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Cardiovascular disease is correlated with hypertriglyceridemia. Increased circulating triglycerides result from greater production, reduced clearance from bloodstream, or both. Lipoprotein lipase (LpL) is the enzyme responsible for plasma triglyceride clearance. The aim of this proposal is to determine the role of LpL in adipose tissue in triglyceride uptake and development of inflammation. We have created an adipose tissue specific LpL knockout mouse (ATLO). ATLO mice have >80% deletion of LpL in both brown and white adipose tissues and show hypertriglyceridemia associated with defective chylomicron lipid uptake into brown adipose. The white adipose shows normal morphology and function. In preliminary experiments, we compared ATLO mice with the total body LpL knockout mice rescued by muscle LpL overexpression (MCK-LpL/L0). Fatty acid composition of MCK-LpL/L0 but not ATLO, white adipose tissue suggests enhanced de novo lipogenesis; greater concentration of saturated fatty acids. In contrast, both ATLO and MCK-LpL/L0 brown adipose had reduced proportion of essential fatty acids. So the importance of LpL in brown and white adipocytes differs. To explain the development of white adipose tissue in ATLO, we hypothesize that adipocyte loss of LpL is compensated by adipose tissue macrophage LpL. To test this, I plan to do bone marrow transplants to create ATLO mice with macrophage LpL deletion and MCK-LpL/L0 mice with replacement of macrophage LpL. If the hypothesis is correct, macrophage LpL replenished MCK-LpL/L0 mice will have restored fatty acid composition and fatty acid synthase expression in adipose tissue. The ATLO mice transplanted with MCK-LpL/L0 bone marrow will show defective dietary fatty acids in white adipose and will be resistant to diet induced obesity. We also observed that the MCK-LpL/L0 mice have high macrophage infiltration in their white adipose and express high levels of TNFa. We hypothesize that these macrophages are different from those accumulated during obesity and propose to isolate them and characterize their polarization. We plan to analyze the ceramide and diacylglycerol content of white and brown adipose tissues in chow and high fat diet and compare them to control mice to decipher if the mechanism for insulin resistance is connected to inflammation or to the lipid composition of the adipose tissue. These studies will provide new information on the roles of adipose macrophages in inflammation and cardiovascular risk.