High fat diet induced lymphatic changes may play a role in promoting fatty liver disease

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Background: Non-alcoholic fatty liver disease (NAFLD), the hepatic manifestation of metabolic syndrome, is the leading cause of liver disease worldwide. NAFLD is characterised by abnormal hepatocyte lipid accumulation, inflammatory and metabolic changes, and insulin resistance (IR). These changes are similar to those observed in visceral adipose tissue (VAT) in obesity. Recently our group found that the lymphatic vessels flowing through the VAT undergo marked changes in response to chronic high fat diet (HFD) feeding. As obesity progresses, the lymphatic collecting vessels in VAT become progressively branched, tangled and 'leaky' around the new branches. The lymph fluid within the vessels is rich in lipids, inflammatory mediators and cells that promote lymphangiogenesis and also adipose expansion, inflammatory and metabolic changes that promoted IR. In the current study, we aimed to determine whether similar changes in lymph vascular structure, function and composition occur within the liver to promote NAFLD.

Methods: C57BL/6 mice and SD rats were fed HFD or chow fat diet (CFD) for 15-32 weeks and 7-10 weeks, respectively. Body weight and oral glucose tolerance were determined. Mice were euthanised via intraperitoneal injection of pentobarbitone and the liver was collected for immunofluorescence analysis of lymph vessel structure. Blood, hepatic and mesenteric lymph were collected from euthanised or unconscious animals maintained with inhaled isoflurane (1-3%), for blood or lymph, respectively, and the composition of metabolic and immune markers assessed via colorimetry, ELISA and flow cytometry. Collected lymph was also used to treat lymphatic endothelial cells (LECs) and primary hepatocytes in vitro to determine impact on LEC migration and hepatocyte metabolism.

Results: HFD fed mice gained more weight, displayed glucose intolerance and had fatty livers with dilated and disrupted lymphatic vessels, compared to CFD fed mice. The concentration of lipids, inflammatory mediators and immune cells in liver and mesenteric lymph fluid were increased in HFD fed rats. Liver and mesenteric lymph, particularly from HFD fed rodents, increased LEC migration but not proliferation consistent with the finding that the mesenteric lymphatic vessels were branched and hyperpermeable in vivo. Mesenteric and liver lymph fluid were found to mix through interconnecting branches in vivo suggesting that backflow of mesenteric lymph to the liver is possible. Mesenteric but not liver lymph fluid significantly altered hepatocyte metabolism (increased fatty acid uptake, oxidation and lipid accumulation).

Conclusions: HFD feeding promoted weight gain, fatty liver, glucose intolerance and remodelling of the liver and mesenteric lymphatic vasculature which altered lymph access to hepatocytes in the liver. Liver lymph had little impact on hepatocyte lipid metabolism. In contrast, HFD mesenteric lymph access to the liver may promote lipid accumulation and metabolic changes characteristic of NAFLD. Future work will further define the mechanisms driving lymphatic changes in response to HFD and the impact of lymphatic changes on NAFLD progression.