFD-fed mice confirmed the development of NASH. In the lung, we observed histopathologic alterations including inflammatory cell infiltration, lipid-laden macrophages, septal damage, and epithelial thickening; these alterations were most notable in HFD-fed DKO mice. Flow cytometric analysis also revealed increases in BAL inflammatory macrophage populations in HFD-fed WT mice. These results characterize an association of pulmonary complications during simple steatosis to NASH transition, suggesting lung-liver crosstalk. Supported by NIH R25ES020721, R21ES029258, P30ES005022, and R01ES004738.

