Adipose Triglyceride Lipase Deficiency Strongly Affects Macrophage Morphology and Function and Significantly Reduces Atherosclerosis in LDLR-deficient Mice

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In adipose and non-adipose tissues adipose triglyceride lipase (ATGL) was shown to be the rate-limiting enzyme for the hydrolysis of triglycerides (TG). The aim of this study was to investigate whether ATGL is also expressed in murine macrophages and foam cells and to examine the impact of ATGL deficiency on macrophage morphology, function, and atherogenesis. We found that ATGL is highly expressed in macrophages and foam cells. Macrophages deficient in ATGL have significantly reduced TG hydrolase activity resulting in increased TG concentrations, unchanged cholesteryl ester and free cholesterol levels, whereas unesterified fatty acid (FA) concentrations were markedly decreased. Confocal microscopy after nile red staining revealed that ATGL-deficient macrophages accumulate lipids in lipid droplets even without the addition of exogenous modified lipoproteins. Although the uptake of FA was significantly increased in ATGL-deficient macrophages the intracellular unesterified FA content was decreased. We found a substantial amount of FA which are taken up by ATGL-deficient macrophages to be incorporated into TG. Thus we hypothesize that FA are first converted to TG (and CE) and stored in lipid droplets. ATGL and neutral cholesteryl ester hydrolase(s) are then required for FA release. The reduced availability of FA for energy production significantly reduced the phagocytotic potency of ATGL-deficient macrophages. To elucidate the effect of TG accumulation in macrophages *in vivo*, we performed bone marrow transplantation of ATGL-deficient bone marrow into low density lipoprotein receptor (LDLR)-deficient mice, which resulted in a significant 42% reduction in the lesion area of high-fat, high-cholesterol diet-induced atherosclerosis. We conclude that TG accumulation in macrophages caused by ATGL deficiency is anti-atherosclerotic and that macrophage ATGL might be a potential novel target to attenuate atherogenesis.