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Mini-review

Triglyceride-rich lipoproteins and cytosolic lipid droplets in enterocytes: Key players in intestinal physiology and metabolic disorders☆

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ABSTRACT

During the post-prandial phase, intestinal triglyceride-rich lipoproteins (TRL) *i.e.* chylomicrons are the main contributors to the serum lipid level, which is linked to coronary artery diseases. Hypertriglyceridemia can originate from decreased clearance or increased production of TRL. During lipid absorption, enterocytes produce and secrete chylomicrons and transiently store lipid droplets (LDs) in the cytosol. The dynamic fluctuation of triglycerides in cytosolic LDs suggests that they contribute to TRL production and may thus control the length and amplitude of the post-prandial hypertriglyceridemia. In this review, we will describe the recent advances in the characterization of enterocytic LDs. The role of LDs in chylomicron production and secretion as well as potential previously unsuspected functions in the metabolism of vitamins, steroids and prostaglandins and in viral infection will also be discussed.

Fat absorption by the small intestine is a very efficient process. Triglycerides (TG) are exported from enterocytes as chylomicrons that are triglyceride-rich lipoproteins (TRL). They are subsequently hydrolyzed in the circulation to provide the body with fatty acids. Thus, serum lipid levels result from the production of lipoproteins by liver and intestine and from their clearance. Chylomicrons are important contributors to the circulating lipids during the post-prandial state and it is well established that post-prandial serum lipid levels have a positive correlation with coronary artery diseases [1,2]. Recent studies have shown that a transient formation of lipid droplets (LDs) in the cytosol of enterocytes may be a part of the physiological process contributing to chylomicron assembly and secretion after a meal, and thus to the control of the amplitude and duration of postprandial hypertriglyceridemia [3,4]. Despite their promising impact in the understanding of metabolic disorders, the molecular mechanisms governing intestinal cytosolic LD formation and mobilization and triglyceride distribution between the cytosol for transient storage and the endoplasmic reticulum (ER) lumen for chylomicron assembly, are only beginning to be explored. Although chylomicrons and cytosolic LDs are both composed of a core of neutral lipids (TG and cholesterol esters) surrounded by a monolayer of amphipathic lipids (phospholipids and cholesterol), they differ in many aspects as summarized in Table 1.

In this review, we will present the links between the production and metabolism of chylomicrons and the risk factors of cardiovascular diseases. We will review the present knowledge on enterocyte cytosolic LDs including their dynamics and composition, and we will discuss their potential roles in the control of chylomicron assembly and production, as well as their potential functions in the metabolism of hydrophobic molecules (summarized in Fig. 1).

Abbreviations: ABHD5/CGI-58, α/β hydrolase domain 5/comparative gene identification-58; Apo, apolipoprotein; ATGL, adipose triglyceride lipase; CIDE, cell death-inducing DNA fragmentation factor 45-like effector; Cox-2, cyclooxygenase-2; DGAT, diacylglycerol: acylCoA transferase; ER, endoplasmic reticulum; HDL, high density lipoprotein; LD, lipid droplet; LDL, low density lipoprotein; LPCAT, lysophosphatidylcholine acyltransferase; LPS, lipopolysaccharide; MGAT, monoacylglycerol: acylCoA transferase; MTP, microsomal triglyceride transfer protein; PC, phosphatidylcholine; TG, triglycerides; TRL, triglyceride-rich lipoprotein; UBXD8/FAF2, UBX domain-containing protein 8/FAS-associated factor 2; VLDL, very low density lipoprotein.

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Table 1
Differences between cytosolic lipid droplets and chylomicrons.

	Cytosolic lipid droplet	Chylomicron
Size	Up to 6 μm (non adipocyte LDs)	75–1200 nm
Localization	Cytosol	Lumen of the secretory pathway (endoplasmic reticulum, Golgi apparatus) and extracellular
Specific protein coat		
Apolipoprotein B	No	Yes
Perilipin family	Yes	No
Function	Intracellular lipid storage	Lipid distribution to the body

1. Chylomicrons and risk factors of cardiovascular diseases

Chylomicrons are mainly produced by the jejunum after a meal, during the post-prandial phase. They are low density particles ($d < 1.006$ g/mL) and are very heterogeneous in size (diameters 75–1200 nm) [5,6]. A chylomicron is composed of a core of neutral lipids (more than 90%), predominantly TG, with traces of cholesteryl ester, stabilized by a shell of amphipathic lipids (phospholipids, cholesterol) and one structural protein, the apolipoprotein (apo) B48, as well as other exchangeable apolipoproteins [7]. In the blood circulation, TG derived from the chylomicrons are hydrolyzed by lipoprotein lipase into fatty acids that are taken up by organs such as the skeletal muscles and the heart for energy supply, or the adipose tissue for storage. The chylomicron remnants are taken up primarily by the liver, especially by the low density lipoprotein (LDL) receptor that has a high affinity for apoE, but other routes are involved including the LDL receptor-related protein 1 (LRP1) and the heparin sulfate proteoglycan (HSPG) pathway (for review, see Refs. [8–10]).

Cardiovascular diseases, type 2 diabetes and dyslipidemia are comorbidities of obesity [11]. Chylomicron metabolism can contribute to the development of these diseases. First, being directly exposed to dietary fat, the small intestine is instrumental in the control of the amount of lipids that enter the body and might contribute to the development of obesity. Second, liver and intestine produce TRL, called very low density lipoproteins (VLDL) and chylomicron respectively, and, under post-prandial conditions, the chylomicrons are important contributors to the circulating lipids. Furthermore, post-prandial serum lipid levels have a stronger positive correlation with coronary artery diseases than the fasting serum lipid levels [1,2]. Third, chylomicron remnants can rapidly penetrate the arterial wall suggesting a contribution in atherosclerosis development [12,13]. Fourth, an accumulation of lipoproteins in the plasma can result from decreased catabolism but also from increased production rates. Intestinal apoB48 lipoprotein overproduction was demonstrated for the first time in an insulin-resistant animal model, the fructose fed hamster [14]. This demonstrates that the intestine is not just an absorptive organ: it is also able to modulate lipoprotein production, a capacity previously strictly devoted to the liver.

Overall, establishing strategies to optimize chylomicron metabolism in order to reduce postprandial lipemia and chylomicron remnant accumulation would be a promising avenue for the prevention of cardiovascular diseases.

2. Chylomicron assembly and secretion

2.1. Chylomicron assembly: a two-step process

Absorption of dietary lipids by the enterocytes of the jejunum is a highly specialized and complex process (Fig. 1) (for reviews, see Refs. [15–17]). The hydrolysis of TG, which is the main dietary lipid, initiates in the stomach by the gastric lipase then in the lumen of the upper part of the small intestine by pancreatic lipase and leads

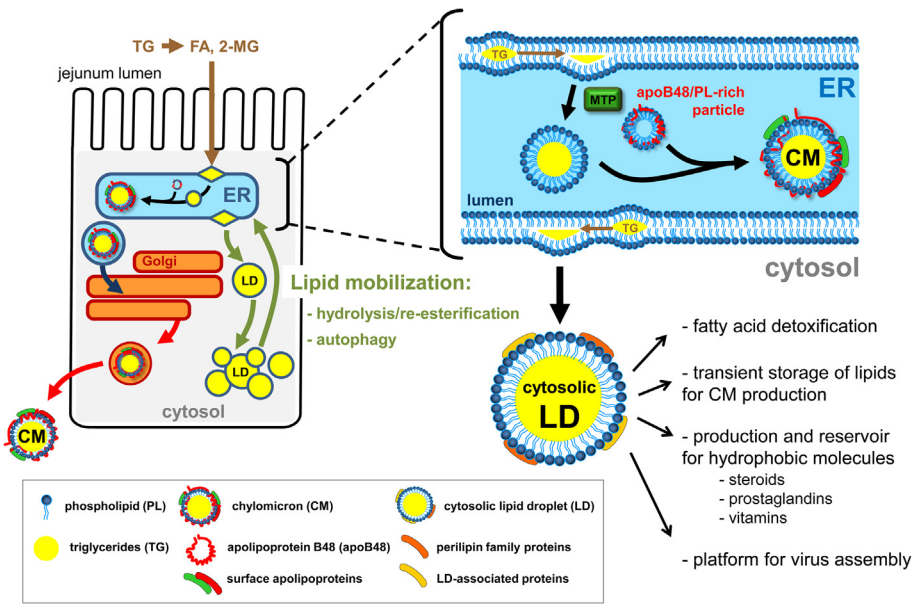

Fig. 1. Schematic model of neutral lipid distribution and trafficking in enterocytes, with a focus on chylomicron (CM) and cytosolic lipid droplets (LDs) biogenesis, fate, and functions. Triglycerides (TG), the main dietary lipid, are hydrolyzed in the lumen of the jejunum into fatty acids (FA) and 2-monoacylglycerols (2-MG), which are taken up by enterocytes and metabolized into TG at the endoplasmic reticulum (ER) membrane. The newly synthesized TGs accumulate between the two leaflets of the ER phospholipid (PL) membrane. A nascent LD buds off the ER in the ER lumen and fuses with an apoB48/PL-rich particle to form a CM that will traffic along the Golgi apparatus and will be secreted at the basal pole of enterocytes to provide lipids to the body. Microsomal triglyceride transfer protein (MTP) is required for CM assembly. After an acute dietary lipid load, the nascent LDs also bud off the ER in the cytosol for transient lipid storage. They will be mobilized between meals for CM formation through hydrolysis/re-esterification and/or autophagy. Additional potential functions of cytosolic LDs in enterocytes are indicated.

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