ROLE OF THE GUT IN LIPID HOMEOSTASIS

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Abstract

Intestinal lipid transport plays a central role in fat homeostasis. Here we review the pathways regulating intestinal absorption and delivery of dietary and biliary lipid substrates, principally long-chain fatty acid, cholesterol, and other sterols. We discuss the regulation and functions of CD36 in fatty acid absorption, NPC1L1 in cholesterol absorption, as well as other lipid transporters including FATP4 and SRB1. We discuss the pathways of intestinal sterol efflux via ABCG5/G8 and ABCA1 as well as the role of the small intestine in high-density lipoprotein (HDL) biogenesis and reverse cholesterol transport. We review the pathways and genetic regulation of chylomicron assembly, the role of dominant restriction points such as microsomal triglyceride transfer protein and apolipoprotein B, and the role of CD36, L-FABP, and other proteins in formation of the prechylomicron complex. We will summarize current concepts of regulated lipoprotein secretion (including HDL and chylomicron pathways) and include lessons learned from families with genetic mutations in dominant pathways (i.e., abetalipoproteinemia, chylomicron retention disease, and familial hypobetalipoproteinemia). Finally, we will provide an integrative view of intestinal lipid homeostasis through recent findings on the role of lipid flux and fatty acid signaling via diverse receptor pathways in regulating absorption and production of satiety factors.

I. INTRODUCTION

The current pandemic of obesity, coupled to increased consumption of fat and energy-rich foods, has led to renewed interest in the role of the small intestine in the integrated regulation of lipid homeostasis. This review examines how the evolutionary adaptations that promote efficiency in coordinating dietary and biliary lipid absorption and processing in turn influence lipid homeostatic mechanisms throughout the body. We examine the specific transporters and pathways that determine substrate specificity in uptake across the brush-border membrane and review the biochemical and genetic mechanisms that modulate the net transintestinal transport of fatty acids and cholesterol, as well as other lipids. We review the regulatory mechanisms and pathways that modulate villus enterocyte cholesterol uptake and the formation of intestinal HDL as well as integrating these pathways with those involved in canalicular cholesterol secretion and cholesterol efflux. We also describe the mechanisms for complex lipid reassembly within the enterocyte and review the pathways that lead to lipid droplet formation and mobilization. We discuss the mechanisms by which lipid droplets are mobilized into the lumen of the endoplasmic reticulum and the key steps that involve microsomal triglyceride transfer protein (MTTP) and the structural protein apolipoprotein B (apoB). We review the steps in maturation of the primordial lipoprotein

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particle through the distal elements of the secretory pathway and the formation of chylomicron particles. In a final section, we present an overview of recent findings related to important signaling roles for intestinal lipids in the regulation of lipid absorption and satiety. These themes will frame a summary discussion that outlines future research directions in the field.

II. FATTY ACID AND STEROL TRAFFICKING

Dietary fats are important for human health, providing a densely caloric energy source in addition to essential fatty acids (FA) and fat-soluble vitamins. However, changes in the amount and composition of dietary fat brought about by the industrial revolution have contributed to the current epidemic of obesity (37). Fat content of the Western diet averages ~35% of energy intake and is mostly in the form of triglycerides (TG). Typically the fat contains equal amounts of saturated and monounsaturated FA (~14% of energy) and 6% polyunsaturated FA (PUFA). Alterations in dietary fatty acid composition, notably an increase in the ratio of omega 6 to omega 3 PUFA (reflecting increased use of vegetable oils), may also contribute to adipogenesis and obesity (3). While evolution resulted in the gut gaining highly effective mechanisms for fat absorption, there is intense focus nowadays on interventions designed to reduce fat intake by inhibiting intestinal absorption (233) or by surgically reducing the absorptive area (178). These interventions are often associated with dramatic metabolic changes but also raise some health concerns. A better understanding of the complex absorptive functions of the gut and the role they play in regulating overall energy homeostasis is more important than ever before. In addition, there have been significant advances in our understanding of the mechanisms by which long-chain FA (LCFA), cholesterol, and other sterols traverse the aqueous milieu of the mucus layer adjacent to the microvillus membrane and are then subsequently transported into the subapical domain of the villus enterocyte. Key among these has been the functional genetic and biochemical characterization of several classes of apical transporters that function in the selective uptake or export of lipid substrates.

A. Brush-Border FA Transporters

Hydrolysis of dietary TG in the intestinal lumen by pancreatic lipases generates two FA and one sn-2-monoacylglycerol (2-MG). These products are absorbed through the apical membrane of enterocytes and directed to the endoplasmic reticulum (ER) for resynthesis into TG. The newly synthesized TG are packaged for secretion into chylomicrons, the lipoproteins unique to the intestine. In the circulation, the TG of chylomicrons are hydrolyzed by lipoprotein lipase (LPL), which is located at the surface of capillaries, and the released FAs are rapidly taken up by peripheral tissues where they are used for various cellular pathways (70). In view of the importance of dietary TG as a nutrient, attention has focused on the uptake and processing of its component LCFA and also but to a lesser extent on the uptake and processing of 2-MG.

1. Uptake of LCFA by enterocytes: transporters versus diffusional mechanisms—Small intestinal cells absorb LCFA both via passive diffusion as well as protein-facilitated FA transfer. LCFA diffuse across the brush-border membrane via "flip-flop" of protonated FA down a favorable concentration gradient. Trapping of FA through binding to abundant intracellular FA binding proteins (205) and/or metabolic trapping by conversion to acyl-CoA derivatives are likely to play an important role in the initial phases of LCFA transport into small intestinal enterocytes (141). This section of the review is focused on the protein-mediated component of the membrane transfer of FA. This component may not contribute quantitatively to LCFA uptake by the intestine, but it appears

to exert a regulatory role with respect to the downstream metabolic targeting of the absorbed FA.

Membrane FA permeation was documented in many cell types to exhibit features of a protein-facilitated process. This includes specificity for LCFA (with hydrocarbon chains longer than 8 carbons) and a transport K_m in the low nanomolar range (207) that is well suited to the concentration of unbound FA dissociated from albumin in the circulation (175). However, enterocytes are a special case in view of the distinctive mode of presentation of FA for uptake by these cells. In the intestine, the FA released from TG digestion by lipases is incorporated into bile salt micelles. Like serum albumin, micelles solubilize millimolar concentrations of FA and are in equilibrium with FA monomers in solution. The concentration of monomeric FA is estimated in the low micromolar range (154, 225), which is orders of magnitude higher than that of unbound FA in the circulation. Early studies argued against cellular uptake of whole micelles (237), and more recent work showed that enterocyte FA uptake is a saturable function of the FA monomer (154). In addition, enterocyte processing of FA was shown to be dependent on the cellular entry site, i.e., apical (AP) versus basolateral (BL) (206). The ratio of TG to phospholipid formed was 10-fold higher for AP uptake, while a 3-fold higher level of FA oxidation was measured for BL delivery. There was also twofold greater FA incorporation into phosphatidylethanolamine (PE) with a threefold decrease in the phosphatidylcholine:PE ratio for AP compared with BL delivery (206). These observations suggested that apical membrane proteins on enterocytes may facilitate FA transfer and direct the FA to the appropriate metabolic sites. Regulatory effects of protein-mediated transport were also suggested by the adaptive changes in brush-border membrane FA uptake in response to environmental challenges (208, 221) and by the variability, possibly genetically determined, of FA uptake by intestinal segments from various mice strains (103). In the following discussion we will try to integrate the data related to intestinal FA transport into a working model that could provide a starting point for further work. Among the candidate LCFA transporters identified in the small intestine, we will discuss the role of CD36 (45-47) as well as one member of the very long chain acyl-CoA synthetases, otherwise known as fatty acid transport proteins (FATPs), namely FATP4 (198).

A) FAT/CD36: A TRANSPORTER OR A TRANSPORT REGULATOR: A role for CD36 in LCFA uptake was uncovered in 1993 (1), and in the same year it was identified as a receptor for oxidized low-density lipoproteins (52). CD36 is a 75- to 88-kDa, 472-amino acid heavily glycosylated transmembrane protein with broad ligand specificity that now includes LCFA, native or modified lipoproteins, glycated proteins, thrombospondin-1, collagen, amyloid B, and malaria-infected erythrocytes (192). CD36 is ubiquitously expressed, abundant in the heart, skeletal muscle, adipose tissue, intestine (1), and the capillary endothelium (73). There is now extensive in vivo evidence both in rodents and humans for an important role of CD36 in facilitating tissue FA uptake and for its contribution to diet-induced metabolic pathology. Studies in CD36-deficient mice (36, 78) and humans (83, 236, 244) have documented a defect in tissue FA uptake and abnormalities of FA metabolism. Polymorphisms in the CD36 gene have been linked to alterations in plasma lipid levels and susceptibility to the metabolic syndrome (133-135). For recent reviews on CD36's role in FA transport, refer to References 184 and 207. CD36 is abundantly expressed in the small intestine where it was shown to play a number of roles related to fat absorption (discussion below) and also in fat taste perception and the regulation of food intake (see sect. IV).

I) CD36's role in chylomicron formation: In the small intestines of mice (155) and humans (132), CD36 is most abundant in the proximal third of the intestine. In both species CD36 is detected on the brush-border membranes of duodenal and jejunal villi (132, 170). However,

epithelial cell immunochemical staining of CD36 is almost absent in the ileum and colon, although CD36 is detectable in blood vessels throughout the whole intestine of humans (132) and mice (Sundaresan and Abumrad, unpublished data). This expression pattern with proximal abundance and apical localization to intestinal villus tips supports a function in lipid absorption. The nature of this function is still incompletely understood, but it is now well established that CD36 plays an important role in directing the FA absorbed proximally to chylomicron formation (46, 156, 190).

There is no evidence of lipid malabsorption in CD36 null mice based on blood appearance of intestinally derived TG (46, 71) or using the 24 h fecal lipid recovery (46, 156) except for very-long-chain FA (VLCFA) (47). However, CD36 deficiency shifts more of lipid absorption to the distal parts of the small intestine (156). In addition, a larger part of the absorbed lipid may bypass the lymphatic system. Intestinal lipid secretion into the mesenteric lymph duct is decreased by 50%, the lipoproteins secreted are 35% smaller (46, 156), and as a result their clearance from the blood is significantly delayed in CD36 null mice (46). In humans deficient in CD36, there is postprandial hypertriglyceridemia with intestinal secretion of lipoproteins smaller than chylomicrons, suggesting impaired chylomicron formation (142).

How does CD36 deficiency impair chylomicron production without affecting net FA absorption? One possibility is that the proximal intestinal defect in FA uptake is compensated for by non-CD36-mediated uptake in distal segments. Primary enterocytes isolated from the proximal but not distal intestine of *CD36* null mice showed a 50% reduction in FA uptake compared with enterocytes from wild-type mice (155). Also intragastric administration of triolein to *CD36* null mice was associated with reduced oleic acid enrichment of mucosal lipids in the proximal intestine (155). Similarly, *CD36* deletion suppressed oleic acid uptake for oleoylethanolamide (OEA) formation by the duodenum of mice fed after a 6-h fast, which may in turn play a role in modulating the integrated satiety response following lipid ingestion (183). Thus CD36 appears to function in high-affinity uptake of FA in proximal enterocytes similar to its role in other cell types (207). However, despite evidence for its participation in enterocyte FA uptake, the contribution of CD36 to net intestinal FA absorption is likely to be small based on two considerations. *1*) The K_m for FA uptake by enterocyte CD36 is in the nanomolar range (155), meaning CD36 will be rapidly saturated and its function would be important only in very early stages of the digestive process. In addition, there is evidence that FAs downregulate levels of the CD36 protein by promoting its ubiquitination (196, 207). This regulation that was observed in muscle (196) and liver cells (F. Nassir and N. A. Abumrad, unpublished observations) also occurs in enterocytes (138, 223) where it would tend to further minimize CD36 contribution to net LCFA absorption. Based on all the above, the current view of CD36-mediated FA uptake in intestinal absorption would favor that of a regulatory nature designed to optimize the packaging of FA and cholesterol into chylomicrons (FIGURE 1*A*). Recently, CD36 was identified together with liver fatty acid binding protein (L-Fabp), a member of the cytosolic lipid binding protein family, to be required for assembly of the multiprotein complex that generates the prechylomicron transport vesicle from the intestinal ER (190). The intestinal peptide glucagon-like peptide-2 (GLP-2) was also recently reported to regulate intestinal lipid absorption and the assembly and secretion of TG-rich lipoproteins in a CD36-dependent manner (88). GLP-2 was found to promote glycosylation and membrane localization of enterocyte CD36, where it could conceivably modulate lipid trafficking (158).

As alluded to above, the mechanisms involved in CD36 promotion of chylomicron formation remain unclear. One mechanism may involve CD36 signaling possibly to the extracellular regulated kinase 1/2 (ERK1/2) (109, 223), leading to the phosphorylation of

proteins important for ER lipid processing (FIGURE 1*A*). Recent studies demonstrated that CD36 internalization was promoted upon binding LCFA but prevented by a rise in cellular calcium (109) (FIGURE 1*B*). These events may be related to intracellular lipid transport, but the details remain to be elucidated. It can be speculated that CD36's ability to influence store-operated calcium flux (FIGURE 1*B*) and the secretion of bioactive compounds (50, 109) may contribute to its effects on chylomicron production by influencing vesicular transport and/or the release of intestinal regulatory peptides.

In summary, the findings to date suggest that CD36 functions at different stages of fat digestion. CD36 mediates perception of FA in lingual taste bud cells and the initiation of the cephalic phase of digestion. In the small intestine, CD36 transport provides the oleic acid needed for generation of OEA, which reduces food intake. CD36 also facilitates uptake of FA, but its contribution to net absorption is small and under excess fat supply may be manifested in a shift of fat absorption to more distal parts of the intestine.

However, CD36, most likely via its signal transduction capabilities, plays an important role in coordinating the incorporation of FA and cholesterol into TG for chylomicron production and appears required for assembly of the prechylomicron transport vesicle and its secretion from the ER. As a result, CD36 may mediate the effect of some regulatory influences on lipoprotein assembly like in the case of GLP-2.

II) CD36 in humans: deficiency and genetic polymorphisms: In humans, CD36 deficiency is relatively common (2-6%) in persons of Asian and African descent (38, 83) and is associated with abnormalities of plasma lipids (63, 148, 245). Single nucleotide polymorphisms (SNPs) in the *CD36* gene influence susceptibility to the metabolic syndrome (134) and the risk of stroke (93) and are associated with alterations in the concentrations of serum FA (135) and TGs that in many cases reflect the effect of the SNP on CD36 protein levels (133).

The abnormal plasma lipids in humans with CD36 deficiency or with polymorphisms in the CD36 gene reflect at least in part abnormal peripheral clearance of plasma FA, since impaired tissue FA uptake has been documented in humans with CD36 deficiency (161, 213, 220). A contribution of defective lipid processing by the small intestine to lipid abnormalities is strongly suggested by findings of postprandial lipemia and of high levels of apoB48 in CD36-deficient subjects (111). A more recent study (142) showed CD36-deficient humans to have high levels of plasma TG, apolipoprotein B-48, free FA, and glycerol. The authors suggested that CD36 deficiency might increase atherosclerotic risk by enhancing plasma level of lipoprotein remnants due to intestinal secretion of particles that are smaller in size than chylomicrons (142).

B) IS FATP4 REQUIRED OR DISPENSABLE FOR INTESTINAL FA UPTAKE?:
Among the various candidate intestinal FA transporters, FATP4 attracted considerable attention by virtue of its high expression in mammalian villus enterocytes and, by virtue of its endogenous acyl CoA synthetase (ACS) activity, the capacity to function not only in FA transport but also in the process of metabolic trapping of LCFA through conversion to the CoA derivative (198). It is worth noting that FATP4 is not strictly a brush-border transporter, since its location is confined to the ER and subapical membranes where it participates in FA uptake that is mediated through metabolic trapping of the acyl-CoA product mediated by its ACS activity (147). Unlike the native LCFA substrate, which is freely diffusible, fatty acyl CoA products are hydrophilic and undergo rapid metabolic conversion into complex lipid species (di- and triglycerides, phospholipids). Germline deletion of FATP4 led variably to embryonic lethality or perinatal death that was associated with thickened, abnormal skin that led to restricted breathing and fatal dehydration (152)

and which complicated understanding of the role of intestinal FATP4. Rescue of the perinatal lethality was accomplished by keratinocyte-specific transgenic expression of FATP4 (*Fatp4*$^{-/-}$; *Ivl-Fatp4*$^{tg/+}$), which permitted an evaluation of the role of intestinal FATP4 since these "rescued" mice only expressed FATP4 in the skin, with no expression in the small intestine (151). However, there was no detectable effect of intestinal FATP4 deletion on any aspect of intestinal fat (cholesterol or triglyceride) absorption in the *Fatp4*$^{-/-}$; *Ivl-Fatp4*$^{tg/+}$ mice, no protection from high-fat diet-induced weight gain, or other evidence for a physiological role of intestinal FATP4 in dietary lipid transport (188). The findings do not imply that FATP4 is without a role in intestinal lipid transport, but strongly suggest that FATP4 appears dispensable for the process.

2. Monoglyceride transport into enterocytes—Digestion of dietary TG within the intestinal lumen yields 2-MG together with unesterified FA. Studies that examined 2-MG transport into Caco-2 cells as a model of enterocytes showed that uptake was a saturable function of the MG monomer concentration and exhibited sensitivity to trypsin digestion, implying that a membrane protein might be involved in mediating 2-MG uptake (153, 154). An interesting observation was that 2-MG inhibited cellular FA uptake while triolein (glyceryltrioleate), glycerol, diacylglycerol, and monooctanoate had no effect. This suggested that the transport of FA and 2-MG may be coordinated to optimize TG resynthesis inside the cell. Further support for this interpretation is provided by data showing that the metabolic fate of 2-MG in enterocytes, like that of FA, is dependent on the site of cellular entry (206). Esterification of 2-MG delivered in vivo either to the AP or the BL surface of rat and mouse intestine demonstrated differences that reflect the entry site. The ratio of TG to phospholipid (TG:PL) formed from 2-MG was ~10-fold higher for AP compared with BL delivery, findings that were qualitatively similar to those with FA (206). More studies are needed to understand what membrane proteins may facilitate uptake of 2-MG and how this may be linked to its metabolic processing.

3. Intracellular FA transport by cytosolic FA binding proteins and FA esterification—Once inside the small intestinal enterocyte, fatty acids are targeted and delivered to specific metabolic sites, a process which may be mediated by FA binding to small (~14 kDa) cytosolic fatty acid binding proteins (FABP). Two proteins of the FABP mutigene family are expressed in the intestine where they comprise 4-6% of the cytosolic proteins: liver-FABP (LFABP or FABP1) and intestinal-FABP (IFABP or FABP2) (12). The two FABPs were shown to deliver FA to membranes by different mechanisms, namely, diffusion versus collision for LFABP and IFABP, respectively (222). A collisional mechanism has been conclusively demonstrated for IFABP (204, 205). However, LFABP may also interact with membranes and in particular with ER membranes, where it helps initiate budding of lipid transport vesicles (157). The specific roles of LFABP versus IFABP in lipid absorption remain poorly defined, but are unlikely to be redundant based on the distinctive properties of the two proteins. While IFABP binds one FA molecule, LFABP binds two FA molecules in addition to its capacity to bind a variety of other lipids, including bile salts, lysophospholipids, cholesterol, acyl-CoA, and monoacylglycerol (MG) (79, 205).

Recent work using murine models with genetic deletion of LFABP or IFABP suggests a minor role of the two proteins in intestinal fat absorption but supports their involvement in the differential metabolic targeting of FA (114, 140, 159). Mice null for either protein have normal intestinal fat absorption, but LFABP null mice exhibit a reduction of chylomicron output (159), probably reflecting LFABP contribution to enterocyte chylomicron trafficking (157). There is evidence that LFABP may target FA toward oxidation while IFABP would favor FA incorporation into triacylglycerols. Fasted LFABP-null mice lose less lean mass while fasted IFABP-null mice lose more fat mass compared with wild-type mice (114).

Processing of FA by enterocytes is initiated by activation of the FA to its CoA derivative by the acyl-CoA synthetase enzymes specific for long chain (ACSL) or very-long-chain (ACSVL) FA (51). In the intestine, ACLS3 and ACLS5 are the major synthetases present, with lower expression levels found for ACSL1 (61, 163, 209). These ACSLs may contribute to the metabolic channeling of FA as there is evidence from studies in the liver or with hepatocyte cell models that ACLS3 delivers FA-CoA for phospholipid synthesis while ACLS5 delivers acyl FA for TGs, as reviewed in Reference 51.

The FA-acyl-CoA is transferred to MG to generate diacylgycerol (DG) by the MG acyltransferase (MGAT) enzymes. MGAT activity is important for TG absorption, since ~75% of the secreted intestinal TG may be synthesized from absorbed MG (4). Of the 3 MGAT isoenzymes, MGAT2 is expressed in both mouse and human intestine (249), while MGAT3 is also present in the human ileum (33). MGAT2 null mice absorb dietary fat, but the secretion of dietary TG into the circulation occurs at a reduced rate. This appears to favor more partitioning of dietary fat toward energy dissipation, which protects the mice from high fat induced obesity, glucose intolerance, and fatty liver (248).

The FA-acyl-CoA is transferred to DG to form TG by diacylglycerol acyltransferases (DGAT), the enzymes that catalyze the terminal step in TG synthesis (250). The intestine expresses two DGATs (DGAT1 and DGAT2). DGAT1 is a member of the same family as acyl-CoA cholesterol acyltransferase (ACAT) while DGAT2 is considered part of the same family as MGAT2 (250).

DGAT1 knockout mice are resistant to high fat induced obesity (197) and exhibit reduced chylomicron output (25), which is reversed by rescue of intestinal DGAT1 expression (120). DGAT1 contributes to the formation of a major fraction of the postprandial TG secreted by the intestine (32). Assigning a specific role for DGAT2 in intestinal fat absorption is challenging since the DGAT2 null mice die shortly after birth due to loss of skin barrier function and to markedly low nutrient levels (203). This phenotype reflects the importance of DGAT2 for TG synthesis in most tissues other than the intestine (203). DGAT2 localizes to a subdomain of the ER, and its active site is presumed to face the cytosol, in contrast to DGAT1 where the active site faces the ER lumen. DGAT2 is also present in mitochondria-associated ER membranes, subdomains that are highly enriched in lipid synthetic enzymes. The NH_2 terminus of DGAT2 contains domains that promote its association with mitochondria and thus favor its subcellular localization (202).

B. Cholesterol and Sterol Transporters

Intestinal cholesterol homeostasis is regulated through an intricate balance of sterol uptake, absorption, and de novo synthesis, daily losses through shedding of enterocytes and through the regulated export of intestinal lipoproteins, principally chylomicrons. Evidence from in vitro studies, however, suggests that intestinal cholesterol transport may occur through an alternative pathway involving HDL formation, mediated through the efflux pump ABCA1 (FIGURE 2) (95). The functional importance of ABCA1 is illustrated through the loss-of-function phenotype in patients with Tangier disease, an autosomal recessive allele associated with mutations in *ABCA1* that cause cholesterol accumulation in the intestine, spleen, and tonsils with virtually no detectable plasma HDL, because of defective cholesterol transfer to an extracellular apolipoprotein A-1 acceptor particle (86, 100). Advances in the understanding of cholesterol transporters and their role in the integrated regulation of intestinal and hepatobiliary cholesterol metabolism are discussed below.

1. NPC1L1—The mechanisms by which sterols interact with brush-border membrane transporters are still debated, but evidence suggests that interaction with the NPC1L1 transporter is a key step (8). NPC1L1 was identified as a molecular target for ezetimibe, a

pharmacological agent that inhibits intestinal cholesterol absorption by binding to the NPC1L1 transporter and blocking its sterol-dependent internalization via clathrin-coated vesicles (41, 66). NPC1L1 has 13 predicted transmembrane domains (reviewed in Ref. 15; FIGURE 2) that include a sterol-sensing domain in the NH_2-terminal half of the protein, whose structure and function is proposed to be similar to that demonstrated in a homolgous sterol transporter, NPC1 (112). It is likely that conformational specificity for sterol binding (i.e., cholesterol versus plant and other sterols) resides within the sterol-sensing domain and that, following binding of cholesterol, there is a conformational change in the protein that in turn functions to direct its subcellular localization and intracellular transport (reviewed in Ref. 15). Recent information on human variants of NPC1L1 associated with low cholesterol absorption indeed suggests that a range of posttranslational modifications including alterations in glycosylation and recycling appear to influence the function of the protein (234). Other studies have demonstrated that the function of NPC1L1 is independent of caveolin-1, as evidenced by the finding that cholesterol absorption and NPC1L1 expression are unaltered in Caveolin1 (*Cav1*) null mice (229). More recent studies have provided insight into the mechanisms and pathways that regulate NPC1L1 trafficking in response to cholesterol binding, specifically the demonstration that the small Rho GTPase Cdc42 plays a key role in recycling activity in response to cholesterol binding (240). Other studies have demonstrated an important role for Flottilins, essential lipid raft components, in forming cholesterol-enriched domains that function with NPC1L1 in cholesterol delivery (65).

Endogenous NPC1L1 mRNA is expressed in murine proximal small intestine villi and at much lower levels in the liver (8). In contrast, human NPC1L1 mRNA is expressed at equivalent levels in the small intestine and liver as well as tissues not involved in cholesterol absorption such as ovary, lung, and muscle (8). Intestinal NPC1L1 expression is modulated in response to cholesterol feeding in mice (41), but details of its physiological regulation in humans are still to be defined. In contrast, emerging information suggests that NPC1L1 is expressed on the canalicular membrane in human liver and may play a role in the fine regulation of biliary cholesterol secretion (218). Intestinal NPC1L1 expression is regulated at least in part through peroxisome proliferator-activated receptor α (PPARα)-dependent pathways, as evidenced by the decreased expression of NPC1L1 and decreased cholesterol absorption in mice treated over several days with fenofibrate (228). The mechanisms that account for the reduced expression of NPC1L1 following fenofibrate treatment remain to be elucidated, particularly whether intestinal PPARα activation leads to modulation of other factors that in turn downregulate NPC1L1 expression.

Insight into the physiological importance of NPC1L1 in intestinal cholesterol homeostasis emerged from studies showing greatly reduced cholesterol absorption in *NPC1L1*$^{-/-}$ mice (40), a phenotype similar to wild-type mice treated with ezetimibe. In regard to sterol substrate selectivity, both sitosterol and cholesterol absorption were similarly impaired in *NPC1L1*$^{-/-}$ mice (40), although structural selectivity for NPC1L1 in phytosterol transport was inferred using a gain-of-function approach in hepatoma cells (21). While there was no evidence of overt triglyceride malabsorption in *NPC1L1*$^{-/-}$ mice (40), other studies have suggested a defect in saturated FA absorption in *NPC1L1*$^{-/-}$ mice (113). More recent work has demonstrated attenuated postprandial hypertriglyceridemia in wild-type and *CD36*$^{-/-}$ mice treated with ezetimibe, again suggesting that intracellular trafficking of LCFA and chylomicron secretion may be impaired (180). The implications for patients treated with ezetimibe, in whom there has been no evidence of intestinal TG malabsorption, remain to be determined.

As alluded to above, NPC1L1 undergoes a highly regulated intracellular itinerary (FIGURE 2), which is initiated following sterol uptake across the microvillus membrane, where-upon the liganded NPC1L1 is directed through a recycling endocytic compartment that eventually

allows presentation of cholesterol as well as other sterols from the NPC1L1-sterol complex to the ER membrane (15, 66). Studies using intestinal organ explant cultures have demonstrated that cholesterol binding may induce the trafficking of NPC1L1 from domains close to the apical brush border towards endosomal compartments in a process that appears distinct from lipid rafts (195). Once delivered to the ER, sterols bound to NPC1L1, including cholesterol and other plant (sitosterol, campesterol, sitostanol) and shellfish sterols (brassicasterol), are then selectively esterified by acyl-CoA cholesterol acyl transferase 2 (ACAT2) (179). There are remaining questions regarding the role of NPC1L1 in intracellular cholesterol trafficking, however, as highlighted by recent studies demonstrating that the accumulation and transport of a fluorescent cholesterol analog (NBD-cholesterol) was similar in wild-type and *NPC1L1*$^{-/-}$ mice, suggesting that there may be an NPC1L1-independent pathway for intestinal trafficking of some sterol substrates (2). Sitosterol and other noncholesterol sterols are less effective substrates for ACAT2 (FIGURE 2) and are directed to the efflux pump ABCG5/G8 for resecretion back into the lumen. This efflux mechanism also accounts for excretion of at least some excess intracellular free cholesterol (FIGURE 2).

2. ABCG5/G8—The sterol export pump ABCG5/G8 is composed of a functional heterodimer (FIGURE 2), whose genes are organized in a head to head (i.e., 3′ to 5′ and 5′ to 3′) configuration and coordinately regulated by a shared promoter promoter (13, 122). Ho-modimeric complexes have not been demonstrated, and the functional transporter is normally composed of an obligate 1:1 heteromeric complex of ABCG5 and ABCG8, encoding a 12 membrane-spanning protein found in the brush-border membrane of villus enterocytes (72), the canalicular membrane of hepatocytes, and also the apical membrane of gallbladder epithelial cells (107). Most ABCG5/ABCG8 mutant proteins are retained in the ER rather than inserting into the apical membrane of the enterocyte (72). Cholesterol transporter gene expression is upregulated by dietary sterol intake, through production of oxysterol derivatives that signal through the orphan nuclear receptors LXRα and LRH-1 (60, 174). In addition, adaptive changes in cholesterol transporters were found in mice fed cholesterol-free high-fat diets and through pathways that are LXR independent (42). Plant sterols and stanol esters reduce cholesterol absorption in mice at least in part through upregulation of ABCG5/8 (174). However, species-specific differences emerged in other studies where ABCG5/G8 transporter mRNA was found to decrease following stanol ester supplementation in hamsters, and the decreased cholesterol absorption noted in these stanol ester supplemented animals occurred independent of changes in ABC transporter or NPC1L1 expression (56). Which of these two possible responses occurs in human intestine is unknown, but becomes relevant because of widespread use of plant stanol supplementation in commercial oils and fats. These findings suggest that intestinal cholesterol transport is regulated by multiple pathways and highlight the potential for therapeutic interventions. This suggestion is particularly relevant in terms of strategies that target LXRα in an intestine-restricted manner, since the gain-of-function phenotype in mice expressing the activated form of LXRα in the small intestine demonstrate reduced cholesterol absorption (through upregulation of ABCG5/G8), enhanced cholesterol efflux (through upregulation of ABCA1), and protection from atherosclerosis (FIGURE 2) (131). Those findings are consistent with earlier findings that LXRα/β double knockout mice have reduced cholesterol absorption, observations consistent with a role for LXR expression in the regulation of cholesterol absorption via an effect on ABCG5/G8 expression (228). It is worth noting that ABCG5/G8 knockout mice demonstrated a 3-fold increase in plant sterol absorption and a 30-fold increase in plasma sitosterol levels (251), suggesting that ABCG5/G8 functions in the regulated efflux of a range of sterols from enterocytes back into the intestinal lumen. These findings were confirmed in transgenic mice overexpressing ABCG5/G8, which demonstrated reduced cholesterol absorption, consistent with the predicted role of

the apical heterodimer in promoting cholesterol efflux back into the lumen (252). Despite the array of evidence that modulation of ABCG5/G8 expression in murine intestine is associated with changes in cholesterol absorption and sterol efflux, the findings from human studies imply only a modest role for genetic variations at the *ABCG5/8* locus as a contributor to population-wide variations in cholesterol homeostasis (97).

3. Regulation of intestinal sterol transporters and the role of transintestinal cholesterol export—Emerging evidence suggests that the small intestine plays an important role in the overall homeostatic regulation of cholesterol dynamics by regulating both cholesterol uptake and delivery to the systemic circulation as well as its regulated efflux back into the intestinal lumen. Elements of intestinal cholesterol uptake and efflux are therefore likely to represent key components of a homeostatic mechanism previously designated as reverse cholesterol transport (RCT). While the concepts of RCT date back several decades (232), there is great interest in the role of the intestine in facilitating cholesterol efflux from the body (186) and also in its role in the biogenesis of HDL as a carrier of cholesterol destined for selective excretion (105). Cellular free cholesterol (including intestinal cholesterol) may be mobilized for secretion through the actions of the basolateral efflux pump ABC1A1 (FIGURE 2), whose actions facilitate the transfer of membrane cholesterol to an apolipoprotein A-1 acceptor molecule with the net formation of discoidal HDL particles (100). A crucial role of the ABCA1 transporter in HDL formation was established by findings (alluded to above) in patients with Tangier Disease in whom mutations in the *ABCA1* gene were associated with virtual absence of plasma HDL (100). As noted above, ABCA1 is a transcriptional target of intestinal LXRα, and it is possible that under certain circumstances (such as LXR agonist treatment), intestinal ABCA1 may play a role in intestinal cholesterol mobilization and HDL formation. However, there is conflicting data on the role of ABCA1 in cholesterol absorption from germline *Abca1* knockout mice (144, 216), and the findings in intestine-specific *Abca1* knockout mice showed no change in cholesterol absorption (22). Taken together, the findings suggest a minor role, if any, for ABCA1 in the physiological regulation of cholesterol absorption, although the expression of ABCA1 in the intestine plays a key role in HDL biogenesis (23). As alluded to above, HDL biogenesis is regulated in mice by LXR agonist administration, and work has demonstrated that this may further represent a viable strategy to promote cholesterol efflux by attenuating cholesterol absorption (131, 247). In this regard, recent studies have suggested that cholesterol absorption per se is required for the LXR agonist-mediated increase in intestinal HDL biogenesis, because *Npc1l1*$^{-/-}$ mice (where cholesterol absorption was greatly decreased) were found to demonstrate no increased HDL biogenesis upon administration of an LXR agonist (214). Those findings imply a role for luminal cholesterol delivery, likely via NPC1L1-mediated pathways, in providing the substrate for ABCA1-mediated HDL biogenesis. Further study will be required to resolve the metabolic compartmentalization of intestinal cholesterol in relation to HDL biogenesis and reverse cholesterol transport.

In regard to other potential transport pathways for cholesterol absorption, the HDL receptor SR-B1 was also considered a candidate gene in regulating intestinal cholesterol uptake, but *Srb1*$^{-/-}$ mice demonstrated no change in intestinal cholesterol absorption from their wild-type controls (7). The multifunctional ligand receptor CD36 is expressed on the microvillus membrane of mammalian enterocytes and has been implicated in intestinal lipid transport and in the regulation of NPC1L1 expression (155). *Cd36*$^{-/-}$ mice, however, exhibited no alteration in intestinal cholesterol absorption compared with wild-type controls (despite upregulation of NPC1L1 expression), suggesting a complex role in regulating FA versus cholesterol transport, which remains to be fully understood (156, 158). Furthermore, mice with combined deletion of both Srb1 and Cd36 (*Srb1*$^{-/-}$ *Cd36*$^{-/-}$) also exhibited no decrease in cholesterol absorption (160), suggesting that neither transporter is rate limiting for intestinal cholesterol uptake under physiological conditions. Interestingly, findings in

humans support a role of CD36 in cholesterol homeostasis. Multiple polymorphisms in the CD36 gene exhibited strong association with plasma HDL which were inversely related to CD36 protein levels determined on monocytes (133, 134). CD36 may influence cholesterol flux by an effect on translocation of membrane phospholipid or by altering localization/ function of ABCA1 (253). A role for ACAT2 in intestinal cholesterol transport emerged from studies in ACAT2 knockout mice where mice were protected from diet-induced hypercholesterolemia and gallstones, in association with reduced cholesterol absorption (24). Other studies have demonstrated that a range of adaptive mechanisms function to limit cholesterol absorption and intestinal cholesterol accumulation in ACAT2 knockout mice (including decreased NPC1L1 expression and upregulation of ABCG5/G8), which together promote cholesterol efflux (227). Finally, in regard to the dominant pathways that regulate intestinal cholesterol transport, it is worth noting that most dietary cholesterol is transported in the form of chylomicrons and, as will be discussed in a later section, blocking chylomicron assembly results in the virtual elimination of cholesterol absorption (243).

There is yet another possible pathway for cholesterol efflux through the intestine, whose molecular and biochemical characterization is still very much in progress. This pathway, designated "transintestinal cholesterol export" (TICE), has been implicated in reverse cholesterol transport, through studies in mice that have utilized intestinal perfusion to examine sterol efflux across the intestine (217, 231). Those studies suggest that a luminal acceptor particle (bile salt plus phospholipid micelles) facilitates net efflux of cholesterol from the blood to the intestinal lumen (230). Studies have demonstrated that TICE is independent of ABCG5/G8, suggesting that this particular apical cholesterol efflux pathway is not required, while other studies demonstrated that TICE was increased in $Srb1^{-/-}$ mice (230, 231). It is important to emphasize that details of the transporter(s) involved, the lipoprotein carriers implicated, and the physiological regulation (if any) of this plasma-to-enterocyte cholesterol efflux pathway are yet to be determined. The observation that biliary cholesterol secretion is not required for the augmented efflux of cholesterol (217) challenges the concept that biliary cholesterol secretion is required for reverse cholesterol transport (at least in mice), but the implications remain to be tested in humans. Other recent studies have demonstrated a key role for intestinal LXR activation in reverse cholesterol transport (131). These studies demonstrated augmented cholesterol secretion of macrophage cholesterol into both bile and feces (reflecting upregulation of ABCG5/G8) along with decreased cholesterol absorption in mice expressing a constitutively active LXR in small intestinal (but not liver) epithelium (131).

III. LIPOPROTEIN ASSEMBLY, VECTORIAL TRANSPORT, AND SECRETION

Following lipid uptake (FA, cholesterol) across the brush-border membrane, there exist dominant genetic restriction points that regulate intestinal lipoprotein assembly. Fatty acids, their CoA derivatives, monoglyceride, and sterols are transported by a network of transporters and metabolically regulated pathways (outlined above) that ultimately provide the substrate for complex lipid biosynthesis and the assembly of lipoproteins within the enterocyte. These metabolic pathways intersect at the apical domains of the ER and involve crucial interactions between apoB and MTTP that facilitate complex lipid delivery into the secretory pathway (FIGURE 3). ApoB is the requisite surface structural protein that facilitates the formation of lipoproteins within the ER. MTTP promotes lipoprotein biogenesis by shuttling neutral lipid from within the bilayer of the ER to an acceptor apoB molecule. The current concept is that both apoB and MTTP are obligate requirements for intestinal lipoprotein biogenesis. Genetic mutations or pharmacological inhibition of either protein greatly attenuates the formation of lipoproteins. Key to the mechanisms regulating intestinal lipoprotein biogenesis is a detailed understanding of the tissue-specific production of distinctive isoforms of apoB, the result of posttranscriptional RNA editing. There also

exists an important metabolic partitioning of complex lipid between their sites of formation within the bilayer of the ER membrane and lipid droplets within the cytosol and the ER lumen. Finally, lipoprotein biogenesis involves maturation and transport of the prechylomicron transport vesicle from the ER to Golgi compartments and eventually vectorial delivery of a mature chylomicron particle for secretion into the lymphatic circulation.

A. ApoB and MTTP: Functional Domains Involved in Lipoprotein Biogenesis

The regulated assembly of chylomicrons brings together apoB and complex lipids in a fixed temporal sequence, followed by progressive maturation in the ER with vesicle formation and fusion steps involving Golgi membranes (FIGURE 3). The assembly of apoB-containing lipoprotein particles begins with translocation of nascent apoB into the ER lumen while still attached to the polysome and before translation of apoB48 is complete (57, 168). The NH_2 terminus of apoB contains almost all the *N*-glycosylation sites as well as a region for physical interaction with MTTP (89, 98). In addition, the α_1 domain contained within apoB48 contains seven of the eight paired disulfide bonds and plays a critical role in the optimal folding of hydrophobic domains of apoB mediated by physical interactions with MTTP (91). The first step in lipoprotein biogenesis thus occurs with transmembrane forms of the nascent apoB peptide undergoing partial lipidation and organization into a primordial particle within the rough ER. This primordial particle is further modified through a second-step "fusion" process that requires MTTP, resulting in lipid enrichment and expansion of the lipoprotein particle. Accordingly, the size range of lipoprotein particles varies depending on lipid availability and the size of lipid droplets within the smooth ER (27). These initial steps in apoB-containing lipoprotein biogenesis likely also govern the number of lipoprotein particles produced and may be influenced by physiological variations in apoB gene expression, the rates of apoB synthesis, and the rates and efficiency of secretion of the newly synthesized apoB protein. Genetic defects associated with abnormal apoB are clinically heterogeneous, but most cases are caused by nonsense and frameshift mutations in the *APOB* gene that lead to formation of COOH-terminal-truncated apoB (181). The population frequency of *APOB* gene mutations causing truncated apoB proteins is ~1:3,000, but by clinical criteria heterozygous FHBL may occur in 1:500-1: 1,000, although homozygous FHBL is very rare (215).

MTTP is a 97-kDa heterodimeric protein found in complex with the resident ER chaperone protein disulfide isomerase (90) (FIGURE 3). MTTP is most abundantly expressed in small intestinal enterocytes and hepatocytes (90); in cardiomyocytes (11), placenta (136), retinal (124), and proximal renal tubular epithelial cells (108); and also in CD1 restricted T cells, where there is no apoB and presumably no lipid export (44). Mammalian MTTP principally transfers triglycerides to facilitate optimal folding of nascent apoB, but also shuttles other lipid classes such as cholesteryl esters, free cholesterol, and phospholipids to further promote lipoprotein formation (173). In the case of CD1 restricted T cells, MTTP transfers lipid antigens to a variety of CD1 molecules and may play an important evolutionary role in antigen presentation, since human subjects with genetic deficiencies in MTTP exhibit impaired activation of CD1 restricted T cells and invariant natural killer T cells (44, 254). MTTP is necessary and (with apoB) sufficient for lipoprotein formation and secretion and confers lipid secretion capability to non-lipoprotein-secreting cell lines when coexpressed with lipid-binding competent forms of apoB (98). In contrast, pharmacological MTTP inhibition (110), or conditional genetic deletion, blocks both apoB and lipoprotein secretion from hepatocytes (171, 172) and enterocytes (243). In humans, homozygous or compound heterozygous truncating or missense mutations in the *MTTP* gene result in abetalipoproteinemia (14), a rare disorder characterized by extremely low TG and cholesterol levels in serum and lipid droplet accumulation in the liver and small intestine.

Intestinal MTTP exhibits diurnal regulation in concert with the diurnal changes in plasma TG levels (166), which involve CLOCK genes and the transcriptional repressor SHP (short heterodimeric partner) (167). These findings suggest that both nutritional and visual cues work in concert to accommodate rapid fluxes in dietary lipid availability. Other findings demonstrated a role for leptin signaling in the regulation of intestinal MTTP, involving leptin receptor and melanocortin 4 receptor pathways (96). A theme of emerging importance in lipid homeostasis concerns the regulation of ER stress (176). Recent studies demonstrated that interruption with one of the effector limbs of the unfolded protein response (176), specifically using inositol requiring enzyme 1β knockout mice, revealed increased intestinal MTTP expression and augmented lipid mobilization, along with increased chylomicron secretion (94).

B. Requisite Structural Components for Intestinal Lipoprotein Biogenesis: Molecular Isoforms of ApoB

ApoB is the requisite scaffold for intestinal TG-rich lipoprotein formation, whose regulation is coordinated in a developmental and tissue-specific manner. The dominant form of apoB expressed in the small intestine is referred to as apoB48. Mammalian *APOB* gene transcription yields a ~14 kb mRNA, in which C to U RNA editing, mediated by apobec-1, introduces a translational stop codon into the nuclear transcript and directs production of apoB48 in the small intestine (17). The unedited apoB mRNA (found in human liver, which does not express apobec-1) encodes apoB100, while mouse and rat liver (as well as other species that express apobec-1 more widely) synthesize both apoB100 and B48 (17, 74). Intestinal apoB mRNA editing is mediated by a heterodimeric complex containing apo-bec-1, the catalytic deaminase and an obligate RNA binding subunit, apobec-1 complementation factor (ACF) (123, 145, 219). The tissue-specific distribution of apoB mRNA editing reflects the tissue- and cell-specific distribution of apobec-1, which is expressed in enterocytes and subepithelial cells throughout the luminal gastrointestinal tract (68, 76). ACF is predominantly expressed in the liver, kidney, and intestine, but low levels are found in almost all tissues in humans, rats, and mice (39, 48, 82). Apobec-1 and ACF shuttle between nuclear and cytoplasmic compartments (19, 34), but whether ACF and apobec-1 shuttle independently or together has yet to be resolved. Recombinant apo-bec-1 and ACF can each be isolated as homodimers (64, 117), and in addition, ACF forms multimers in complex with apoB RNA (64).

Apobec-1 mediates C to U deamination of a cytidine base in apoB RNA, which is embedded in an A+U rich context, raising the question of whether alternate targets (beyond apoB RNA) exist. Earlier work identified a canonical apo-bec-1 binding site containing an UUUN[A/U]U motif (9), which has been confirmed in transcriptome-wide RNA sequencing of intestinal RNA from the *Apobec-1$^{-/-}$* mice, which revealed other RNA targets for C to U editing, all within 3′ untranslated regions (UTRs) (177). The physiological relevance of apobec-1-mediated RNA editing in these 3′ UTRs remains to be defined. Other work has examined the parallel possibility that alternate (non-apoB RNA) targets exist for ACF, particularly in view of the observation that germline deletion of ACF is early embryonic lethal (18). These findings were extended recently with the finding that ACF modulates cytokine (specifically interleukin 6) mRNA stability (20). Taken together, the findings suggest that apobec-1 and ACF each have a range of targets distinct from apoB mRNA, whose biological implications have yet to be formally defined.

There are functional consequences for intestinal lipid absorption of the different apoB isoforms associated with alterations in apoB RNA editing. *Apobec-1$^{-/-}$* mice (which express only apoB100) absorb TG over a longer time interval than wild-type (apoB48) controls, and apoB100-containing chylomicron are paradoxically larger than those from wild-type (i.e., apoB48-expressing) controls (130, 242). These findings suggest that intestinal chylomicron

production in an apoB100 background results in fewer, larger particles and less efficient intestinal TG delivery than wild-type (apoB48) controls (130). A major consequence of eliminating intestinal apoB RNA editing, however, emerged from the striking intestinal lipotoxicity following compound genetic deletion of intestinal *Mttp* in the *Apobec-1*$^{-/-}$ background with an exaggerated unfolded protein response and death (241). Considered together, the findings suggest that intestinal apoB mRNA editing, and the production of apoB48, is a critical adaptation for accommodating high fat intake or under conditions where intestinal MTTP abundance may be limiting (210).

C. ApoB Degradation Pathways and the Regulation of Lipoprotein Biogenesis

As modeled in hepatoma cell lines, primary murine hepatocytes, and enterocyte cell culture experiments, several distinctive pathways have emerged to account for apoB degradation, including ER-associated degradation (ERAD), autophagy (59), and the proteasomal pathway (57, 58) (FIGURE 3). The proteasomal degradation pathway involves ubiquitination of the nascent apoB polypeptide, typically due to misfolding as a consequence of insufficient lipidation or defective MTTP function (125). The misfolded apoB100 undergoes retrograde transport via a Sec61-mediated mechanism across the ER membrane (dislocation) and is ubiquinylated and targeted for degradation (57, 58). Studies in Caco-2 cells also demonstrate that intracellular apoB degradation occurs when MTTP activity is blocked using pharmacological inhibitors (126). Other studies revealed extensive apoB100 degradation (range 70-90%) in enterocytes from *Apobec-1*$^{-/-}$ mice, particularly with conditional intestinal *Mttp* deletion (241-243). A small fraction of apoB48 in the enterocytes of wild-type mice is degraded, but to a lesser extent (~30%) than noted for apoB100 (242, 243). Similarly, apoB48 is more efficiently secreted than apoB100 and appears less susceptible to presecretory degradation in murine hepatocytes (110). Thus, despite the shared NH$_2$ terminus between apoB48 and apoB100 and the requirement for physical interaction with MTTP to initiate lipoprotein biogenesis, the findings suggest that apoB48 undergoes translocation more efficiently than apoB100 and requires less lipidation (via MTTP) to become secretion-competent (187).

D. Lipid Droplet Formation and Metabolism

One of the cardinal features of intestinal lipid homeostatic function is the presence of cytoplasmic lipid droplets, whose emergence as metabolically active structures in other tissues has stimulated interest in their metabolic origin and fate within enterocytes (54). TG-rich lipid droplets are formed within the ER bilayer, synthesized by DGAT, especially DGAT-1, which is located within the ER membrane (250) (FIGURE 3). Mice that lack DGAT1 (*Dgat1*$^{-/-}$ mice) have no obvious defect in dietary fat absorption yet are protected against high-fat diet-induced obesity, at least in part due to increased energy expenditure (25). However, *Dgat1*$^{-/-}$ mice also exhibit a reduced surge in postprandial plasma TG levels and accumulate numerous large cytoplasmic lipid droplets (25). This phenotype was rescued in transgenic mice that express Dgat-1 only in enterocytes (Dgat-1^{IntONLY}), where over-expression of DGAT1 resulted in normalization of postprandial TG accumulation in plasma and reversal of the protection against high-fat diet-induced obesity along with a decrease in the accumulation of cytosolic lipid droplets (120). The results of these studies suggest that DGAT1 stimulates and promotes TG mobilization from enterocytes and in turn plays a key role in whole body energy homeostasis. Detailed understanding of the mechanisms for intestinal cytoplasmic lipid droplet formation and mobilization awaits further study, but recent findings have emphasized the dynamic formation of lipid droplets in vivo following lipid administration along with demonstrating the presence of perilipin proteins in association with these droplets (FIGURE 3) (121, 256). Studies suggest that perilipin 2 (Adipophilin) and perilipin 3 (TIP47) play distinctive roles in lipid droplet formation and metabolic compartmentalization, specifically in regard to storage versus rapid mobilization

with perilipin 2 coating lipid droplets in response to sustained high-fat intake while perilipin 3 but not perilipin 2 coats lipid droplets following an acute lipid challenge (121).

Findings suggest that MTTP plays a critical role in extracting TGs from the ER bilayer membrane (110, 172) into lipid droplets within the ER lumen and ultimately promotes fusion with primordial lipoprotein particles to allow their progressive lipid engorgement (FIGURE 3). These conclusions are in accord with earlier findings from electron microscopic observations showing tubules and vesicles of a typical hepatocyte smooth ER did not contain apoB but contained lipid droplets, suggesting that the TG-rich lipid droplets originate from the smooth ER and fuse with apoB synthesized within the rough ER (6). These findings were extended in electron microscopic studies of intestinal apoB-deficient mice, which showed that even without apoB synthesis there were large lipid particles present in the ER lumen (80). These lipid droplets were on occasion even larger than chylomicron-sized particles, from enterocytes of wild-type mice. In other words, the ability of the enterocyte to synthesize apoB does not affect the formation of large lipid droplets per se in the ER lumen, but rather plays a critical role in their mobilization and secretion.

The role of MTTP in the formation of intraluminal ER-associated lipid droplets was further established in hepatocytes from liver-specific MTTP-deficient (*Mttp-LKO*) mice (172). *Mttp-LKO* mice accumulated large cytosolic TG droplets, reflecting the block in VLDL assembly. Similarly, intraluminal lipid droplets were also absent from the rough and smooth ER in *Mttp-LKO* hepatocytes compared with wild-type controls (172). Indistinguishable findings were elicited in enterocytes from intestine-specific MTTP-deficient mice (*Mttp-IKO*), where enormous cytosolic lipid droplets were present in the apical cytoplasmic compartment but no lipid droplets were found within profiles of the ER or Golgi, suggesting a crucial role for MTTP in lipid droplet formation and partitioning between cytosol and ER (243). In summary, intestinal lipoprotein biogenesis requires two simultaneous events (both considered part of the so-called "first step" of lipoprotein biogenesis), namely, cotranslational lipidation of the nascent apoB polypeptide and MTTP-mediated accumulation of luminal lipid droplets. The first of these events requires both apoB and MTTP, while the second event requires only MTTP.

E. Distal Elements of Chylomicron Formation

Once the initial steps of chylomicron formation are completed, the nascent intracellular prechylomicron particles leave the ER and are transported through the secretory pathway and further modified. The COPII machinery plays a role in vesicular budding and transport of ER cargo destined for secretion through the Golgi apparatus (137). Studies using rat enterocytes demonstrated the sequential interaction of heterodimeric COPII proteins (Sec 23/24 and Sec 13/31) to be required for budding of prechylomicrons from ER to the Golgi apparatus (190, 191). Interestingly, liver fatty acid-binding protein (L-FABP) promotes budding of prechylomicron transport vesicles (PCTV) from the ER, with decreased budding and fusion in enterocyte extracts from *L-Fabp*$^{-/-}$ mice (157). PCTV budding was also impaired in intestinal extracts prepared from *CD36*$^{-/-}$ mice, suggesting a role for this multifunctional receptor (190). These findings together are of interest since the kinetics of intestinal TG secretion were significantly slower in *L-Fabp*$^{-/-}$ mice and in *CD36*$^{-/-}$ mice, suggesting an important functional counterpart to the kinetic delays in PCTV formation (46, 47, 159). Studies in intestinal extracts suggest that COPII proteins are required for the step involving Golgi fusion but not at the step of ER budding and formation of the prechylomicron transport vesicle (190). On the other hand, studies in a rat hepatoma cell model demonstrated that a functional COPII complex was required for ER budding of the nascent apoB100-VLDL particle (75). The reasons for this apparent discrepancy in the role of COPII proteins in ER export of TG-rich lipoproteins is not known but may reflect the different models examined. From the perspective of human disease, an integral component

of the COPII machinery, SAR1B, a member of the Sar1/Arf family of small GTPases, has been implicated in defective chylomicron formation (189). Mutations in the *SARA2* gene, encoding SAR1B, are associated with Anderson/chylomicron-retention disease (CRD) (99), in which enterocytes assemble prechylomicrons in the ER but fail to transport them through the secretory pathway, causing intestinal lipid droplet accumulation (28, 30, 99, 189). In addition, compensatory increases in SAR1A that have been shown to accompany defective SAR1B expression in some CRD subjects fail to complement the functional block in intestinal lipid mobilization despite 90% sequence identity (67). CRD subjects have no defect in hepatic VLDL secretion, suggesting that the mechanisms of lipid droplet formation and mobilization in enterocytes are distinct from that in hepatocytes. Whether this observation reflects a tissue-specific defect or an effect mediated by the intrinsic difference between apoB48 versus apoB100 is currently unknown.

IV. LCFA SENSING BY THE GUT AND ITS SIGNALING FUNCTIONS

The homeostatic mechanisms that maintain body weight in the face of fluctuating energy rely on a complex network of afferent and efferent signals that connect various metabolic organs to the hypothalamus and brain stem. Afferent signals from the gastrointestinal tract are transmitted to the brain via the blood or vagal afferent fibers. Dietary fat in the small intestine is associated with suppression of the secretion of ghrelin (55), a hormone with positive effects on appetite and food intake at the same time it stimulates secretion of a number of intestinal peptides that promote satiety and reduce intake (5, 106; FIGURE 4) as discussed in following sections. Fat-induced suppression of ghrelin requires digestion, but it is unclear whether it is mediated by LCFA (55).

Dietary fat intake has been shown to contribute to obesity in a manner related to both its quantity and composition, with the gut playing an important role in this contribution. The gut links fat sensing to the regulation of food intake and energy utilization. This section will be restricted to high-lights of the major concepts involved, and the reader is referred to a number of excellent reviews that delve at length into this topic (115, 143, 199, 201).

In the case of dietary fat, the nutrient that is sensed by the digestive system is LCFA, which have the capacity for cellular signal transduction and are generated from intraluminal digestion of TGs. In regard to FA sensing, several studies have demonstrated the presence of membrane receptors (149, 207). Studies in rats have demonstrated that it is oral sensing of free fatty acids rather than TG that may be involved (101). Those findings were confirmed more recently in humans (169), with the data showing that inhibition of lingual lipase, which releases FA from TG in the oral cavity, reduces preference for TG but not for FA. LCFA are recognized on the cell surface by membrane receptors that include CD36 (discussed earlier) and a number of G protein-coupled receptors (GPRs) (162, 182, 211).

A. GPRs for FA, CD36, and Fat Perception

The GPRs are members of a large family of receptors possessing several transmembrane segments that can activate heterotrimeric G proteins to stimulate activation of signal transduction pathways (84). As shown in TABLE 1, LCFAs can activate GPR40 and GPR120, while GPR84 responds to medium-chain FAs and GPR41 and GPR43 to short-chain FA (84).

CD36 was identified on the apical surface of taste bud cells in the tongue (62, 119) where it was shown to contribute to fat taste perception/preference and to the early cephalic phase of digestion (119, 138). These events are mediated by a signaling cascade triggered by LCFA binding to CD36, which involves the CD36-associated src kinase fyn, resulting in neurotransmitter release and signal relay to the central nervous system (50). Mice taste buds

express both CD36 and GPR120, but only CD36 is responsive to regulation by food intake, which produces parallel reductions in CD36 level and in preference for FA (139). Consistent with this, the 50% reduction of CD36 expression in mice heterozygous for CD36 deficiency was associated with a significant blunting of fat preference (139). The possibility that these findings may apply to humans has been recently suggested by the observations that human taste buds express CD36 (193) and humans carrying a genetic polymorphism which associates with reduced CD36 levels have a severalfold lower sensitivity for perceiving the taste of oleic acid (169).

High fat feeding downregulates CD36 expression on taste buds, and it has been proposed that this would increase fat consumption as more fat is needed for a satisfactory fat taste (255). In the small intestine, CD36 contributes to fat-induced satiety by providing oleic acid for production of the messenger OEA, which prolongs the intermeal interval (183). OEA, in turn, increases intestinal CD36 expression and FA uptake (246). Although this might suggest that CD36 deficiency would enhance food intake, studies demonstrate that food intake was decreased in CD36-deficient mice (77), possibly a postingestive effect (185) of delayed fat absorption as discussed in earlier sections.

GPR40 and GPR120, which bind LCFA (TABLE 1), have been implicated in fat taste perception, and mice null for these receptors exhibit reduced sensitivity to FA (26). Whether these receptors also play a role in fat taste perception in humans remains unexplored. There is a wealth of studies to document that humans can detect various FA in the oral cavity and that this triggers the cephalic digestive response possibly influencing subsequent absorption (143). There is also large interindividual variability in FA perception, which may play a potentially important role in food intake and obesity (200). The identification of taste receptors for FA should allow a mechanistic examination of the steps involved in fat perception and how they influence fat preference and digestion in humans.

In addition to influencing perception and possibly preference for fat, as already alluded to, an important physiological function of taste bud LCFA receptors is to prepare the digestive system for fat intake to optimize absorption. Taste perception triggers the first phase of the digestion (i.e., cephalic phase, FIGURE 4), which is characterized by an increase of pancreatic secretion and a rise in serum TG (138, 143). The role of neural input from taste receptors to facilitate absorption was demonstrated in early studies (146) and later firmly linked to higher levels of postprandial TGs in the blood (143). The increase in serum TG in response to oral fat detection appears to reflect stimulation of intestinal chylomicron secretion and may be influenced by enterocyte lipid stores (31).

Fat-specific cephalic phase responses also include secretion of lipases; transient increases of intestinal cholecystokinin (CCK), pancreatic polypeptide (PP), and PYY; and the release of insulin (143, 201). As demonstrated for CD36 (104), gustatory nerves generate central signals to initiate secretions that prepare the organism for absorption of the fat and its peripheral utilization.

In humans and rodents, there is an association between taste sensitivity to FA, fat intake, and susceptibility to obesity (143, 201). It is suggested that excess fat intake that is prevalent among obese subjects could result in attenuated sensitivity to LCFA, which would encourage even more fat consumption to reach satisfactory taste perception.

B. Intestinal FA Sensing and Lipid Absorption

In addition to the oral cavity, LCFA receptors are distributed throughout the gastrointestinal tract (162) where they may act to coordinate absorption with nutrient processing and to trigger the release of gut peptides (116) (TABLE 2). As discussed in a previous section,

CD36 is abundantly expressed in the proximal intestine and contributes to processes that optimize chylomicron formation, probably operating at the very beginning of digestion when luminal FA is still low (223). The small fraction of FA uptake that occurs early and the signal transduction triggered by FA interaction with CD36 appear important to initiate TG packaging into lipoproteins (223). Interestingly, both CD36 (109) and GPR120 signal to ERK1/2 (85), which might be a convergence point for receptor-mediated FA signaling. However, the distribution patterns of CD36 and GPR120 in the intestine do not overlap. GPR120 is not detectable in the proximal intestine, where CD36 is prominently expressed, while it is abundant in the colon and to a lesser extent the ileum (85), locations where epithelial CD36 expression is relatively low (132). This would suggest that these two receptors might act in parallel rather than cooperatively in FA-mediated signaling in the intestine.

LCFA released from fat digestion in the intestinal lumen influences secretion of a number of intestinal peptides that modulate the digestive process (49, 149, 201) (TABLE 2). Among the most studied in the context of responsiveness to LCFA are CCK and GLP-1. Enteroendocrine cells in the intestine are the primary chemosensors and constitute <1% of the epithelial cell population (TABLE 2). These cells express a number of FA receptors including the LCFA receptor GPR40 and GPR120, and upon stimulation secrete GLP-1 and CCK (49, 149, 201). CCK is secreted by enteroendocrine cells (I cells), which are found in the mucosa of the duodenum, jejunum, and proximal ileum. CCK is important for optimizing fat digestion as it plays a key role in regulating gastric emptying, gallbladder contraction, pancreatic secretion, and intestinal motility (29). Secretion of CCK is stimulated by LCFA (129), although the mechanisms underlying this effect are only partially understood. Studies in the enteroendocrine cells STC-1 showed that fatty acids of at least 12-carbon length stimulate CCK secretion by these cells via two separate pathways, one involving FA monomers in solution and one involving FA aggregates (102). The two LCFA receptors GPR120 (212) and GPR40 (127) have been implicated in mediating the effect of FA on CCK. In the case of GPR40, using fluorescence-activated cell sorting to isolate I cells from the duodenal mucosa of mice, it could be shown that I cells that express GPR40 respond to linoleic acid addition with increases in intracellular calcium and CCK release, and these are reduced in I cells from GPR40 null mice. In vivo, secretion of CCK in response to oleic acid is also reduced in these mice (127). In addition to CCK, LCFA stimulate S and K cells present in the duodenum and jejunum to release secretin and glucose insulinotropic peptide (GIP), respectively. Secretin inhibits gastric emptying and synergizes with CCK to regulate pancreatic secretions (35), while GIP together with GLP-1 has insulinotropic effects (10).

GLP-1 is formed in intestinal L-cells in the jejunum, distal ileum, and colon from the posttranslational processing of a proglucagon precursor (87). GLP-1 influences digestion by delaying gastric emptying and inhibiting gastrointestinal secretion and motility (81, 87). Release of GLP-1 is stimulated in vivo by FA reaching the distal intestine (or administered directly into it) and was shown to require protein kinase C-ζ (92). GLP-1 release from the distal intestine, in response to predominantly PUFA, involves the FA receptor GPR120 (85). GPR40 has been colocalized with enteroendocrine cells that express GLP-1, GIP, and CCK-expressing cells, and its disruption reduces secretion of these hormones (49).

C. Satiety Effect of Intestinal Dietary Lipid

Dietary lipid while present in the gut inhibits food intake in both rats and humans, and this is mediated by LCFA signaling to release peptides that have regulatory effects on food intake or energy utilization (116, 128, 182) (FIGURE 4). As already mentioned, the release of CCK is sensitive to nutrients including LCFA, and CCK has satiety-inducing actions in addition to its effects in the gut to influence the digestive process. CCK binds to its receptors

on vagal afferents in the duodenum, and a central signal is transmitted to the nucleus of tractus solitarius in the brain to induce satiety and reduce the feeling of hunger (29). Similarly GLP-1 induces satiety and reduces food intake in addition to its gastrointestinal effects (87). This section is focused on the satiety-inducing role of LCFA, but it is worth mentioning that short-chain FA were shown to induce PYY release from intestinal L cells of (129) which has central prosatiety effects (194) (TABLE 2). PYY release in vivo may in addition be responsive to LCFA (F. Nassir and N. A. Abumrad, unpublished observations).

As noted above, LCFA also induce satiety via the production of OEA, a bioactive lipid that is generated by the small intestine from absorbed oleic acid and acts centrally to reduce food intake and body weight gain in rodents (165, 182). Generation of OEA from dietary oleic acid is CD36 dependent, and disruption of CD36 or PPARα blunts fat-induced satiety (182). Some of the effects of OEA may be mediated via inducing release of GLP-1. This effect is mediated by GPR119, which binds OEA (118). In addition to OEA, fat ingestion promotes secretion by the intestine of *N*-acylphosphatidylethanolamine (NAPE) (69) and of apoA-IV (226), which have centrally mediated satiety effects. It is not clear whether LCFA sensing plays a role in these events.

In summary, dietary LCFA in the gut signal the release of various intestinal peptides that influence gut function and also act at the level of the brain to promote satiety. This would seem paradoxical considering the established link between fat intake and obesity. However, the satiety signaling property of fat can be blunted or overridden by other factors (194, 238). Consumption of fat together with other foods such as carbohydrates reduces the response of satiety peptides. In addition, the release of endocannabinoids by the palatable fat-sugar mix in food will promote hunger and blunt the fat-induced satiety response. Furthermore, the satiety-inducing property of fat requires complete digestion to release the LCFA, which then induce secretion of the satiety peptides. These peptide effectors delay gastric emptying and decrease the rate of fat absorption. Furthermore, there is good evidence to suggest that FA oxidation (FAO) may suppress eating, an effect based on the use of the FAO inhibitor mercaptoacetate (MA). The effect of MA was initially ascribed to inhibition of liver FAO acting via a vagal afferent signal. However, evidence against an effect of hepatic FAO led to the proposal that mercaptoacetate may be acting by inhibiting FAO in enterocytes and that changes in intestinal FAO can affect eating. Indeed, the effect of MA to increase eating was blocked by surgical elimination of vagal afferents from the upper gut (116). This adds further complexity to fat regulation of food intake, which involves a number of factors with positive (e.g., ghrelin, galanin) versus negative (CCK, PYY, OEA, FAO) effects (53).

D. LCFA Sensing and Glucose Metabolism

Sensing of LCFA by the gut-brain axis contributes to the regulation of glucose homeostasis (115) (FIGURE 4). GIP and GLP-1 are secreted by enteroendocrine cells early during the digestive process in response to LCFA released from digestion of dietary fat and have important effects on glucose homeostasis. Both act on pancreatic β-cells to enhance glucose-dependent insulin secretion, dubbed the incretin effect. In addition, GLP-1 has antihyperglycemic action via inhibition of liver glucagon secretion after a meal and by slowing gastric emptying (43). GIP has direct effects on adipose tissue to promote glucose uptake and energy storage. GLP-1 receptor agonists that are resistant to hydrolysis by the enzyme dipeptidyl peptidase-4 are current effective therapies for the treatment of type 2 diabetes (10). As discussed earlier, several of the intestinal hormones released by LCFA inhibit gastric emptying, which influences levels of blood glucose (239), and contribute to the glucoregulatory actions of gut FA sensing. Lipid sensing in the upper gut also activates an intestine-brain-liver axis to inhibit hepatic glucose production (FIGURE 4). This particular axis was shown to be dependent on generation and accumulation of LCFA-CoA and becomes defective in fat-fed rodents (235). In the brain, LCFA accumulation as LCFA-

CoA and the subsequent activation of PKC directly regulate the centers responsible for modulating glucose production and energy homeostasis (115) (FIGURE 4).

V. SUMMARY, CONCLUSIONS, AND FUTURE QUESTIONS

As highlighted in this review, emerging evidence strongly suggests that the gut plays an important role in the regulation of fat homeostasis and of energy balance in general, and there is evidence that this regulation is impaired in obesity and diabetes. A complete understanding of the steps involved in intestinal fat absorption as related to the function of various membrane and intracellular proteins is still lacking. The events involved in chylomicron formation also remain to be fully elucidated. How, for example, are cytosolic lipid droplets formed and what if any relationship do they have on the formation of luminal lipid droplets within the ER? Do intestinal lipid droplet contents undergo a similar cycle of hydrolysis and metabolic partitioning to that described for hepatocytes? What are the pathways involved in partitioning intracellular cholesterol mobilization for chylomicron versus HDL biogenesis? How is intestinal cholesterol efflux promoted and what are the intracellular carriers and pathways involved? To what extent is HDL formation by the intestine a regulated event? How is the overall homeostatic regulation of canalicular cholesterol output integrated with intestinal pathways for cholesterol efflux? How does apoB48 promote chylomicron formation and result in the production of particles that are so much larger than those formed with apoB100? What proteins are involved in the distal elements of the secretory pathway and how are they regulated? Recent evidence suggests a role for LCFA sensing in chylomicron formation, but the molecular details and even the precise site(s) of action are unknown. The identification and cloning of several LCFA membrane receptors have stimulated studies into the mechanisms of lipid-induced secretion of intestinal hormones, but much more remains to be learned about the role of these receptors in mediating physiological and pathophysiological effects of various FAs. There is little information on whether these receptors are regulated and if their function is impacted by fat intake, over-feeding, diabetes, or a combination of all the above. For example, does the activity or regulation of intestinal MTTP play a permissive or pathogenic role in type 2 diabetes? Information on the potential role of the LCFA receptor CD36 in intestinal nutrient sensing and how this influences chylomicron production and possibly intestinal peptide secretion also remain to be elucidated. Why does fat intake promote obesity despite the well-established ability of lipid in the intestine to signal for satiety? Is the food-reducing property of dietary fat overridden by fat perception and the brain reward system, and what are the molecular steps involved in this regulation? Much remains to be learned in this area, and the findings are likely to have major implications with respect to the etiology of obesity.

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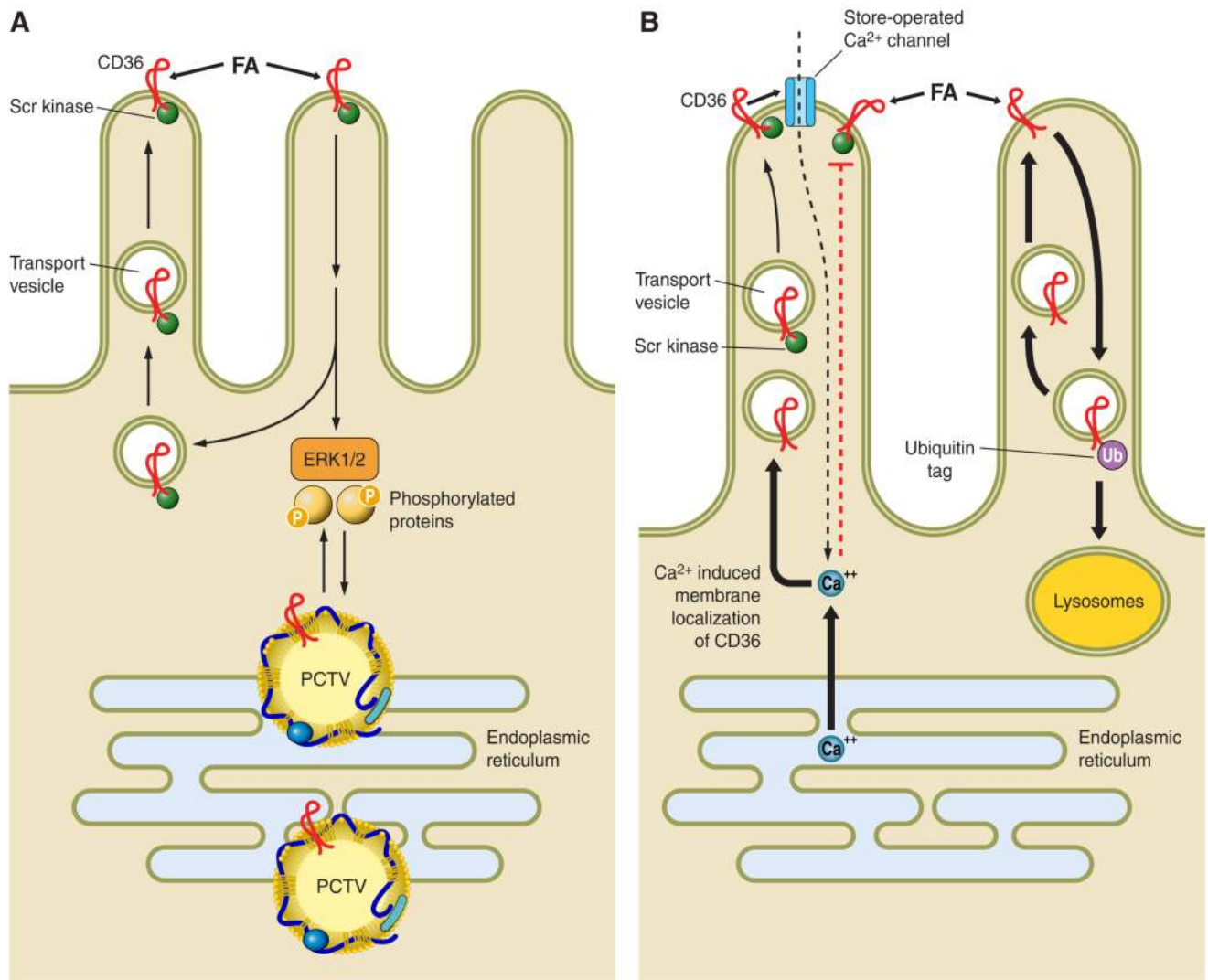
FIGURE 1.

Aspects of CD36 signaling and trafficking that may have potential relevance to the regulation of intestinal lipid metabolism. The figure proposes some hypothetical working concepts regarding steps that may be involved in the effect of intestinal CD36 to facilitate fatty acid (FA) uptake and chylomicron formation. *A*: CD36 is highly expressed on enterocytes of the proximal intestine and localizes to the apical side of intestinal villi (132, 155, 170) where it interacts with FA released from the digestion of dietary triglycerides. While CD36 functions in facilitating uptake of FA by proximal enterocytes (155, 183), it does not contribute quantitatively to FA absorption (47, 156), since it would be rapidly saturated at the levels of monomeric FA present in the lumen. However, CD36-mediated FA uptake and associated signaling, operating at the very early stages of absorption, may promote intracellular events that facilitate chylomicron assembly (46, 88, 156). CD36 signaling is in most cases initiated via the CD36-associated Src kinases and downstream via the extracellular regulated kinase ERK1/2 (109). This signaling pathway may be important for phosphorylating proteins required for coordinating ER processing of prechylomicron vesicles (PCTV). CD36 has also been identified in the protein complex that is required for formation of the PCTV (190). *B*: recent data indicate that CD36 signaling may also be mediated by a rise in intracellular calcium. Calcium release from the ER promotes

membrane CD36 localization, which regulates calcium influx via the store-operated calcium channel. The sustained increase in intracellular calcium could influence multiple events related to lipid processing or secretion (16, 109). *B* also illustrates the concept that CD36 is downregulated by FA via ubiquitination and lysosomal degradation (196), and this feedback loop may work to reduce CD36 function in the presence of high concentrations of long-chain fatty acids (LCFA) (207). In the enterocytes, the LCFA-induced decrease in CD36 associates with reduced activation of ERK1/2 which may serve to upregulate MTTP abundance (138).
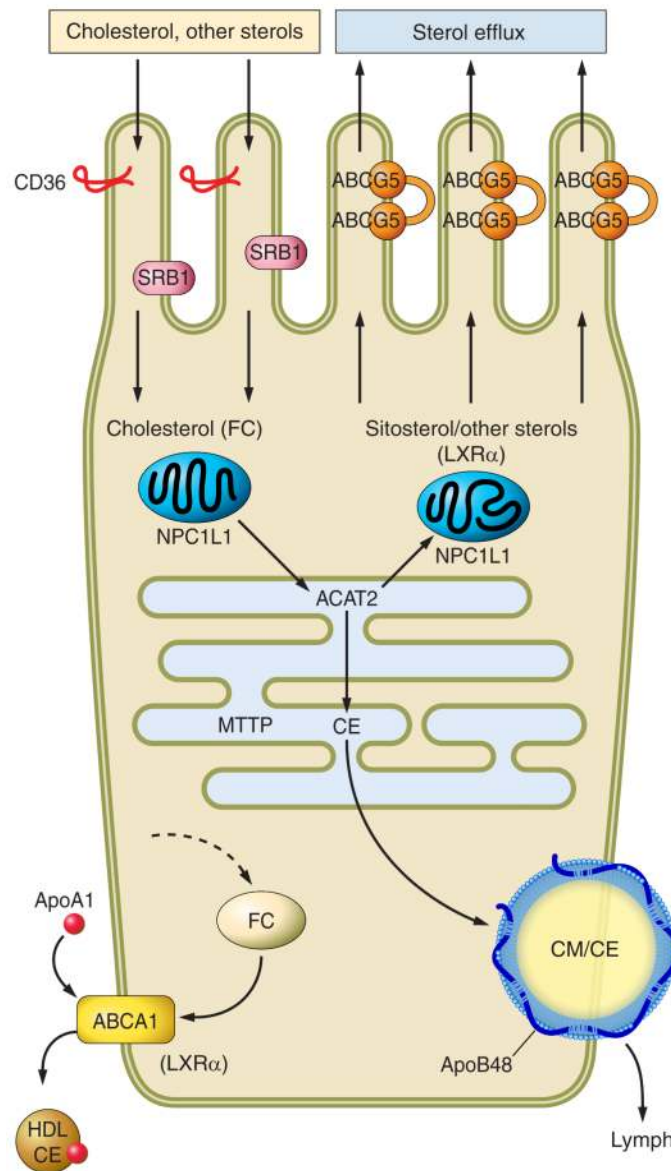
FIGURE 2.
Pathways regulating intestinal sterol absorption and homeostasis. Dietary/biliary cholesterol and other sterols are transported across the brush border principally via NPC1L1, a 13-transmembrane domain protein (shown only schematically here) with a sterol-sensing domain, that functions possibly in association with CD36. Note that the figure illustrates a conformational change in NPC1L1 upon sterol binding. NPC1L1 is expressed in subapical domains but not within the brush-border membrane and undergoes clathrin-mediated internalization following sterol binding, after which the sterol cargo is vectorially delivered to the endoplasmic reticulum for esterification via acyl cholesterol acyltransferase-2 (ACAT2). NPC1L1 then recycles back in proximity to the brush border. Sitosterol and other sterols are less effective substrates for ACAT2 and are preferentially secreted back into the intestinal lumen through the paired half-transporters ABCG5/G8. A portion of cytoplasmic intestinal free cholesterol is also selectively secreted back into the lumen through ABCG5/G8. An alternative pathway has been proposed to account for the portion of intestinal

cholesterol excretion that operates independently of ABCG5/G8, referred to as transintestinal cholesterol efflux (TICE). The transporters involved and the metabolic source of cholesterol are unknown. Other apical transporters have been described, including SR-B1 and CD-36, but the significance of these two transporters in absorption of cholesterol and other sterols is yet to be established. Intestinal cholesterol ester (CE) is partitioned into distinct metabolic pools, including a dominant apoB48-dependent chylomicron pathway (CM) that requires microsomal triglyceride transfer protein (MTTP). Cholesterol, in the form of cholesterol ester (CE), can also be secreted via apoA1-dependent pathways, although the quantitative importance of this pathway is unknown. The metabolic pool of free cholesterol (FC) arises through de novo synthesis, from receptor-dependent lipoprotein uptake and also through mobilization of membrane free cholesterol. These pathways are summarized schematically by the dashed arrow. Intracellular free cholesterol from any of these sources may also enter the metabolic pool from which ACAT2 derives its substrate. In addition, membrane free cholesterol may be mobilized, along with phospholipid, through the export pump ABCA1, resulting in transfer to an extracellular apoA-I acceptor with the formation of discoidal HDL particles that enter the lymphatic circulation.
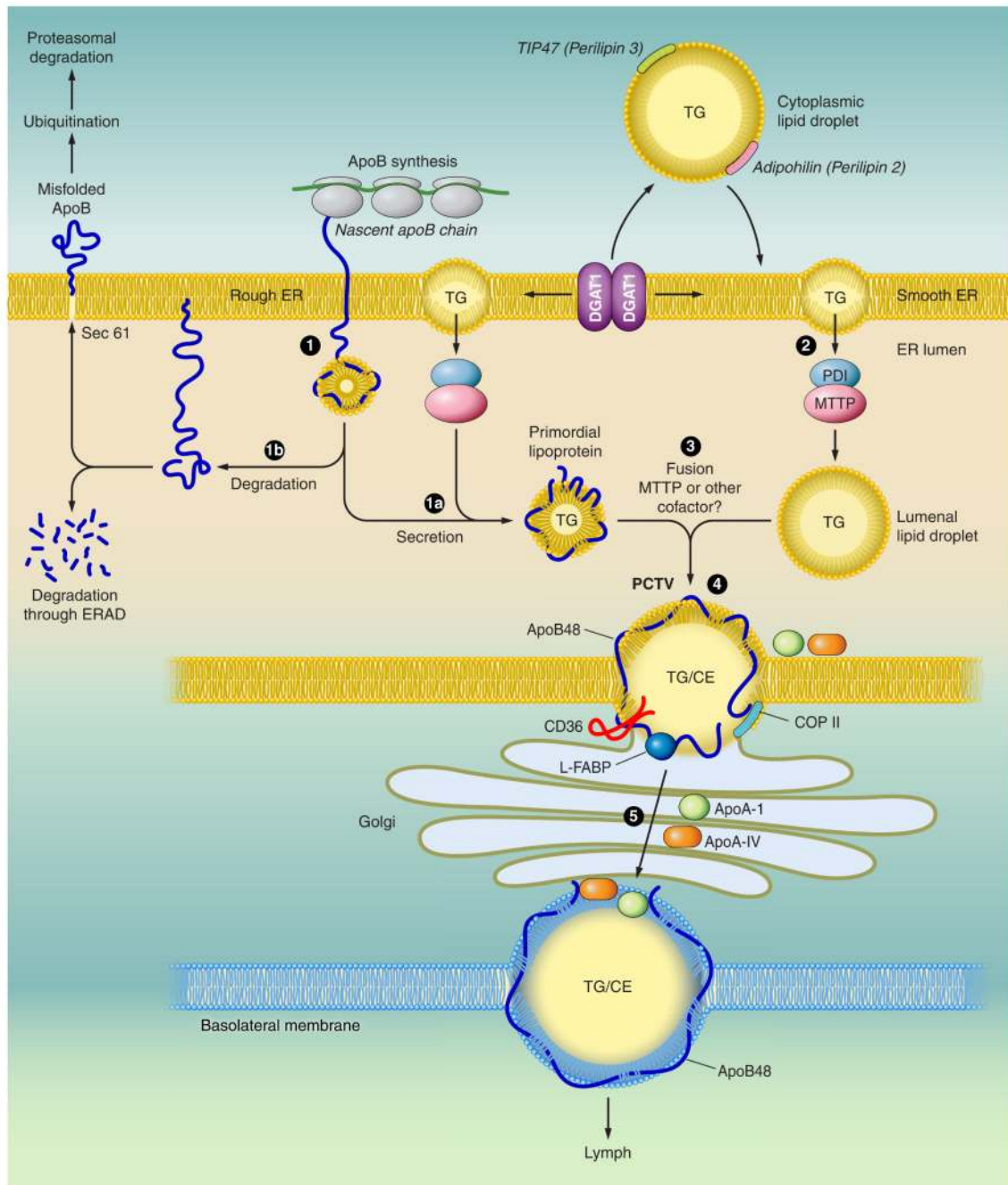
FIGURE 3.
Model of intestinal triglyceride-rich lipoprotein assembly. The nascent apoB polypeptide is cotranslationally translocated across the rough endoplasmic reticulum (ER) membrane (*1*). The membranes of the ER are shown in yellow. When lipid (triglyceride, TG) is available, physical interactions between the NH_2-terminal domain of apoB and the microsomal triglyceride transfer protein (MTTP) promote optimal folding and direct biogenesis of a primordial lipoprotein particle (*1a*). MTTP exists as a heterodimeric complex with the chaperone protein protein disulfide isomerase (PDI). MTTP also promotes mobilization of triglyceride-rich lipid droplets from the bilayer of the adjacent smooth ER into the lumen of the ER to become luminal lipid droplets (*2*). When lipid availability is limited or MTTP

function is impaired, nascent apoB becomes misfolded (*1b*) and is degraded, either within the ER lumen via ER-associated degradation pathways (ERAD), or the misfolded protein undergoes ubiquitination and is degraded by the proteasomal pathway. During the second step of lipoprotein assembly, the primordial lipoprotein particle fuses with endoluminal lipid droplets, resulting in prechylomicron transport vesicle (PCTV) formation (*3*). Other proteins, including CD36 and L-Fabp, also participate in PCTV formation. After fusion with key vesicular transport proteins, including COP II proteins, the prechylomicron particles are incorporated into a vesicular complex that buds from the ER and fuses with Golgi membranes. Vectorial transport of these prechylomicron particles (*4*) results in their continued maturation and eventually secretion (*5*) of the mature, nascent chylomicron particles into the pericellular spaces adjacent to lymphatic fenestrae. The basolateral membrane (shown schematically with a mature chylomicron traversing into the lymphatic fenestrae) is illustrated in blue.
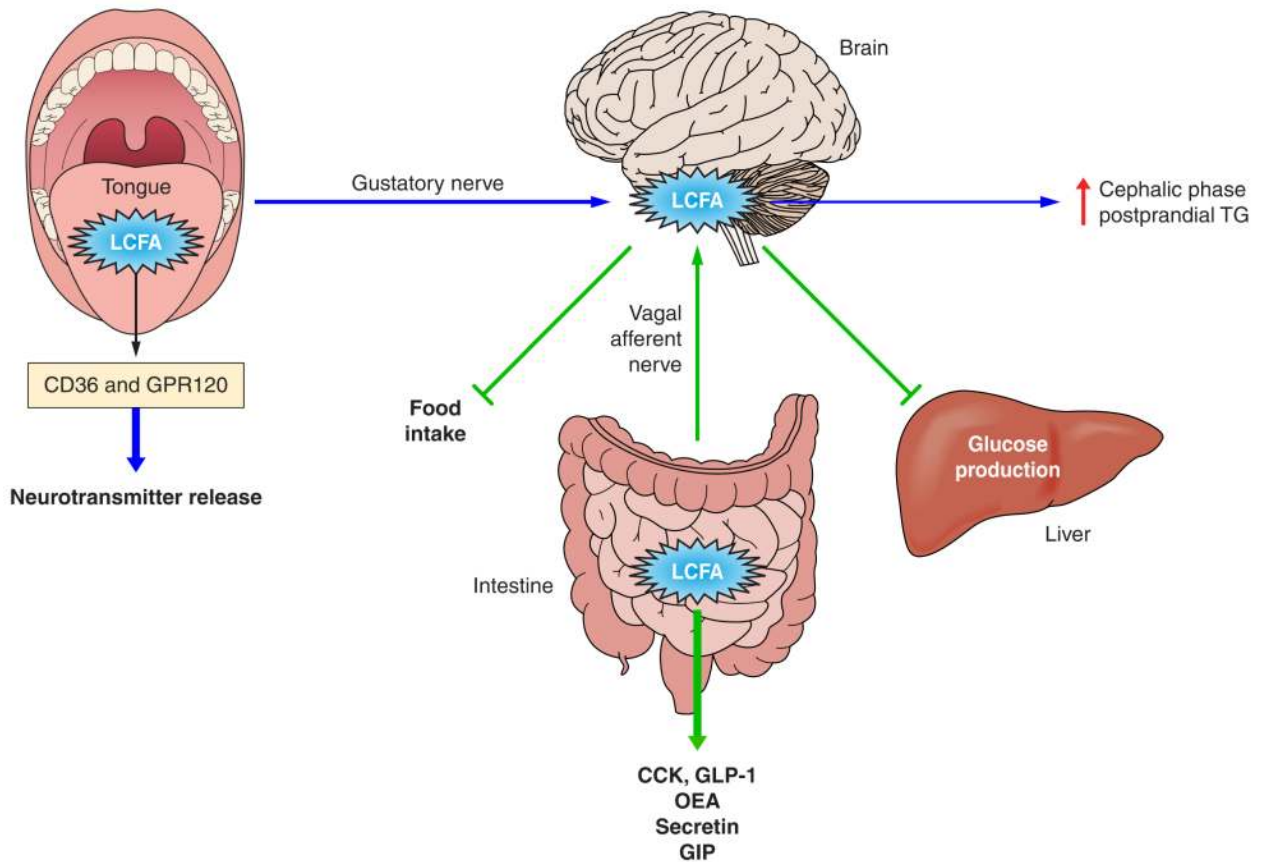
FIGURE 4.
Signaling functions of LCFA. Dietary triglyceride hydrolysis during digestion releases LCFA that have important signaling functions at various levels of the digestive tract. In the oral cavity, LCFA receptors (CD36, GPR120) present on the apical surface of taste bud cells in the tongue (49, 102) contribute to fat taste perception which associates with secretion of neurotransmitters, signal transmission to brain centers, and induction of the early cephalic phase of digestion (102) (blue arrows). In the intestinal lumen, dietary lipids have satiety effects (green arrows) mediated by LCFA signaling to release peptides with inhibitory effects on food intake (GLP-1, CCK, OEA). GLP-1 and CCK also delay gastric emptying and lipid absorption (23). GLP-1 and GIP enhance insulin release from the pancreas and glucose metabolism (10). Lipid sensing in the proximal gut mediated by accumulation of long-chain fatty acyl-coenzyme A also activates an intestine-brain-liver axis to inhibit glucose production by the liver (194).

Table 1

Specificity of various fatty acid receptors expressed in the gut

Receptor	Fatty Acid Specificity	Distribution
GPR40	Medium and LCFA	Taste bud cells; K, L, I, and S cells
GPR120	Medium and LCFA	Taste bud cells; I and L cells
GPR119	OEA	L and K cells
GPR41	Short-chain fatty acid	L cells
CD36	LCFA	?

LCFA, long-chain fatty acid; OEA, oleoyl ethanolamide.

Table 2

Enteroendocrine cell peptides that are induced by fatty acids

Cell	Peptide	Most Abundant Site	Fat Type	Fatty Acid Receptor
K	GIP	Duodenum/jejunum	LCFA (10)	GPR40, 119, 120
S	Secretin	Duodenum/jejunum	LCFA (35)	
I	CCK	Duodenum/jejunum	LCFA (127)	GPR120
L	PYY	Ileum/colon	ShFA (129)	GPR41, 43
	GLP-1		LCFA, OEA (10)	GPR40, 119, 120

Reference numbers are given in parentheses.