The impact of intestinal lymph extravasation on adipose tissue function and whole body insulin resistance

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Insulin resistance (IR) underpins a spectrum of prevalent and inadequately treated cardiometabolic diseases, including type 2 diabetes (T2D). Excess adipose, particularly visceral adipose tissue (VAT) in the abdomen, increases the risk of IR. The expanded VAT releases pathogenic pro-inflammatory and metabolic mediators that promote IR. In diabetic *db/db* mice the permeability of intestinal collecting lymphatic vessels is significantly increased and in transgenic mice with hyperpermeable lymphatics the adipose surrounding lymphatics is expanded. The content of inflammatory and metabolic mediators in intestinal lymph is also increased in response to high fat diet (HFD). Together these findings suggest that increased intestinal lymph extravasation to surrounding VAT promotes VAT expansion. Our aim is to determine whether intestinal lymph access to VAT is increased in HFD thereby promoting VAT expansion and pathogenic changes that promote whole body IR.

Firstly, to confirm that intestinal lymph access to surrounding VAT is increased in response to HFD, the structure and permeability of intestinal lymphatic vessels within VAT was assessed in mice fed standard chow fat diet (CFD) or HFD using immunofluorescence analysis of mesenteric lymph vessels and evans blue lymphangiography, respectively. In mice fed the HFD *vs* the CFD there were increased lymph vessel complexity and the permeability of collecting mesenteric lymph vessels within the VAT. Secondly, metabolomics and FACS analysis revealed increases in >20 lipid species, several pro-inflammatory mediators and CD4+ and CD8+ T cells in the HFD *vs* CFD fed mesenteric lymph. Finally, to determine whether increased lymph access to VAT promotes pathogenic changes in adipocytes with the potential to induce whole body IR, mesenteric lymph collected from the rats fed CFD *vs* HFD was used to treat 3T3-L1 adipocytes and explore the impact on adipocyte function. Lymph, particularly HFD fed lymph enhanced adipocyte adipogenesis (*PPARγ, leptin, C/EBPα*), inflammation (*IL-6*), lipogenesis (*Ap2*, triglyceride), and lipolysis (*ATGL, HSL, FFA*).

In conclusion, intestinal lymph access to surrounding VAT is enhanced in response to HFD and increased lymph exposure to adipocytes, particularly pro-inflammatory HFD fed lymph, promotes functional changes in adipocytes consistent with the changes that promote adipose expansion and IR *in vivo*. These studies provide evidence that intestinal lymph access to VAT is increased in HFD thereby promoting VAT expansion and pathogenic changes that promote whole body IR. These studies advance the fundamental understanding of the pathogenic drivers of IR. Subsequent studies will probe the potential to attenuate pathogenic changes in VAT and thereby treat whole-body IR by modulating lymph content and/or lymph access to VAT.