Editorial

Adipocyte Membrane Cholesterol Regulates Obesity

Anouk M. la Rose, Venetia Bazioti, Marit Westerterp

The adipose tissue represents the body's largest free cholesterol reservoir.[1] Adipocytes almost exclusively accumulate free cholesterol.[2] During obesity, free cholesterol accumulation in adipocytes can increase ≤≈50% of the total body free cholesterol pool.[1] Free cholesterol accumulation is a balance between cholesterol uptake and efflux pathways mediated by ABCA1 and ABCG1 (ATP-binding cassette transporters A1 and G1), SR-BI (scavenger receptor BI), apoA1 (apolipoprotein A1), and HDL (high-density-lipoproteins).[3–6] In obesity, adipocyte inflammation promotes macrophage infiltration into adipose tissue, amplifying inflammatory responses and leading to insulin resistance.[7] Increased plasma HDL cholesterol levels suppress inflammation and macrophage recruitment in a diet-induced obese mouse model, which was attributed to enhanced cholesterol efflux from adipocytes[5] and macrophages.[8]

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ABCA1 represents a major cholesterol efflux pathway in adipocytes.[3,6] Deletion of *Abca1* in adipocytes of *aP2-CreAbca1$^{fl/fl}$* mice enhances diet-induced obesity and insulin resistance.[9] However, the aP2-Cre promoter also deletes *Abca1* in macrophages[9]; *Abca1*-deficient macrophages are proinflammatory,[10] and therefore, a contribution of macrophages could not be excluded. Using the adipocyte-specific adiponectin-Cre model, in this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Cuffe et al[11] elegantly show that adipocyte *Abca1* impairs diet-induced obesity. Surprisingly, adipocyte *Abca1* deficiency prevented weight gain in a diet-induced obesity model and decreased fat pad weight.[11] Food intake was not affected, and adipocyte *Abca1* deficiency only slightly increased energy expenditure, presumably because of a modest increase in thermogenesis, whereas brown adipose tissue function was unchanged.[11]

Remarkably, adipocyte *Abca1* deficiency resulted in smaller adipocytes with decreased triglyceride accumulation, and increased cholesterol content, particularly in the plasma membrane.[11] Although triglyceride lipolysis in adipocytes was unaffected, triglyceride synthesis was decreased, and this was accompanied by decreased expression of the active (cleaved) form of SREBP-1c (sterol regulatory element binding protein-1c). The authors propose that *Abca1* deficiency enhances endoplasmic reticulum cholesterol content, which inhibits SREBP-1c processing,[12] leading to reduction of its target genes. This includes PPARγ (peroxisome proliferator-activator receptor γ)[11] that stimulates adipocyte differentiation.[13] *Abca1* deficiency thus decreases adipocyte size and triglyceride accumulation by suppression of SREBP-1c and PPARγ expression and their target genes (Figure). Concomitantly, expression of the SREBP-2 target gene *HMG-CoA synthase* was decreased,[11] suggesting decreases in cholesterol biosynthesis, presumably because SREBP-2 processing was impaired in response to cholesterol accumulation.[12]

These observations offer interesting novel insights into adipocyte lipid trafficking and storage. Previous studies have suggested that free cholesterol is redistributed from the plasma membrane to the triglyceride-rich lipid droplets during obesity,[1] associated with SREBP-2 activation and increased cholesterol synthesis.[14] The study by Cuffe et al[11] shows that in the absence of *Abca1*, cholesterol accumulates in the plasma membrane, decreasing cholesterol synthesis, triglyceride-rich droplet formation, and adipocyte differentiation (Figure). These observations also suggest that in addition to its contribution to 15% of plasma HDL cholesterol levels,[3] adipocyte *Abca1* plays a key role in intracellular cholesterol redistribution in adipocytes, which enhances adipocyte differentiation.

These findings[11] are in seeming discrepancy with the increased obesity in *aP2-CreAbca1$^{fl/fl}$* mice.[9] Additional *Abca1* deficiency in macrophages cannot explain this discrepancy because myeloid *Abca1* deficiency does not affect obesity.[15] The authors claim that *Adiponectin-CreAbca1$^{fl/fl}$* mice show a more dramatic accumulation of cholesterol in the plasma membrane than *aP2-CreAbca1$^{fl/fl}$* mice, implying a more efficient adipocyte *Abca1* deletion.[11] Adipocyte *Abca1* deficiency enhanced the formation of lipid rafts, which in contrast to in vitro studies in 3T3L1 adipocytes[5] did not affect adipocyte inflammation. In line with these observations, insulin sensitivity was unaltered.[11] However, *aP2-CreAbca1$^{fl/fl}$* mice showed enhanced adipose tissue inflammation and insulin resistance,[9] suggesting that *Abca1* deficiency in both adipocytes and macrophages promotes this phenotype.

Similar to observations in macrophages,[16] deficiency of *Abca1* in adipocytes led to a compensatory upregulation of *Abcg1*.[9,11] Combined *Abca1/g1* deficiency in macrophages enhanced inflammation and atherogenesis to a greater extent than each of these transporters alone,[17,18] suggesting they have overlapping roles and show mutual compensation. The question is whether this also occurs in adipocytes. Single deficiency of *Abcg1* in adipocytes decreases diet-induced obesity, associated with decreased triglyceride accumulation.[4] Lipid rafts were increased, and sphingomyelin, which relies on ABCG1 for efflux, accumulated. Sphingomyelin inhibited the activity of lipoprotein lipase, decreasing triglyceride

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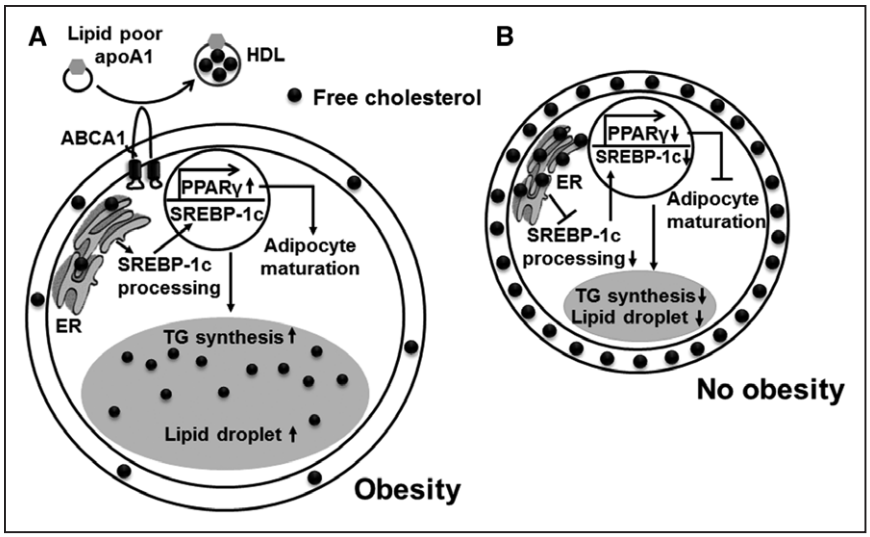

Figure. Model of impaired diet-induced obesity in adipocyte *Abca1* deficiency. **A**, When ABCA1 (ATP-binding cassette transporter A1) is present in adipocytes, cholesterol is effluxed to apoA1 (apolipoprotein A1), contributing to HDL (high-density lipoprotein) formation. Upon high-fat, high-cholesterol diet feeding, triglyceride (TG) accumulates in lipid droplets, leading to obesity. **B**, When ABCA1 is absent in adipocytes, free cholesterol accumulates, particularly in the plasma membrane, and presumably also in the endoplasmic reticulum (ER). SREBP-1c (sterol regulatory element binding protein-1c) processing is inhibited decreasing nuclear SREBP-1c and its target genes, such as PPARγ (peroxisome proliferator-activator receptor γ). As a consequence, adipocyte maturation, TG synthesis, and lipid droplet formation are reduced. These processes impair diet-induced obesity.

storage. Perhaps related to the decreased triglyceride content, intracellular cholesterol levels were decreased in *Abcg1*-deficient adipocytes.[4] It would be of interest to study obesity in an adipocyte *Abca1/g1*-deficient model, particularly in fasting-refeeding studies, or in a cold environment, where lipolysis is stimulated.

Abca1 and *Abcg1* expression in other cell types such as pancreatic β cells also affect adiposity and insulin resistance.[19] Combined *Abca1/g1* deficiency in pancreatic β cells impaired insulin secretion, diverting glucose disposal from skeletal muscle to adipose tissue and increasing adiposity. Pancreatic β-cell *Abca1/g1* deficiency did not affect local insulin resistance, despite enhanced adipose tissue inflammation.[19] Also heterozygous *ABCA1* mutation carriers that exhibit a reduction of HDL cholesterol of ≈50% show impaired insulin secretion by β cells,[20] suggesting that part of these findings translate. Cholesterol efflux pathways thus act in several cell types to modulate obesity and insulin resistance.

Although obesity is associated with decreased HDL cholesterol levels in humans,[21] the study by Cuffe et al provides compelling evidence that membrane cholesterol accumulation in adipocytes impairs obesity.[11] However, when membrane cholesterol accumulation is less dramatic, as observed in *aP2-CreAbca1*$^{fl/fl}$ mice, adipocyte cholesterol accumulation enhances obesity.[9] Additional studies would be warranted to address these discrepancies. Membrane cholesterol accumulation in monocytes and macrophages drives inflammation in mice and humans, contributing to atherogenesis,[18,22,23] and potentially also to insulin resistance, still suggesting that stimulation of HDL-mediated cholesterol efflux may be beneficial.

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Disclosures

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