Caveolin-1 facilitates lipid uptake into endothelium by stabilizing Cd36 at the plasma membrane

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Endothelial cells (ECs) can take up lipids from the circulation through Caveolin-1 (Cav1)-mediated endocytosis. In metabolic disease, fatty acids accumulate in blood plasma, creating a pathological role for ECs as lipid metabolizing cells. ScRNAseq performed on adipose endothelium shows an inverse relationship between Cav1 expression and dietary fat percentage; with increased dietary fat consumption, there is a decrease in Cav1 mRNA. To investigate the link between EC Cav1 and lipids we employed the use of an inducible EC-specific Cav1 knockout mouse ($Cav1^{fl/fl}$/Cdh5-$CreER^{T2+}$). Cav1 genetic deletion from endothelium was induced at 6 weeks, and mice were fed either a normal chow (NC; 5% fat) or high fat diet (HFD; 60% fat) with all mice examined at 20 weeks. Within diet groups, all mice regardless of genotype had comparable weight gain, gonadal fat pad mass, and food consumption. Following induction, electron microscopy was used to confirm presence of caveolae in adipocytes, but not endothelium. The gross vascular network of adipose, from all experimental mice, was visualized using fluorescence microscopy following tissue clearing of whole epididymal fat pads. Deletion of EC Cav1 resulted in increased blood lipids (triglycerides, cholesterol, LDL) independent of diet, suggesting Cav1-mediated endocytosis as a major mechanism of endothelial lipid uptake under normal and pathophysiological conditions. Further investigation determined that intact endothelium of adipose arteries from mice lacking EC Cav1 had decreased cellular lipid content when compared to mice with functional Cav1. Caveolae serve as signaling microdomains in ECs, leading us to question whether the lipid uptake impairments could be due to the failure to enrich proper fatty acid uptake machinery to caveolae decreasing circulating fatty acid uptake. We found Cd36, a known fatty acid translocase, to be located within these Cav1-mediated signaling microdomains via immune staining of an adipose artery *en face* and cellular membrane fractionation. EC Cav1 stabilizes Cd36 at the plasma membrane and with loss of Cav1, Cd36 gets recycled into the endosomal network. The decreased localization of Cd36 at the plasma membrane impairs endothelial lipid uptake and increases plasma lipids as seen in the EC Cav1 deficient mice. This work provides initial evidence for the unique metabolic roles of endothelial Cav1 during periods of homeostasis and high lipid circulation.

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