Macrophage ATP-citrate lyase (ACLY) deficiency affects cellular cholesterol homeostasis and stabilizes atherosclerotic lesions

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Background and objective

ATP-citrate lyase (ACLY) is a cytosolic enzyme and cleaves citrate in to oxaloacetate and acetyl-CoA. Cytosolic acetyl-CoA synthesized by ACLY serves several metabolic pathways, including the *de novo* synthesis of fatty acids and cholesterol. Specific inhibition of ACLY in hepatocytes has recently emerged as an attractive therapeutic target to lower lipid levels in hypercholesteremic patients. Additionally, ACLY was previously linked to macrophage activation. Here, using a novel myeloid-specific genetic knockdown model of ACLY we investigated the role of this enzyme in macrophages in atherosclerosis.

Experimental setup

To asses the role of macrophage ACLY in atherosclerosis, we crossed *Acly^{fl/fl}* mice with mice expressing Cre under control of the myeloid cell-specific gene encoding LysM (*Lyz2-Cre*) to breed mice with a myeloid-specific deletion of *Acly* (*Acly^{fl/fl} * Lyz2-Cre*, called *Acly^{M-KO}* here). Next, we transplanted LDL-receptor deficient mice with bone marrow from either control or *Acly^{M-KO}* mice and fed them a high-fat diet (0,15% cholesterol, 15% fat) for 10 weeks.

Myeloid deficiency of *Acly* stabilizes atherosclerosis

Loss of *Acly* deregulates cholesterol biosynthesis and blunts LXR-mediated gene expression

Deletion of *Acly* generates hyperinflammatory macrophages

Macrophages lacking *Acly* are more apoptotic and demonstrate improved efferocytosis