Human Macrophage derived Myeloperoxidase exacerbates Nonalcoholic steatohepatitis (NASH) in Diet-induced Obesity

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Background: Hepatic infiltration of polymorphonuclear leukocytes (PMNs) is a key driver of pathogenesis in non-alcoholic steatohepatitis (NASH). Lipotoxicity arising from elevated free fatty acids in NASH is postulated to advance PMN activation and recruitment. Myeloperoxidase (MPO), a PMN-derived enzyme mechanistically linked to oxidative stress (ROS) in inflammation, may contribute to this feedback. Chlorinated fatty acids (2-CIFAs) are an MPO by-product produced when HOCl targets plasmalogen phospholipids. 2-CIFAs induce PMN activation, adhesion and ROS mediated cellular damage. In human patients, a strong positive correlation between MPO expressing cells and severity of NASH has been observed. However, mouse macrophages lack MPO and this is a critical limitation of current models. As a result, the contribution of MPO to NASH remains poorly understood.

Methods: To investigate the role of MPO in hepatosis C57Bl/6J mice expressing macrophage transgenic human MPO (hMPOTg) were fed a 40% high fat (HF) diet for 10 weeks. At the end of the study biomarkers of hepatocellular damage and PMN infiltration were measured. Alterations in lipid species were detected using electrospray ionization tandem mass spectrometry (ESI-MS/MS) lipidomics in order to elucidate contributing lipids to NASH.

Results: Here we show hMPOTg is associated with significant alteration in the hepatic lipidome, increased infiltration of PMNs, levels of MPO lipid by-products and exacerbated hepatic steatosis. HF fed hMPOTg mice showed greater weight gain and hepatomegaly. Increased infiltration of PMN in hMPOTg HF livers was supported by immunohistochemistry and PCR analysis of PMN biomarkers. Significantly higher triglyceride levels were detected in hMPOTg HF fed plasma and livers. Major hepatic lipid species of cholesterol esters, phosphatidylcholine, and phosphatidylserine were also significantly altered. Systemic pro-inflammatory 2-CIFA levels were increased in HF fed hMPOTg.

Conclusion: Together, our results highlight the significant contribution of hMPO to hepatic lipid homeostasis. MPO is currently exploited as a biomarker and therapeutic target in cardiovascular disease. Expanding our understanding of MPO may extend the benefits of similar therapeutic strategies to patients suffering from NASH and metabolic syndrome.