

## Intestinal lymphatic transport of lipids and drugs are promoted by systemic and dietary triglyceride: implications for health and disease

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The most well described transport route for dietary and endogenous lipids from the intestine involves assembly into lipoproteins and transport to the systemic circulation *via* the intestinal lymphatic system. However, lipids are also transported from the intestine *via* the mesenteric capillaries and portal vein. As cardiometabolic disease is promoted by excess lipid accumulation in immune and metabolic cells, we examined the hypotheses that: i) alterations in intestinal lipid partitioning (lymph *vs* portal vein) in response to increased systemic plasma and dietary lipid levels modify lipid accumulation patterns in immune-metabolic cells, ii) cardiometabolic disease modifying drugs can be delivered to immune-metabolic cell targets *via* integration in intestinal lymph transport pathways.

Firstly, the impact of systemic and dietary lipid levels on intestinal lipid partitioning was investigated. Intestinal administration of increasing lipid doses (0-1000 mg/kg oleic acid) (Trevaskis *et al.*, 2013) and high fat (36% w/v) feeding for 2 weeks led to significant, dose proportional increases in total mass transport and lymphatic partitioning of triglyceride (TG) lipids in mesenteric lymph-cannulated C57BL/6 mice and SD rats. Similarly, acute systemic hyper-triglyceridemia induced *via* IV chylomicron administration increased total transport and lymphatic partitioning of lipids in SD rats (Trevaskis *et al.*, 2011). Increased systemic and dietary lipid thus promoted intestinal lipid partitioning to lymph transport pathways.

Subsequently, the impact of changes to intestinal lipid partitioning on lipid accumulation in immune-metabolic cells was evaluated. To mimic lipid entry into the systemic circulation *via* the portal vein *vs* intestinal lymphatics, SD rats were given, *via* IV administration, <sup>14</sup>C-oleic acid as free fatty acid in plasma or esterified to TG in lymph lipoproteins (Caliph *et al.*, 2013). <sup>14</sup>C-lipid deposition in adipose tissue was significantly increased (1.8 fold at 4h) following entry in lymph lipoproteins whereas deposition in skeletal muscle was significantly increased (2.2 fold at 4h) after entry in the portal vein transport simulation. Liver uptake at 4h was not statistically different. Promotion of intestinal lymphatic lipid transport *via* administration of increasing lipid doses (13-133 mg/kg oleic acid) also stimulated increased accumulation of administered lipids in lymph lymphocytes (5 fold over 6 h) in mesenteric lymph-cannulated SD rats (Trevaskis *et al.*, 2010). Partitioning to lymph lipoprotein transport pathways thus modified lipid accumulation in lymphocytes, adipocytes and skeletal muscle.

Finally, we synthesised biomimetic lipid pro-drugs with immune and metabolic disease modifying drugs (mycophenolic acid (MPA) and aspirin (ASP)) linked at the sn-2 position of a TG backbone. The pro-drugs integrated into intestinal TG hydrolysis, re-synthesis and lipoprotein assembly pathways and substantially increased mesenteric lymph transport of MPA (from 0.14 to 13.4% of dose) and ASP (from 1.2 to 6.5% of dose) following intestinal administration to SD rats. Importantly, the prodrugs enhanced MPA delivery to lymphocytes and lymph nodes (10-100 fold at 1-8h post-dose), and ASP delivery to lymph nodes and adipose depots (~3 fold at 4h post-dose). MPA and ASP delivery to lymphocytes, lymph nodes and adipocytes was thus promoted by partitioning into intestinal lymph transport pathways.

Alterations in intestinal lipid partitioning (lymph *vs* portal vein) in response to increased systemic and dietary lipid loads thus modified the patterns of lipid accumulation in immune-metabolic cells in rodents. Integration of drugs into intestinal lymph transport pathways *via* administration as biomimetic lipid pro-drugs also facilitated targeted delivery to specific immune-metabolic cells. These results suggest the potential utility in cardiometabolic disease treatment of pharmaceutical strategies and diets that modify intestinal partitioning of lipids and drugs.

Note anaesthesia used during studies: Rats received 40, 10 and 0.4 mg/kg ketamine, xylazine and acepromazine then 40 and 0.4 mg/kg ketamine and acepromazine SC as required. Mice received 133 and 10 mg/kg ketamine and xylazine then 40 and 3 mg/kg ketamine and xylazine SC as required.

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