SCAP deficiency drives classical adipose tissue macrophages via downregulation of Ch25H in obesity

Seung-Soon Im, PhD

Department of Physiology, Keimyung University School of Medicine, Daegu 42601 South Korea

**Abstract**

Sterol regulatory element binding proteins (SREBPs) are key transcriptional regulatory proteins that sense the intracellular lipid environment and modulate expression of key genes of fatty acid and cholesterol metabolism to maintain lipid homeostasis. And SREBP cleavage-associating protein (SCAP) is a key regulator of SREBP processing by translocating SREBPs from the endoplasmic reticulum to the Golgi apparatus. Although SREBP regulates lipid metabolism in metabolic tissues such as the liver and muscle, function of SREBP-1a in macrophages and the effect of macrophage-specific SREBP-1a deficiency in adipose tissue macrophages (ATMs) of metabolic diseases are not completely understood. Here, we show that TLR4-dependent stimulation of macrophage phagocytosis requires mTORC1-directed SREBP-1a-dependent lipid synthesis and the phagocytic defect in macrophages from SREBP-1a-deficient mice results from decreased interaction between membrane lipid rafts and the actin cytoskeleton, presumably due to reduced accumulation of newly synthesized fatty acyl chains within major membrane phospholipids. Moreover, we also demonstrated that fat accumulation increased in high-fat/high-sucrose diet-fed macrophage-specific SCAP knockout (KO) mice due to polarization of classical activated macrophages in adipose tissue. Furthermore, LPS-mediated SREBP-1a activation upregulated Cholesterol 25-hydroxylase (Ch25H) transcription, resulting in increase in 25-hydroxycholesterol (25-HC) production, an endogenous agonist of liver X receptor alpha (LXR), and expression of cholesterol efflux genes, such as those encoding ATP-binding cassette sub-family A1 and ATP-binding cassette sub-family G1. However, SCAP deficiency stimulates M1 macrophage polarization owing to increase in intracellular cholesterol content via suppression of cholesterol efflux by reduction of 25-HC-dependent LXR activation in macrophages. Overall, the activation of SCAP-SREBP-1a complex in macrophages may provide a novel therapeutic strategy that ameliorates obesity by controlling cholesterol homeostasis in ATMs.