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EDITORIAL

Dropping in on Lipid Mobilization From the Gut

Mammalian intestinal lipid absorption represents a multistep process in which fat is digested and its component fatty acids, sterols, and monoacylglycerols are transported across the brush border of the small intestinal enterocyte for re-assembly into complex lipid species (cholesterol esters, phospholipids, and triglycerides) that accumulate temporarily as large cytoplasmic lipid droplets (LDs). Some of those LDs undergo directed delivery across the endoplasmic reticulum (ER) membrane in a process that requires 2 obligate genetic components, namely microsomal triglyceride transfer protein (Mttp) and apolipoproteinB (apoB). Mttp exists as an endoluminal heterodimer in complex with protein disulfide isomerase and functions as a neutral lipid chaperone to transfer bulk lipid from LDs within the ER bilayer to the elongating chain of the acceptor protein, apoB. In normal subjects, apoB and Mttp function in tandem to permit the assembly and secretion of intestinal chylomicrons and facilitate the delivery of dietary lipid from the gut, primarily to the liver.

However, although it has long been known that intestinal LDs appear after a fatty meal, much less is known about the signals that govern the kinetics of LD formation and turnover or the signals involved. New findings from Xiao et al[1] in the current issue of *Cellular and Molecular Gastroenterology and Hepatology* shed light on how dietary glucose regulates LD mobilization and provide some tantalizing new insights into the proteomic pathways that may be involved. Xiao et al[1] studied 6 healthy male recruits on 2 occasions, each involving a high-fat meal followed 5 hours later by either an oral glucose solution or by water. They found that glucose ingestion increased both plasma glucose and insulin, as expected, but also increased plasma triglyceride levels and specifically increased triglyceride abundance in the chylomicron fraction of plasma, when compared with water ingestion. They also examined duodenal biopsy specimens obtained 6 hours after a high-fat meal and after either glucose or water ingestion. They observed that intestinal LDs tended to be both smaller and less numerous after glucose intake. Those findings, together with the increase in plasma chylomicron triglyceride levels after glucose ingestion, suggest that oral glucose promotes remodeling of intestinal LDs and augments chylomicron secretion. In addition, Xiao et al[1] undertook untargeted proteomic analysis of duodenal biopsy specimens, which showed 2900 proteins that were present in both glucose- and water-treated groups, of which 9 were exclusive to the glucose arm and 10 were exclusive to the water arm. Among the most interesting candidates from this screen was ethanolaminephosphotransferase 1, which was found only in the glucose-treated group.

These new findings help illuminate some important concepts in intestinal lipid absorption. In particular, the findings focus attention on the role of glucose as a nutrient signal in modulating intestinal chylomicron export. Those findings are in line with earlier studies from the laboratory of Xiao et al,[2] including work showing that intravenous glucose administration to healthy subjects increased intestinal apoB and chylomicron production. Those earlier findings, coupled with the current findings, strongly suggest that either systemic hyperglycemia or enhanced luminal glucose availability promote intestinal production of triglyceride-rich lipoproteins, which in turn may contribute to dyslipidemia in the setting of type 2 diabetes. Prior work from the laboratory of Xiao et al[3] has suggested that infusion of glucagon like peptide-2 (GLP-2) promoted intestinal chylomicron secretion in human beings, begging the question of whether oral glucose administration in these current studies influenced GLP-2 levels. However, in considering this possibility, Xiao et al[3] argued that glucose ingestion would promote production of both GLP-1 and GLP-2 and that the inhibitory effects of GLP-1 would likely mitigate the effects of increased GLP-2. A further advance from these findings is the concept that intestinal LDs are dynamically remodeled under conditions of glucose-induced lipid mobilization. In other words, although large cytoplasmic enterocyte LDs are formed during lipid absorption, these function as temporary storage sites rather than depots for immediate export. When a second stimulus is applied, in this case increased glucose flux, those large LDs undergo rapid remodeling, presumably with lipolysis of their lipid cargo, and vectorial transport to the ER for chylomicron assembly and secretion. What we do not yet understand is the signal(s) for this remodeling event, or how the protein composition of those LDs changes to promote lipolysis. The proteomic survey identified several candidates, but none are plausible lipases and none of the canonical LD proteins were altered significantly. Among the candidate proteins of interest, ethanolaminephosphotransferase 1 has a role in phosphatidylethanolamine synthesis and it is tempting to speculate it could have a role in phospholipid remodeling, a process recently shown to play a key role in dietary lipid absorption.[4] The current findings add to our understanding of glucose flux in regulating intestinal LD turnover and fat absorption in healthy human beings. The results raise the question of whether those same adaptations are found in patients with diabetes or obesity.

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References

1. Xiao C, Stahel P, Carreiro AL, Hung Y-H, Dash S, Bookman I, Buhman KK, Lewis GF. Oral glucose

mobilizes triglyceride stores from the human intestine. Cell Mol Gastroenterol Hepatol 2019;7:313–337.
2. Xiao C, Dash S, Morgantini C, Lewis GF. Intravenous glucose acutely stimulates intestinal lipoprotein secretion in healthy humans. Arterioscler Thromb Vasc Biol 2016; 36:1457–1463.
3. Xiao C, Bandsma RH, Dash S, Szeto L, Lewis GF. Exenatide, a glucagon-like peptide-1 receptor agonist, acutely inhibits intestinal lipoprotein production in healthy humans. Arterioscler Thromb Vasc Biol 2012; 32:1513–1519.
4. Wang B, Rong X, Duerr MA, Hermanson DJ, Hedde PN, Wong JS, Vallim TQ, Cravatt BF, Gratton E, Ford DA, Tontonoz P. Intestinal phospholipid remodeling is required for dietary-lipid uptake and survival on a high-fat diet. Cell Metab 2016;23:492–504.

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