

The Development of Pulmonary Inflammation and Injury in a Mouse Model of Non-Alcoholic Steatohepatitis

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Non-alcoholic fatty liver disease (NAFLD) is a chronic liver condition that affects 42 million individuals in the United States, of which ~20% progress to non-alcoholic steatohepatitis (NASH). NASH is characterized by the accumulation of fat in the liver and persistent inflammation which can progress to fibrosis. Emerging evidence suggests potential effects of NAFLD and NASH on the development of pathologies in the respiratory tract, 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), Lcn2^{hep-/-}, and Lcn2/Fxr^{hep-/-} (DKO) mice were fed control (10% kCal) or high-fat (HF) (60% kCal) diets (n=5-10 mice/group). Liver, lung, serum, and bronchoalveolar lavage (BAL) fluid were collected after 1, 3, and 6 months of feeding. Histopathologic evaluation of livers 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 at 6 months; these alterations were most notable in HFD-fed DKO mice. Additionally, BAL cell counts were increased in HFD-fed DKO mice at 6 months when compared to HFD-fed WT mice, indicating lung inflammation and injury. Further analysis of expression levels of genes related to lung inflammation and lipid metabolism may reveal mechanisms underlying lung injury following the development of NASH. *Supported by NIH Grants ES029258, ES005022, and ES004738.*