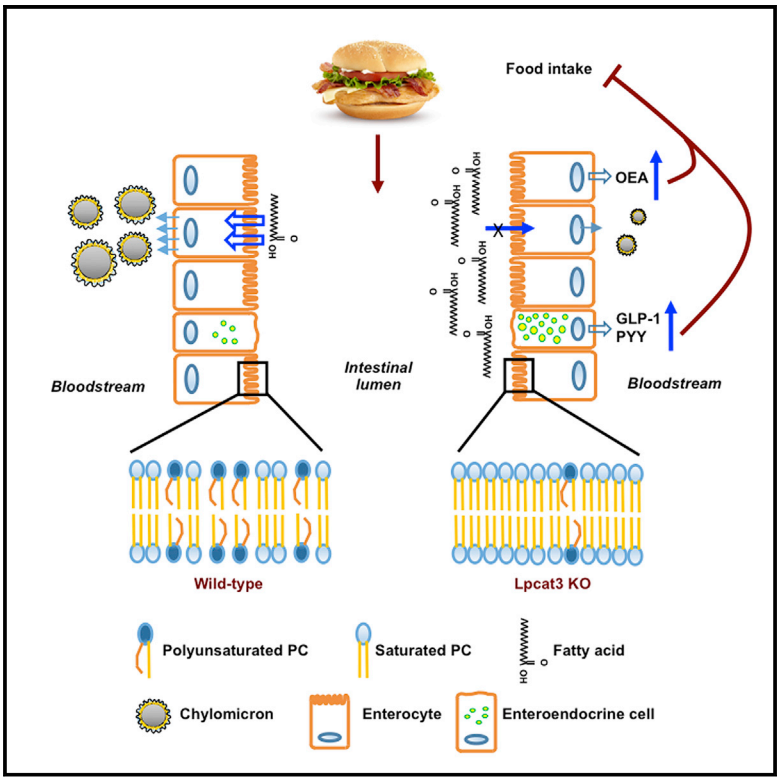
Article

Cell Metabolism

Intestinal Phospholipid Remodeling Is Required for Dietary-Lipid Uptake and Survival on a High-Fat Diet

Graphical Abstract



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In Brief

Wang et al. show that intestinal Lpcat3, a phospholipid-remodeling enzyme, is required for dietary-lipid absorption. Lpcat3 deletion alters membrane fluidity, inhibits lipid transport into enterocytes, and amplifies the production of anorexic gut hormones in response to high-fat feeding, contributing to the paradoxical cessation of food intake despite starvation.

Highlights

- Lpcat3 enzyme activity is critical for dietary-lipid absorption
- Fatty acid uptake and chylomicron production require phospholipid remodeling
- Lpcat3 is essential for the survival of mice fed high-fat, but not low-fat, diet
- Loss of Lpcat3 amplifies the production of gut hormones and OEA on a high-fat diet

Wang et al., 2016, Cell Metabolism *23*, 492–504
March 8, 2016
http://dx.doi.org/10.1016/j.cmet.2016.01.001

CellPress

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Intestinal Phospholipid Remodeling Is Required for Dietary-Lipid Uptake and Survival on a High-Fat Diet

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SUMMARY

Phospholipids are important determinants of membrane biophysical properties, but the impact of membrane acyl chain composition on dietary-lipid absorption is unknown. Here we demonstrate that the LXR-responsive phospholipid-remodeling enzyme Lpcat3 modulates intestinal fatty acid and cholesterol absorption and is required for survival on a high-fat diet. Mice lacking Lpcat3 in the intestine thrive on carbohydrate-based chow but lose body weight rapidly and become moribund on a triglyceride-rich diet. Lpcat3-dependent incorporation of polyunsaturated fatty acids into phospholipids is required for the efficient transport of dietary lipids into enterocytes. Furthermore, loss of Lpcat3 amplifies the production of gut hormones, including GLP-1 and oleoylethanolamide, in response to high-fat feeding, contributing to the paradoxical cessation of food intake in the setting of starvation. These results reveal that membrane phospholipid composition is a gating factor in passive lipid absorption and implicate LXR-Lpcat3 signaling in a gut-brain feedback loop that couples absorption to food intake.

INTRODUCTION

Phospholipid composition is an important determinant of membrane biophysical properties. It is therefore reasonable to hypothesize that changes in the incorporation of polyunsaturated acyl chains into phospholipids might impact lipid transport across cellular membranes. However, it has heretofore been difficult to test this idea, as experimental systems that would allow selective alteration of phospholipid abundance in living animals have not been available. It has been speculated that reduced abundance of the essential fatty acid (EFA) linoleate in intestinal membranes may be linked to malabsorption (Clark et al., 1973; Werner et al., 2002). EFA deficiency was reported to be associated with fat malabsorption in the 1940s (Barnes et al., 1941), but the underlying mechanisms have remained obscure. Studies have suggested that defects in one or more intracellular events, including fatty acid (FA) uptake, triglyceride (TG) re-esterification, and chylomicron secretion, may contribute to reduced fat absorption in EFA deficiency (Clark et al., 1973; Levy et al., 1992; Werner et al., 2002). But how the loss of EFAs may affect these processes is unknown. To date, the hypothesis that altered membrane composition could affect lipid absorption in vivo has not been tested.

It has long been debated whether FAs are transported across the enterocyte apical membrane via passive diffusion or by carrier-mediated processes (Tso et al., 2004). Several candidate FA transporters have been characterized, including FATP4 and CD36 (Harmon et al., 1992; Stahl et al., 1999; Tso et al., 2004). Although conflicting results have been reported, deletion of either CD36 or FATP4 alone in mouse intestine does not appear to dramatically alter FA uptake (Goudriaan et al., 2002; Nauli et al., 2006; Shim et al., 2009). Studies utilizing cultured cell systems have supported a passive diffusion model by showing that the rate of FA uptake is linear, protease resistant, and temperature independent (Chow and Hollander, 1979; Ling et al., 1989; Trotter et al., 1996). By contrast, others have pointed to a carrier-mediated model based on observations that FA uptake is saturable and competitive with other FAs (Ho and Storch, 2001; Murota and Storch, 2005). While the preponderance of in vitro data supports a principal role for diffusion, testing the contribution of passive diffusion in vivo has been difficult due to the lack of an appropriate model system. No genetic mutation has been reported that directly affects passive FA uptake in animals.