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# Postprandial consequences of lipid absorption in the onset of obesity: role of intestinal CD36

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## Abstract

Obesity has reached epidemic proportions and its incidence is still increasing. Obesity is an excess of fat, which can have harmful consequences such as inflammation, insulin resistance or dyslipidemia. Taken together, these conditions are known as metabolic syndrome (MetS). More and more studies consider obesity from a postprandial perspective: parameters such as triglyceridemia, endotoxemia or hormone secretion may have deeper postprandial metabolic consequences than during the fasting state. These effects take even more importance when we consider that humans spend more than half of the day in a postprandial state. This review focuses on the postprandial state in a fat-enriched diet and on the consequences of intestinal lipid absorption, putting the intestine in a central place in the development of obesity / MetS. Finally, we describe the crucial role of the lipid receptor cluster of differentiation 36 (CD36) for gut lipid absorption and the alterations that occur in CD36 dysfunction.

## Keywords

CD36, obesity, postprandial, lipids, hypertriglyceridemia, endotoxemia

## Introduction

The Organization for Economic Co-operation and Development (OECD) estimates that the proportion of the population that is overweight or obese has now reached 60%, and nearly 25% are classified as obese [1]. This is more than the number of undernourished people, and it is three times more than in the 1970s [2]. According to the World Health Organization (WHO), overweight and obesity are characterized by the abnormal or excessive accumulation of fat that may impair health. This perturbation in lipid homeostasis is associated with inflammation and other chronic diseases such as cardiovascular diseases, type 2 diabetes, hepatic steatosis, respiratory anomalies, and some cancers [3]. Moreover, obese people exhibit a greater sensitivity to severe forms of COVID-19 [4]. In 1988, to classify obesity-associated syndromes such as dyslipidemia (hypertriglyceridemia, low level of HDL cholesterol) or insulin resistance, the term metabolic syndrome (MetS) was introduced [5]. While genetic causes represent around 2% of obesity development, this condition is considered to result mainly from a chronic imbalance between energy expenditure and dietary energy intake. During evolution, humans had to overcome alternating periods of scarcity and abundance. In times of food scarcity, in order to limit nutritional deficiencies and maintain body fat storage, humans developed a set of biological and physiological adaptation systems to identify and optimize the digestion and absorption of calorie-rich foods and eating behavior [6]. However, in the current industrialized world, where access to high-calorie foods has become much easier, such systems can become obesogenic and can even be altered by the excess of calories.

Compelling evidence indicates that obesity and MetS are associated with several intestinal disturbances: changes in absorption capacity, elevation of postprandial triglyceridemia, endotoxemia, elevated permeability, dysbiosis, altered release/efficiency of some appetite-regulating peptides and incretins. These disorders may affect lipid storage directly or indirectly. Bariatric surgeries, which consist in the anatomical rearrangement of the gastrointestinal tract, are used to improve obesity-associated consequences. This demonstrates the essential contribution of the intestine and not only as an energy supplier [7]. A better understanding of the pathophysiology of these alterations could provide new therapeutic opportunities to fight obesity. Extensive data from experiments using murine models of diet-induced obesity, in particular high-fat (HF) models, largely recapitulate these intestinal

obesity-associated alterations. Thus, the excess lipid consumption, which has the highest energy density of all nutrients, and an unbalanced intake of different type of fat (saturated, unsaturated...) are surely largely involved in obesity / MetS development.

The mechanism of intestinal absorption of dietary lipids is complex because it requires the synthesis and secretion of triglyceride (TG)-rich lipoproteins, chylomicrons (CMs), which pass through the lymph before entering the bloodstream. Digestion and absorption of fat is associated with the secretion of various peptides, which in addition to regulate digestive function also affect postprandial metabolism and eating behavior [6]. Emerging data indicate that CMs synthesis may affect intestinal permeability and thus allow the entrance into the bloodstream of pro-inflammatory molecules coming from gut microbiota [8]. This microbiota, often ignored until the last 15 years, participates in the digestion and absorption of dietary lipids. Since humans are mostly in a postprandial state (16 h per day), these lipid-induced effects can considerably affect the whole metabolism. Contrary to what has been thought for a long time, the mechanism of lipid absorption is able to adapt to the lipid content of the diet, firstly *via* modulations of intestinal lipid metabolism and intestinal absorption surface [9] and secondly *via* diet-mediated modulations of the microbiota ecology [10].

Over the last twenty years or more, a set of lipid sensors activated by fatty acids (FA) has been discovered along the (oro) intestinal tract. Among these lipid sensors is cluster of differentiation 36 (CD36), an ubiquitous and multifunctional scavenger protein [11,12]. It can be activated by several ligands, including FA, which induce intracellular cell signaling resulting in the optimization of CMs synthesis [13]. At the intestinal level, current data have shown that CD36 also participates in the adaptation of absorption capacities depending on the lipid diet content [9], in the secretion of gut hormones [14] and in the maintenance of intestinal barrier [15]. Emerging data indicate that CD36 may contribute to the lymphatic endothelium integrity [15,16], to the regulation of microbiota ecology [17], and entrance of bacteria-derived lipopolysaccharides (LPS) [18]. The objective of this review is to highlight the importance of the postprandial phenomena in obesity / MetS and the role of the gut in the observed alterations. This review aims to show how the gut responds to chronic lipid excesses and to discuss the arguments that could make intestinal CD36 a key player in the prevention of obesity / MetS, especially in HF diet conditions.

# **1. Obesity and MetS: postprandial abnormalities**

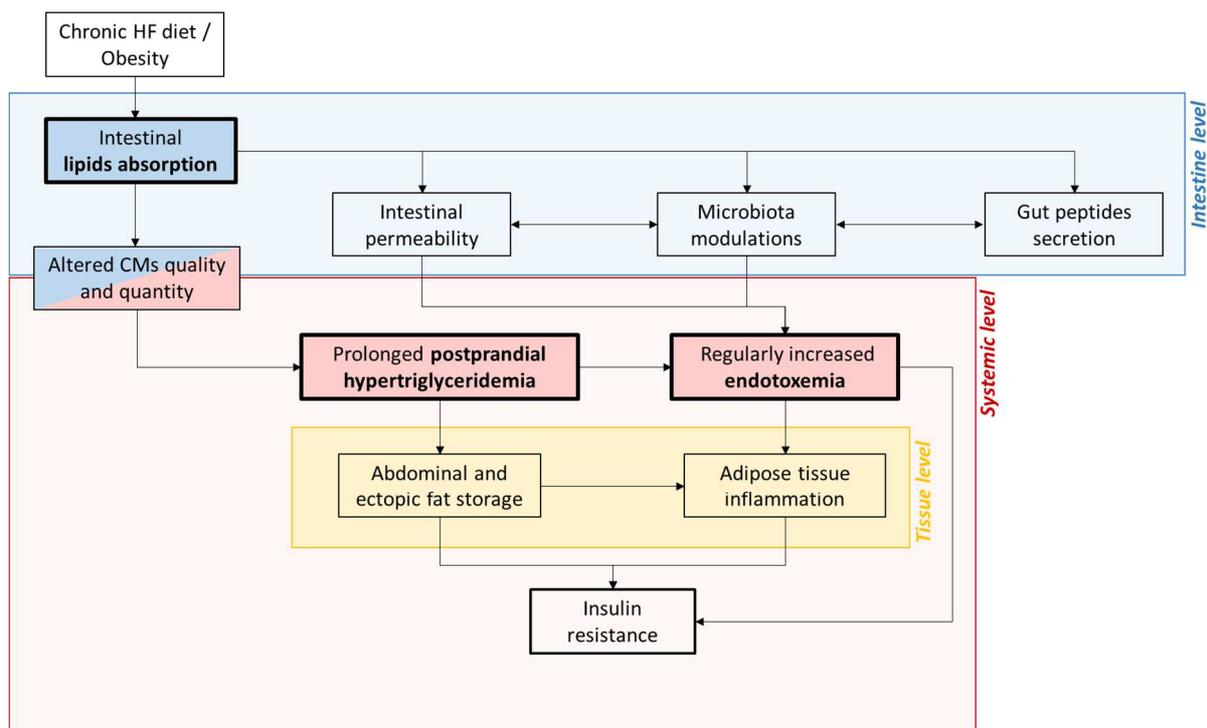
## **1.1. Postprandial hypertriglyceridemia**

During persistent positive energy balance, adipose tissue (AT) expands to facilitate the storage of TG [19]. This phenomenon leads to adipocyte hypertrophy, while increased number of adipocytes (hyperplasia) is a more favorable phenotype [20]. Adipocyte hypertrophy is significantly correlated with dyslipidemia, chronic low-grade inflammation and perturbed carbohydrate metabolism [21]. Localization of AT expansion is critical since an increase in visceral AT, in contrast to subcutaneous AT, is associated with MetS etiology [22]. After food intake, and under the control of several hormones including insulin, AT synthesizes TG from circulating FA and glucose, and stores them in adipocytes. This AT lipogenesis is predominantly a postprandial event [23]. In the postprandial state, TG are carried by lipoproteins called CMs and produced from dietary lipids by small intestine. FA coming from these CMs-TG are preferentially taken up by AT. More precisely, lipid storage occurs as early as one hour after a meal [24]. The rapid uptake of dietary lipids by AT is the consequence of two phenomena. First the endothelium capillary-anchored enzyme responsible for CMs-TG hydrolysis, lipoprotein lipase (LPL), is activated by the insulin in AT [25], while it is the contrary for LPL located in muscle tissue [26]. This also explains why insulin resistance leads to a decrease in the ability to synthesize and store lipids in AT [27]. The second reason is due to the route taken by gut-secreted CMs. They are transported by the lymphatic system to join the bloodstream through the left subclavian vein, thus bypassing the liver to first irrigate the heart and peripheral tissues such as AT. Unfortunately, the role of the lymphatic system on AT has only recently been studied [28,29]. Interestingly, FA from lymph are able to promote proliferation, differentiation of pre-adipocytes and hypertrophy of adipocytes [30]. Some studies have shown a link between disrupted integrity of collecting lymphatic vessels in the mesentery and the development of spontaneous obesity [16,28,31], particularly visceral obesity, and it has also been shown that consumption of a HF diet alters lymphatic vascularization [32].

After a meal, the secretion of CMs leads to TG elevation, also called postprandial hypertriglyceridemia. The level and duration of this phenomenon depend on the quantity and quality of gut-secreted CMs, and also on their clearance efficiency. CMs-TG clearance efficiency is modulated by LPL activity, which is regulated not only by insulin but also by other factors such as intestinally-secreted angiopoietin-4 (Angptl4) [33,34] or the CMs

apolipoprotein (Apo) C-II/ApoC-III ratio (ApoC-II is a LPL specific cofactor). The size and number of CMs also determine their clearance efficiency [35,36]. A growing body of evidence suggests that the characteristics of postprandial hypertriglyceridemia is a better marker of cardiovascular disease risk than fasting triglyceridemia [37]. Higher postprandial hypertriglyceridemia is generally observed in MetS [38,39] and in obesity [40]. More precisely, it has been shown that postprandial hypertriglyceridemia is higher in viscerally obese women than in women with general obesity [41,42]. Several reports showed that elevated postprandial hypertriglyceridemia is generally associated with abdominal fat accumulation in both men and women [43]. This higher postprandial hypertriglyceridemia results from increased CM production after a meal [39] and then delayed clearance of CMs-TG [40,44]. Moreover, MetS individuals also produce more hepatic very low density lipoproteins (VLDL) than healthy individuals [39]. These data indicate that increased production of CMs may also affect how the liver produces VLDL-TG, which are atherogenic [45]. One explanation may be the existence of a CMs-derived FA spillover, which escapes extrahepatic tissue uptake and thus becomes a circulating FA blood pool. These FA could in turn stimulate the synthesis of VLDL by the liver [46]. Such disturbances could be aggravated in a context of insulin resistance when AT lipolysis is less inhibited by insulin in the postprandial phase. Competition with VLDL can therefore lead to a decreased clearance of CMs.

As illustrated in Figure 1, alterations in postprandial hypertriglyceridemia may be responsible for ectopic fat accumulation in various tissues including the liver, heart, muscles, kidney and pancreas. These ectopic fat deposits can lead to lipotoxicity and the activation of inflammatory pathways [47], as well as metabolic complications such as insulin resistance, cellular stress, dysregulated energy metabolism and cellular signaling [48]. It can finally give rise to other metabolic perturbations such as cardiovascular disease, hepatic steatosis and chronic kidney disease. These disorders are all known to be associated with obesity [49]. The importance of chronic pathophysiological effects of high postprandial hypertriglyceridemia is illustrated by the work of Alcalá-Díaz *et al* [50], who found a positive association between the number of MetS criteria and the response of postprandial plasma TG.



**Figure 1: Effects of chronic HF diet or obesity on intestinal lipid absorption and CMs formation, and their metabolic consequences**

In the intestine, lipid absorption can modulate intestinal permeability, microbiota and gut peptides secretions. These three parameters are closely interconnected and even more modulated when high-fat (HF) diet is frequently administered and/or in case of obesity.

At the systemic level, a chronic HF diet and/or obesity induce an alteration of the quality and quantity of chylomicrons (CMs) produced in enterocytes and therefore secreted in the blood. These altered CMs are less hydrolyzed by lipoprotein lipase (LPL), stay longer in the blood and thus favor prolonged postprandial hypertriglyceridemia. Since CMs are known to carry lipopolysaccharides (LPS), this slower clearance of CMs is associated with a regularly increased endotoxemia. Changes in intestinal permeability and microbiota also contribute to this increase in endotoxemia.

In terms of adipose tissue, a chronic HF diet and obesity are associated with an abdominal fat storage. CMs-triglycerides (TG) are hydrolyzed into fatty acids, captured by adipocytes and stored again as TG at the cellular level. Subsequent hypertrophy is limited and ectopic fat deposition can occur in other peripheral organs such as the liver or muscle. Abdominal and ectopic fat storage induce adipose tissue inflammation and the combination of these phenomena can lead to systemic insulin resistance.

## 1.2. Postprandial inflammatory processes

Obesity and MetS are associated with a low-grade inflammation characterized by elevated systemic and local pro-inflammatory cytokines [51]. Besides adipocytes, AT is also composed of a stromal fraction that contains fibroblasts and immune cells. High-calorie diets

(especially HF) lead, during AT expansion, to an infiltration of immune cells, especially macrophages, which can subsequently switch from an anti-inflammatory (M2) to a pro-inflammatory (M1) profile [52]. Chronic inflammation in obesity is considered to be responsible for insulin resistance [53] and to increase the risk of complications such as MetS and cardiovascular disorders [54,55]. In rodents, AT inflammation is a key factor in systemic inflammation but its origin remain to be determined. However this role of AT in whole body inflammatory status is still controversial in humans [56,57]. Interestingly, a recent study including 1000 participants showed that hypertriglyceridemia during the postprandial state is a better predictor of inflammation than glycemia [58].

Another emerging contributor to AT inflammation is LPS blood levels, also called endotoxemia. LPS are components of the cell wall of Gram-negative bacteria and are found in vast amounts in the gut microbiota. It is estimated that the human intestine contains around 1 gram of LPS [59]. LPS are composed of an O antigen, a central region and an A lipid tail. This lipid fraction A has pro-inflammatory properties [60]. As described in the review by Boutagy *et al* [61], studies performed in humans or rodents have shown that experimental treatments with LPS trigger metabolic disturbances close to those observed in obesity and MetS. In mice, chronic injections of LPS lead to increases in weight gain and in the amount of both visceral and subcutaneous AT. Moreover, intestinal infusions of LPS triggered inflammatory reactions [62,63] and LPS are also described as triggering insulin resistance. Finally, endotoxemia was reported to be higher in cases of obesity [61,64]. Interestingly, postprandial LPS levels are also more elevated in obese individuals than in lean subjects [65].

At least three intestinal parameters can explain higher LPS translocation into the blood (Figure 1): alterations in the intestinal barrier, microbiota modifications and LPS transport through CMs. In obese patients, intestinal barrier is known to be altered and it positively correlates with systemic and intestinal inflammation [66,67]. A meal rich in lipids is sufficient to increase endotoxemia in both lean humans and mice [59,68], suggesting that the effects of a high-calorie diet on intestinal permeability precedes the onset of obesity. Interestingly, hyperglycemia was recently also described as disrupting the gut barrier [69]. The second parameter explaining this increase in endotoxemia is changes in the gut microbiota. Since the pioneering work of the Jeffrey Gordon's team [70], the microbiota has been shown to be the link between composition of the diet (HF diet), LPS translocation, AT inflammation and systemic inflammation in rodents. Obesity is generally associated with a reduced bacterial diversity [71,72]. In human and mice, this reduction is frequently associated with higher

quantities of *Firmicutes* (Gram-positive bacteria) and reduced abundance of both *Bacteroidetes* (Gram-negative) and *Bifidobacterium* (Gram-positive) [70,73]. It is worth noting that an abundance of *Bifidobacterium* is positively correlated with the integrity of gut barrier and reduced levels of circulating LPS [74], confirming the close interconnection between diet, microbiota and intestinal permeability [75,76]. Interestingly, intestinal microbiota composition and functions of humans and rodents adapt rapidly to changes in diet [77,78]. The third explanation is that LPS are carried by CMs [79]. This finding also highlights an association between HF diet and postprandial endotoxemia. Thus, the elevation of endotoxemia could also be a postprandial phenomenon.

### **1.3. Postprandial gut hormones in obesity and MetS**

Another postprandial factor that may also participate in the onset of obesity is gut hormones. They are secreted during a meal by enteroendocrine cells localized in the intestinal epithelium, and respond to the ingestion of nutrients [80]. Their main function is to regulate the efficiency of the digestion of nutrients. These hormones act on different organs either after their systemic release in the blood or by the activation of enteric nerve afferences. Most of these postprandial peptide hormones, in addition to regulating gastric emptying and the secretion of digestive juices, are also physiological regulators of appetite, satiety, energy expenditure and glucose and lipid metabolisms (for review see Psichas *et al.* [81]). Many studies suggest that the postprandial response of anorexigenic gut hormones such as glucagon-like peptide (GLP) 1 or cholecystokinin (CCK) are altered or blunted in obesity. For example, GLP-1-expressing cells are reduced in obese rodents compared to lean ones [82]. Moreover, combination of obesity and HF feeding diminishes sensitivity to exendin-4, a GLP-1 receptor agonist [83,84].

### **1.4. Conclusion**

Many postprandial phenomena originating from the intestine, such as hypertriglyceridemia, endotoxemia and gut peptide secretion, are altered in obesity. These postprandial disturbances likely affect not only the intestine but also AT and the whole organism through their contribution to the development of low-grade inflammation, insulin resistance and thus MetS. These findings have led some authors to consider obesity and its aggravation in MetS as a

postprandial condition. The crucial role of the intestine, not only as a supplier of energetic substrates, is also highlighted by current bariatric surgeries (Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy), which improve obesity and numerous of above-described postprandial factors while they only consist in physically removing a portion of small intestine [7,85]. Dietary lipids, more precisely their excess consumption, are generally associated with these postprandial disturbances. Therefore, the second part of our review will focus on the absorption of lipids and the intestinal consequences of this absorption.

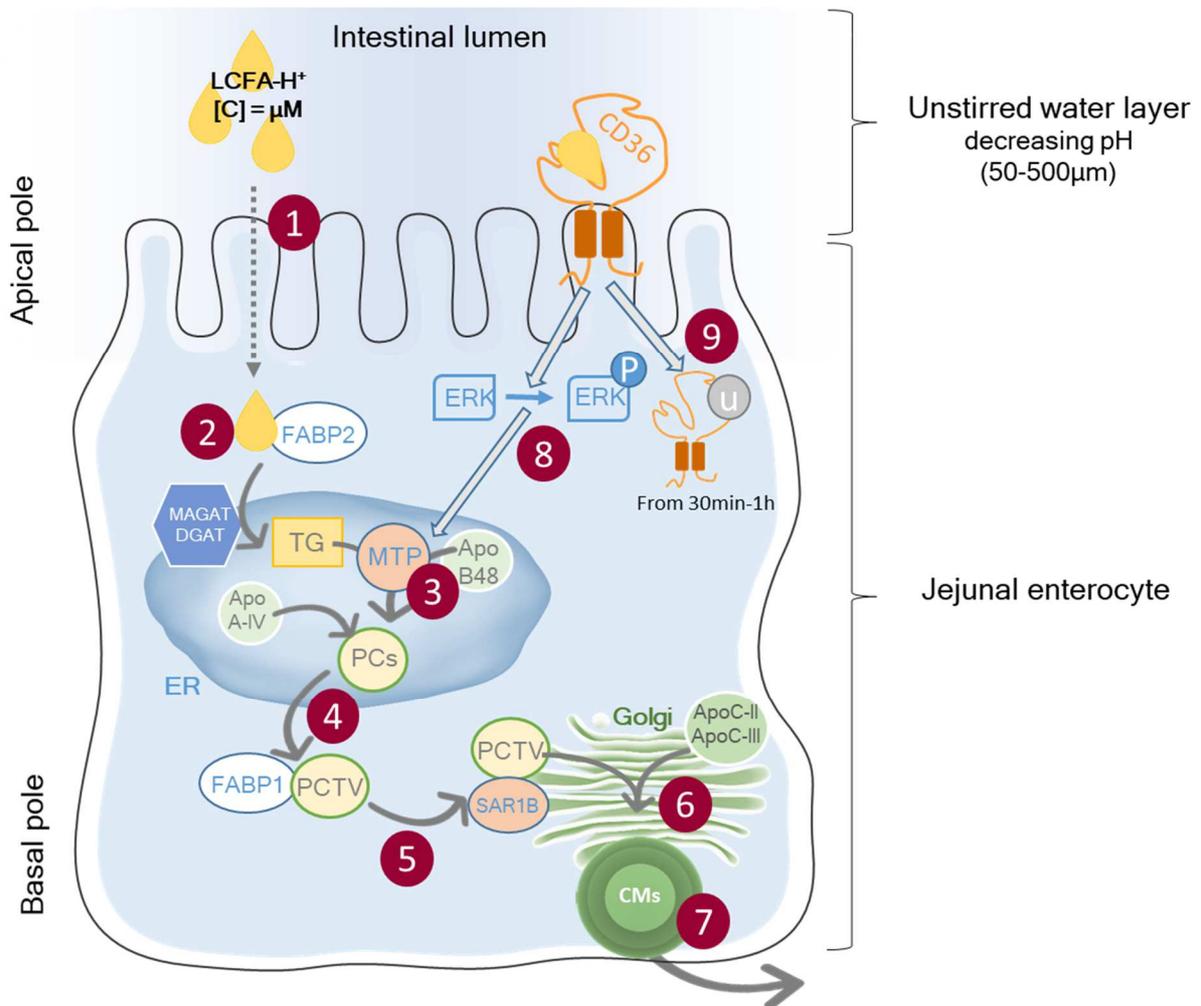
## **2. Mechanisms of fat absorption and associated intestinal effects**

### **2.1. From luminal TG to CMs formation**

TG esterified with long chain fatty acids (LCFA) are the most common form of dietary lipid. However, the intestine cannot directly assimilate TG, they need to be hydrolyzed into FA and 2-mono-acylglycerol (2-MAG) prior to absorption by enterocytes. The digestion of this type of fat is mainly obtained by pancreatic lipase, which is assisted by colipase. However, lingual and gastric lipases are also involved [86,87]. In the intestinal lumen, dietary fats are emulsified by bile acids produced by the liver (conjugated bile salts and phospholipids) in order to optimize their accessibility to lipase. Upon the ingestion of fat, the release of bile juice from the gallbladder to the gut is mainly activated by CCK. It was shown that Angptl4 secreted by enterocytes controls pancreatic lipase activity [88].

The major site of lipid absorption is the jejunum. Figure 2 schematizes the main intracellular steps of this absorption. Products of TG digestion incorporated into mixed micelles have to cross the specific intestinal environment called unstirred water layer before crossing brush border membrane of absorptive cells, enterocyte. This environment characterized by an acidic pH favors the micellar dissociation and the protonation of FA. After many discussions between biochemists and physiologists, it is now accepted that the lipid binding proteins identified at the apical level of enterocytes (CD36, fatty-acid transporter 4 (FATP4)...) are not efficient transporters of FA (for review see Niot *et al.*, 2009 [89] and Ko *et al.*, 2020 [90]) especially during fat absorption. During this period, the concentration of FA in the intestinal lumen reaches the range of micromolar ( $\mu\text{M}$ ). This requires a low affinity and high capacity

transport system, such as passive diffusion, which is facilitated by FA protonation (Figure 2, Step 1).



**Figure 2: Main steps of intestinal lipid absorption in enterocytes**

1) Protonated long chain fatty acids (LCFA-H<sup>+</sup>) passively enter the enterocyte; 2) At the cytosol level, LCFA are taken over by the binding protein FABP2, and sent to the endoplasmic reticulum (ER) membrane, where they are re-esterified into triglycerides (TG) by MAGAT and DGAT; 3) In the ER lumen, MTP combines TG with ApoB48 and then ApoA4 to form pre-chylomicrons (PCs); 4) Transport of PCs requires specific transfer vesicle budding (PCTV), which involves FABP1; 5) These PCTV are addressed to the Golgi where they are recognized by proteins including Sar1B; 6) Maturation of PCs by adding ApoC2 and ApoC3 results in the formation of mature chylomicrons (CMs); 7) CMs are then secreted by exocytosis into the intercellular space; 8) Binding of fatty acids (FA) to CD36 increases expression of MTP and ApoB48 through an activation of ERK1/2 kinase signaling pathway; 9) FA-activated CD36 is rapidly degraded by the proteasome after ubiquitination.

Within enterocytes, FA are transported by fatty-acid-binding protein (FABP) 1 and 2. The precise specific role of these two cytosolic proteins are not totally elucidated but they seem to be involved in trafficking within enterocytes [89,90] at different steps: transport to the endoplasmic reticulum (ER) and then to the Golgi. Then 2-MAG and LCFA reach the ER membrane to be re-esterified into TG through the 2-MAG pathway (Figure 2, Step 2). This pathway is specific to the intestine and the main enzymes involved are acyl-CoA monoacylglycerol acyltransferase (MAGAT) and acyl-CoA-diacylglycerol acyltransferase (DGAT) [90]. At the level of the ER lumen, TG are incorporated into pre-chylomicrons (PCs) *via* the microsomal triglyceride transfer protein (MTP), which leads to the lipidation of one ApoB48 with TG (and also cholesterol ester) (Figure 2, Step 3). The more fat a meal contains, the more the amount of TG per PC increases and the larger it becomes [91]. MTP is essential for the synthesis and secretion of CMs. In mice and humans, a defect in MTP function (knock out or mutation) reduces the production of CMs (for recent review see Alaa Sirwi *et al.*, 2018 [92]). This step is thus considered to be a step that limits fat absorption. In the ER, ApoA-IV is added and is thought to stabilize PCs particle growth. Although absorbed TG are mainly incorporated into PCs, some newly synthesized TG can form cytosolic lipid-droplets. The quantity of lipid-droplets seems dependent on nutritional status, and it may constitute a transient lipid storage pool for fat absorption, probably to avoid saturation of the secretory pathway as well as intestinal lipotoxicity [93]. Interestingly, oral glucose is able to trigger mobilization of stored TG for the secretion of CMs in both rodents and humans [94,95]. This highlights that dietary glucose has an early effect on intestinal lipid metabolism. Then PCs are transferred to the Golgi for maturation before their exocytosis in the intercellular space of the intestinal epithelium. This transit remains poorly understood, but it is thought to occur *via* intestine-specific vesicles, called pre-chylomicron transfer vesicles (PCTV). They are large enough to transport PCs that originate from the budding of ER membranes. It appears that several proteins (transmembrane and cytosolic) participate in PCTV formation, including CD36 and FABP1 (Figure 2, Step 4). Deficiencies in these proteins limit the quantity of PCTV formation in rodents [96] and deficiencies in secretion associated Ras related GTPase 1B (Sar1B), which is involved in ER budding (Figure 2, Step 5), leads to TG retention in enterocytes and absence of CMs secretion [97]. Therefore, the transit step from ER to Golgi is considered as a rate limiting step of lipid absorption [89,90]. In the Golgi, ApoA-I, ApoC-II and ApoC-III are added to PCs. The two latter regulate LPL activity (for recent review see Kersten, 2021 [98]). The passage of CMs into the Golgi is also associated with their glycosylation (Figure 2, Step 6). CMs are then secreted into the intercellular space by

exocytosis (Figure 2, Step 7), where they have to cross the basement membrane lining intestinal epithelial cells to enter into the *lamina propria*. It is not yet clear how CMs cross this membrane, whether it is through fenestrations or by simple rupture of the basal lamina [90,99]. Moreover, according to different authors, the accumulation of CMs in the intercellular space of the intestinal epithelium might increase intestinal permeability by creating distension and therefore altering the tight junctions of the epithelium [100]. In early phase of lipid absorption, FA binding to CD36 increases MTP and ApoB48 expression through the activation of intracellular kinases [13] (Figure 2, Step 8). Then, rapidly during lipid absorption, LCFA induce a rapid drop in gut mucosal CD36 content (see paragraph 3.2). Indeed, dietary FA induce a rapid polyubiquitination of activated CD36 which is then targeted to degradation *via* the ubiquitin-proteasome pathway [13] (Figure 2, Step 9). To sum up, except MTP and Sar1b, other proteins involved in the formation of CMs do not seem to limit the quantitative efficiency of lipid absorption. However, it should be kept in mind that no quantitative modifications of lipid absorption (net absorption) does not mean no qualitative modifications, which may have subsequent relevant physiological consequences. For instance, the secretion of TG in small CMs may affect their clearance because LPL is less effective on small CMs than on large ones [36]. This may result in an elevation of postprandial hypertriglyceridemia.

Less efficient jejunal fat absorption may trigger the recruitment of the ileum for this purpose. Under normal conditions, this part of the intestine is not involved in fat absorption because FA have already been absorbed when the bolus reaches the ileum [101]. However, this change in the intestinal distribution of fat absorption activates the secretion of lipid-induced ileum hormones, such as GLP-1 peptide YY. These secretions contribute to adaptive responses in the digestive tract, known as the ileal brake. Its role is to compensate the lower jejunal fat absorption efficiency by lowering gastric emptying and formation of CMs [102]. Moreover, these hormones stimulate the anorectic pathway in order to decrease food intake. Such adaptive mechanisms are observed when there is an intestine-specific deficiency in MAGAT2 [103], or after treatment with an MTP inhibitor [104]. In the latter situation, a loss in the preference for fat but not for sucrose have even been reported [104]. Moreover, deficiencies in MAGAT2 and CD36 have been reported to lead to increases in energy expenditure under HF conditions [103,105]. This effect could also result from the ileal recruitment and the subsequent increase in GLP-1 secretion [106]. In the short term, this hormone secretion could

contribute to limit obesity development, but a kind of GLP-1 resistance may emerge in the long term (see paragraph 1.3.).

## **2.2. Jejunal microbiota and fat absorption**

Jejunal fat malabsorption is associated with an increased amount of lipids in the jejunal lumen, which modifies the composition of the jejunal microbiota (for more details see the review Lema *et al.*, 2020 [107]). While the frequently-mentioned colon microbiota is estimated to consist of  $10^{12}$  to  $10^{14}$  colony-forming units (CFU)/mL, the jejunal microbiota appears to contain approximately  $10^4$  to  $10^7$  CFU/mL. It is almost exclusively studied in rodents (as it is not easily accessible in humans). The composition is different from the fecal microbiota because it is exposed to different factors: oxygen, nutrients, pH, bile salts, transit time of the food bolus. These factors differ according to the nutritional state and that explains the great variations observed in jejunal microbiota [107]. It seems that unlike in the colon, *Firmicutes* (among them *Lactobacillus*) and *Proteobacteria* are the main phyla (in the colon it is the *Bacteroidetes*). This microbiota can affect the intestinal metabolism by producing different metabolites (such as short-chain FA, secondary bile salts). It is notable that these microorganisms, in particular *Lactobacillus*, also produce lipases that can affect digestion of dietary TG [108]. For example, it was shown that jejunal microorganisms contribute to the increase in fat digestion and to FA uptake in the jejunum [109]. Interestingly, the work of Martinz-Guryn *et al* [109] shows that a HF diet affects the microbiota of the small intestine in addition to the fecal microbiota [110]. These HF-induced changes in jejunal microbiota ecology seem to be responsible for an increase in fat absorption through an up-regulation of proteins involved in CMs formation [109]. Apart from lipids, bile acids, which are released in the gut to facilitate fat absorption, have been reported to affect microbiota composition [64].

## **2.3. Potential adaptations of gut mucosa and microbiota to HF diet**

Interestingly, a HF diet leads to an increase in the activity of pancreatic lipase, indicating that TG digestion is able to adapt to the lipid content of the diet [111]. Contrary to what was initially believed, different groups, including our team, have demonstrated that the intestine is able to adapt the lipid absorption capacity of the jejunum to the lipid content of the diet [112]. This adaptive process was initially shown to occur after three weeks of a chronic HF diet, but

more recently it was also reported after only 3 days of a HF diet [112,113]. We observed an increase in intestinal cell proliferation under HF conditions, which increases intestinal absorption surface and mRNA levels of the main and limiting proteins involved in CMs synthesis and secretion (FABP, MTP...) [112]. These adaptations are reversible and disappear with the return to a normal-fat diet [112]. Increased mRNA levels of these proteins are correlated to fat quantity in the diet [114], and some studies strongly suggest that these regulations can be observed after a single lipid load [115]. HF diet is associated with an increase in the size of secreted particles [91]. Interestingly, an adaptation of the ability to secrete larger CMs is also observed because an increase in the size of basal lamina fenestrations occurs as early as 2 days under HF condition [99]. Jejunal adaptations to the lipid content of the diet has a physiological relevance because a defect in this mechanism is associated with an enhanced sensitivity to diet-induced obesity [116]. Similarly, in mice with MetS, this adaptation is blunted and it seems to be due to hyperinsulinemia: secreted CMs are smaller, postprandial hyperglycemia is higher, and ileal recruitment is observed [115].

Gut adaptations to the quantity of lipids in the diet involves not only mucosal changes but also jejunal microbiota modulations. For instance, germ-free mice under HF conditions display steatorrhea due to impaired fat digestion and absorption. However, these alterations were blunted when the germ-free mice were transplanted with the microbiota of HF-fed conventional mice, but not when microbiota came from conventional mice fed a low-fat diet. The authors showed that fat digestion was enhanced *via* an effect on CCK receptors in the pancreas. They also reported an increased FA uptake associated with higher intestinal level of DGAT2 and CD36 proteins [109]. Overall, this could potentially partially explain the link between microbiota and dyslipidemia [117].

In addition to adaptations in the amount of dietary lipids, adaptive intestinal processes have also been described after bariatric surgery. Bariatric surgeries have been reported to rapidly reduce triglyceridemia (for review see Heffron *et al* 2016 [118]). A recent work shows a reduced TG secretion in lymph of RYGB compared to Sham control rats, a reduction which was associated with an enterocyte lipid metabolism reprogramming [119]. They describe modification of proteins involved in CMs secretion such as a decrease in CD36 and FABP2 expression [119].

## **2.4. Lipid absorption, gut barrier integrity and inflammation**

Eating a HF diet is also known to induce side effects in the intestinal epithelium, including an increase in gut barrier permeability [120–122]. Reports suggest that saturated and unsaturated FA are able to affect both the expression and distribution of tight junction proteins [8,75]. A recent study in mice showed that a single intake of palm oil was sufficient to trigger hyperpermeability (loss of several tight junction proteins at the cell-cell contacts) [75]. This rapid lipid-mediated hyperpermeability is also observed in humans as early as one day after starting a HF diet [66]. Interestingly, dietary lipids are able to exacerbate the intestinal permeability observed in obese humans [66]. This FA effect might be directly (*via* a cell signaling) or indirectly mediated *via* the secretion of pro-inflammatory factors such as cytokines, which are able to affect intestinal permeability [75]. Even if the origin of this phenomenon is not known, a situation of chronic excess in dietary lipids could promote the onset of a vicious circle between inflammatory status and intestinal permeability. Altogether, these alterations could lead to a leaky epithelium and therefore the entrance of luminal pro-inflammatory molecules such as LPS into the bloodstream. Finally, because CMs are known to carry LPS [79], increasing the synthesis of CMs and altering their clearance may increase endotoxemia. All these data explain why numerous studies on HF-diet-induced obesity, at least in rodents, have highlighted a link between increased intestinal permeability, inflammation and metabolic alterations [72,123]. Interestingly, some authors have shown that the effects of a HF diet on intestinal permeability precede the onset of obesity [124].

## **2.5. Conclusion**

Absorption of lipids is a complex phenomenon that is far from being elucidated, particularly concerning CMs exocytosis and passage into the lymph. However, this step may be crucial in the maintenance of the intestinal barrier. Interactions with microbiota seem to be necessary to optimize lipid absorption but also remain poorly understood. The efficient absorption of lipids with the production of well-degradable CMs would favor the systemic distribution of subsequent dietary lipids and therefore limit inflammatory effects. However, the steps of fat absorption are associated with the entrance of pro-inflammatory compounds from the microbiota into the blood. Moreover, the mechanisms of gut lipid absorption are highly adaptable to dietary fat content. If absorption defects are associated with obesity, it remains to be determined whether they are the cause or a consequence of obesity. It is known that

postprandial hyperinsulinemia is responsible for the dysfunction of this adaptation. Logically, intense fat absorption observed under HF condition may aggravate the adverse effects of fat absorption. However, the question that needs to be answered is the importance of the quality of ingested lipids in these phenomena. Some authors suggest that it could depend on the type of FA ([75] and for review see Cândido *et al.*, 2020 [125]). In any case, the mechanism of lipid absorption is governed by several proteins. The third part of this review will thus focus on the lipid-sensing protein CD36. The interest in CD36 is supported by data obtained over the last few years showing that relatively common polymorphisms in the CD36 gene, which often affect CD36 expression [126], are associated with abnormal circulating lipid levels and especially with alterations in postprandial lipemia and a higher likelihood of MetS [127]. Numerous studies using the CD36-deficient mouse model or using specific inhibitors have shown that CD36 is involved or may be involved in all the functions of the intestine related to obesity, even if the mechanisms are not understood.

### **3. Intestinal CD36 may be a key player in the prevention of obesity**

#### **3.1. A lipid receptor in the orodigestive tract**

CD36 is an ubiquitous scavenger expressed in cells with high lipid metabolism (adipocytes, myocytes, platelets, immune cells, enterocytes, microvascular endothelial cells as well as retinal and mammary epithelial cells) but also in neurons, taste bud cells and enteroendocrine cells. The latest structural studies of CD36 have shown that it is composed of a large extracellular loop that binds LCFA with high affinity (nM range), but also hexarelin, oxidized LDL or phospholipids, thrombospondin and erythrocytes infected with *Plasmodium falciparum* [11]. More recent data indicate that it could also bind LPS and some bacteria [18,128]. This last point will be further discussed below. The C-terminal cytoplasmic tail can interact with SRC-tyrosine kinases and thus CD36 is able to activate signal transduction alone or in association with other transmembrane proteins (such as toll like receptors (TLR)). In addition, CD36 can undergo a set of post-transcriptional modifications (glycosylation, ubiquitination, palmitoylation and phosphorylation) that affect its cellular localization (membrane, raft...) and rapidly modulate its functions (For review see Pepino *et al.*, 2014 [11], Martin *et al.*, 2011 [12] and Luiken *et al.*, 2016 [129]). For instance, GLP-2-induced

glycosylation of intestinal CD36 triggers its membrane recruitment and may thus promote CMs formation [130]. Its dephosphorylation by alkaline phosphatase leads to reduced lipid absorption [131] and its ubiquitination may control its temporal action [13]. Altogether, these data show that CD36 is a multifunctional protein that participates to innate immunity, inflammation and lipid metabolism. Moreover, CD36 functions can quickly change according to its environment.

Our team has shown that CD36 is also expressed on the surface of taste receptor cells (in rodents, pigs, and humans) of taste buds, which compose the gustatory papillae [132]. It was shown in taste receptor cells that LCFA-bound CD36 lead to activation of SRC kinases, subsequent increase in intracellular calcium and release of neurotransmitters [133]. It activates gustatory nerves and then fat perception. This mechanism strongly suggests the existence of a sixth taste, the taste of fat, and would explain spontaneous preferences for lipids [12]. If established in rodents, data still need to be confirmed in humans. In addition, this fat-perception triggers the cephalic phase of digestion, resulting in the secretion of small amount of digestive juices [132], preparing intestine for subsequent fat absorption.

At the intestinal level, CD36 is expressed in enterocytes, enteroendocrine cells, endothelial cells as well as gut macrophages [134]. It is not expressed in mucus cells, and to date there is no information regarding its expression in M cells or tuft cells [11], which are implicated in gut immunity and nutrients sensing [135]. Intestinal CD36 is highly expressed at the apical side of differentiated enterocytes (in the 2/3 upper part of villosity) located in the jejunum of rodents and humans [136,137] and it is weakly expressed or undetectable in the ileum and colon. Its involvement in lipid absorption mechanisms is supported by human data showing abnormal postprandial lipemia in CD36-deficient subjects or those with a single nucleotide polymorphism. Indeed, a defect in CMs formation was observed in addition to an altered lipid clearance by extra-intestinal tissues, which also requires local CD36 [138,139].

### **3.2. CD36, intestinal lipids absorption and postprandial hypertriglyceridemia**

Unlike in other tissues such as heart, muscle or adipose tissue (for review, see Glatz and Luiken, 2020 [140]), our team has demonstrated that in the intestine CD36 is not an efficient transporter of dietary FA. Using a physiologically mice model, the *in situ* isolated jejunal

loop, which retains both the dynamism of absorption and the unstirred water layer bordering the intestinal epithelium, we showed that FA uptake of CD36-deficient mice was identical to that of wild-type mice. From a theoretical point of view, a role as an efficient transporter is not relevant for a protein with a high affinity for FA (nM range) when the concentration in the intestinal lumen during lipid absorption is estimated to be much higher (range of  $\mu\text{M}$ ) [9]. However, despite this lack of effect on FA uptake, CD36-deficient mice and humans show less TG secretion and up to 35% smaller CMs whose clearance and degradation is delayed. These alterations partly explain the HF diet- or lipid load-induced postprandial hypertriglyceridemia observed in the absence of CD36 [139,141]. However, CD36 from heart and skeletal muscle cells, by controlling FA utilization, may also contribute to the regulation of hypertriglyceridemia [142,143]. Altogether, these findings highlight a defect in CMs processing in CD36 deficiency, which is also highlighted by the subsequent observed ileal recruitment and retention of TG in jejunal mucosa under HF condition [141].

Our data suggest that CD36 optimizes CMs formation by coordinately stimulating proteins involved in PCs synthesis. Indeed, we have shown that binding of FA to CD36 triggers the activation of cell signaling *via* extracellular signal-regulated (ERK) 1/2 kinases, that leads to an increased expression of MTP and ApoB48. Moreover, this signaling seems also to increase the expression of FABP1, which favors the formation of PCTV, thus the transfer of PCs from ER to the Golgi. This latter possibility makes sense since CD36 is known to be involved in vesicles budding from ER [9,96]. Interestingly, this signaling function of CD36 only occurs in the early phase of fat absorption because CD36 is degraded by the proteasome after ubiquitination, *in vivo*, from 1 h after gastric gavage with oil (-50%) and *ex vivo* after 20 min [13]. This regulation is regularly observed for receptors and it is therefore another argument indicating that CD36 is not an efficient lipid transporter during the intestinal absorption phase of dietary lipids. These data suggest that CD36 acts as a lipid sensor which contributes to the adaptation of CMs synthesis metabolism to the diet lipid content (Figure 2).

From a hormonal point of view, and in addition to the modulation of fat absorption, CD36 is also involved in the enterocyte production of oleoylethanolamide, an anorectic peptide, synthesized from dietary oleic acid. This production is abolished in CD36-deficient mice [144]. CD36 is also expressed at the apical side of enteroendocrine cells secreting CCK and secretin, which facilitate fat digestion but are also satiety-related hormones [14]. In these ways, intestinal CD36 can indirectly contribute to the control of food intake mediated by dietary FA (for review see Niot and Besnard, 2017 [6]).

Using a model of mice with HF diet-induced MetS, we showed that lipid load-induced postprandial hyperinsulinemia is able to alter intestinal CD36 signaling: delay in the induction of proteins expression involved in CMs synthesis/secretion [115]. This translates a less efficient intestinal adaptation to the lipid content of the diet. These alterations result in the secretion of smaller CMs and postprandial hypertriglyceridemia [115]. Interestingly these alterations recapitulate those observed in CD36-deficient humans, which are at risk to develop MetS [127]. Together, these data highlight that in situation of excess fat consumption, intestinal CD36 may be involved in the onset of MetS.

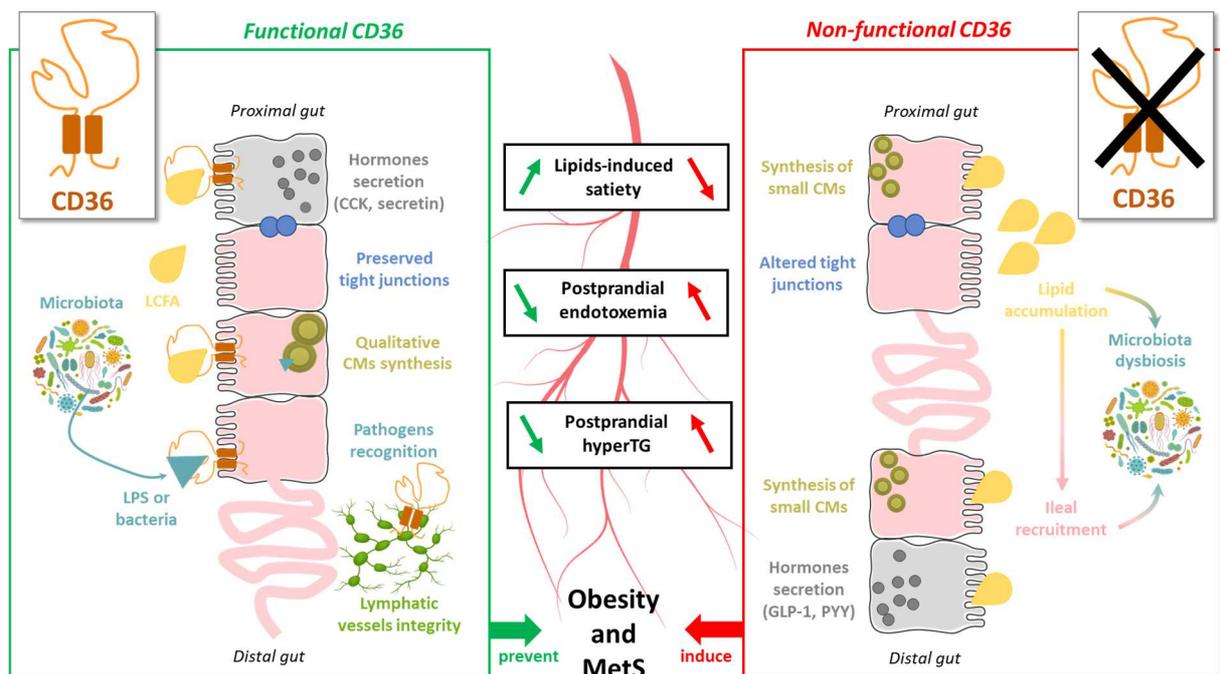
### **3.3. CD36 and postprandial endotoxemia**

As mentioned in the paragraph 2.4. of this review, gut lipid absorption is associated with para- or transcellular passage of LPS into the bloodstream and therefore with an increase in endotoxemia, which is known to contribute to the development of obesity. By altering CMs synthesis (smaller) and clearance, deletion of intestinal CD36 can probably and indirectly increase endotoxemia. As already mentioned an altered secretion of CMs is associated with an increase in gut permeability and if the clearance of small CMs is slowed down, it means that CMs-transported LPS stay longer in the blood prior to be evacuated. In accordance with this hypothesis, blood level of LPS has been reported to be two fold higher in CD36-deficient mice submitted to a triolein bolus [15]. Interestingly, the model of mice with HF diet-induced MetS is also characterized by elevated endotoxemia [145]. The increased gut permeability during lipid absorption and the associated-leakage of LPS is also supported by a decrease in tight junctions proteins such as occludin in CD36-deficient mice [15]. It is interesting to note that such a decrease in occludin has been reported in obese subjects [66]. Thus, intestinal CD36 may be also involved in this tight junction alteration. As mentioned above, some CD36-dependent effects are mediated by ERK1/2 intracellular pathways [13] and it was reported that tight junctions proteins are regulated by ERK kinases. Moreover, another study on rats cells demonstrates that inhibition of occludin expression by mon-(2-ethylhexyl) phthalate was mediated by the activation of the ERK1/2 pathway [146]. In a recent work by Akiba's group [18], they show that after a single lipid bolus, fat absorption-mediated LPS transport is a physiological phenomenon, which is mainly transcellular and not paracellular. Moreover, this study displays that LPS cellular uptake is dependent on raft membrane microdomains and CD36 [18]. Indeed, the pretreatment of intestine with sulfo-N-succinimidyl oleate (SSO), a CD36-inhibitor, reduces the release of LPS. However, these data differ with results obtained on CD36-deficient mice and showing that the absence of CD36 promotes

elevated endotoxemia [15]. Further studies are needed to disentangle this discrepancy. As explained before, CD36 can undergo many posttranslational modifications triggered by different ligands. Therefore, SSO, which has the same CD36 binding site than other ligands, could also induce CD36 posttranslational modifications. One explanation could be that such biochemical structure modifications could modify protein-protein interactions with CD36 in rafts as well as its signaling. For instance, internalization of LPS from *Escherichia coli* is dependent on the interaction between CD36 and TLR4 [147,148]. Another explanation for this discrepancy may be the nature and quantity of used FA. Ghezzal *et al.* [75] demonstrated that palmitic acid induces increase in permeability but not oleic acid. It would be interesting to repeat the same experiment but using animals with altered intestinal permeability such as previously subjected-mice to chronic HF diet.

Increase in postprandial endotoxemia may also be the consequence of microbiota dysbiosis. We have previously indicated that both intestinal lipid absorption and endotoxemia are associated with changes in small intestinal microbiota [109]. Numerous data in the literature show that dysbiosis (especially due to HF diet) is often associated with an increased endotoxemia [149]. First, we can postulate that when CD36 is deleted or dysfunctional, altered efficiency of lipid absorption may increase amount of gut luminal lipids and therefore can affect the local intestinal microbiota. Secondly, a more direct effect of CD36 could be considered on the ecology of the microbiota. A role in the recognition of pro-inflammatory compounds but also of bacteria has been described for CD36 in particular *via* its cooperation with TLR2, TLR4 or TLR6 in other cells [150–152]. Moreover, emerging evidences show that CD36 could be involved in bacteria-induced inflammation through a recognition of both Gram-positive and Gram-negative pathogens (for review see Areshoug and Gordon, 2009 [17]). It has been shown *in vivo* that CD36 can also participate in the internalization of certain bacteria on HeLa epithelial cells [17]. Although not detailed in this review, numerous data have reported an involvement of CD36 in sterile inflammation and atherosclerosis [153]. Interestingly, the inflammation response also involves CD36-mediated mitogen-activated protein (MAP) kinases activation [128]. Thus, if these CD36 functions are transposable, intestinal CD36 could participate in the regulation of intestinal microbial ecology, at the jejunal level. The fact that CD36 is strongly regulated in the postprandial period could consequently also rapidly modify microbiota. Further microbiota analyses in case of CD36 deletion or dysfunction could clarify this point. Finally, a very interesting work using CD36-deficient mice but only in lymphatic endothelial cells (showing that CD36 is expressed in

both lymphatic capillaries and collecting vessels), displays that CD36 is crucial for lymphatic integrity and dietary lipid transport [16]. It is worth noting that disruption of lacteals (the intestinal lymphatic capillaries) blocks CMs production and is protective from obesity (as reviewed in [154]). This CD36 function may partly explain the lower TG secretion [141] observed in the absence of CD36 but not the smaller CMs. These lymphatic data reinforce the above-mentioned link between lymphatic circulation (from lacteals to collective vessels) and obesity.



**Figure 3: Pivotal role of CD36 in gut-mediated postprandial parameters**

When functional (green frame on the left), intestinal CD36 is expressed in enterocytes (pink cells) and enteroendocrine cells (gray cells). Its lumen activation by food long chain fatty acids (LCFA) contributes to the production of qualitative chylomicrons (CMs). CMs are known to transport lipopolysaccharides (LPS). Qualitative CMs are well hydrolyzed lipoprotein lipase (LPL) in the blood and thus rapidly degraded. They increase transiently postprandial hypertriglyceridemia and endotoxemia. CD36 activation also improves tight junction cohesion, which preserves intestinal integrity after a meal and therefore reduce the passage of LPS. And finally, its activation at the surface of enteroendocrine cells induces gut hormone secretion such as secretin and cholecystokinin (CCK), which are able to stimulate satiety. These CD36-dependent effects decrease two postprandial blood parameters, hypertriglyceridemia and endotoxemia and therefore prevent the development of obesity and MetS. When CD36 is not expressed or non-functional (red frame on the right), enterocytes synthesize smaller CMs, which are less recognized by LPL and the subsequent increase in postprandial hypertriglyceridemia and endotoxemia is higher. Deletion in CD36 is also associated with altered tight junctions and increased in both gut permeability and endotoxemia. In the absence of

CD36, dietary lipids accumulate in the gut lumen, are available as substrate for local microbiota and thus generate dysbiosis. Those residual lipids are detected and absorbed in the ileum (distal part of the small intestine) but CMs are not qualitative neither. This ileal recruitment is characterized by lipid-induced secretion of gut hormones such as glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) which reduce gastric emptying and activate satiety. Finally, dietary lipids in distal part of the gut also generate local microbiota dysbiosis. Overall, non-functional CD36 is associated with longer postprandial hypertriglyceridemia and endotoxemia which favor the development of obesity and MetS.

### **3.4. Conclusion**

Both dietary lipids and compounds of the microbiota including LPS can activate CD36. This ligands diversity contributes to its multiple functions at the intestinal level: cell signaling that regulates lipid absorption efficiency, intestinal and lymphatic permeability, inflammation and possibly ecology of the microbiota. These data may indicate that functional intestinal CD36 could have a protective effect during excessive lipid consumption and therefore prevent the onset of metabolic disorders such as postprandial hypertriglyceridemia, endotoxemia and finally obesity. Proven and potential functions of intestinal CD36 could be: 1) intestinal CD36 facilitates lipid digestion; 2) intestinal epithelial CD36 optimizes synthesis of large and well-degraded CMs in the bloodstream, thereby limiting postprandial hypertriglyceridemia and endotoxemia; 3) CD36 would maintain both integrity of intestinal epithelium and lymphatic endothelium. This dual function would avoid passage of pro-inflammatory molecules, lymphatic leakage and inflammation; 4) CD36 may control lipid uptake *via* an action on satiety-related gut peptides. Figure 3 outlines these multifunctional aspects of CD36 as well as the consequences of its dysfunction / deletion.

## **Conclusions and perspectives**

Many intestine-related postprandial phenomena are affected in obesity, including postprandial intestinal metabolism, triglyceridemia, endotoxemia, microbiota modulations and secretion of gut hormones. Knowing that human beings spend most of the day in postprandial conditions, the effect of these alterations on metabolism is surely considerable. These findings place the

intestine, its mucosa and its microbiota as key players, if not the starting point, in the development of HF diet-induced obesity and associated disorders such as inflammation and insulin resistance. Indeed, there is evidence that some metabolic alterations occur after only a single lipid load, and the intestine is the first organ to come into contact with and manage excess dietary lipids. To do so, several adaptive mechanisms take place in the intestine in order to optimize lipid absorption. With a HF diet, chronic excess lipids can alter the gut's adaptive capacity and repeated systemic adverse effects occur. For instance, since CMs carry pro-inflammatory LPS, excess dietary lipids can increase endotoxemia; recurrently enhanced endotoxemia can induce but also maintain inflammation in AT. This would in theory lead to AT insulin resistance and secretion of pro-inflammatory cytokines. All of these factors contribute to the systemic low-grade inflammation reported in obesity [64].

Dysfunction or absence of the multifunctional CD36 receptor could be involved in all these alterations and thus could have a key role in the prevention of obesity, at least obesity induced by lipid excess. Indeed, as suggested by studies on CD36 polymorphisms, people with CD36 dysfunction are more prone to develop MetS. Interestingly, CD36 function is impaired by postprandial hyperinsulinemia, which is partly induced by gut peptides such as the incretin GLP-1. In addition to their role in fat absorption, current findings highlight the involvement of CD36 in the maintenance of the intestinal barrier integrity, LPS entrance, and the control of microbiota ecology and gut hormone secretions. However, most of the data were obtained in CD36-deficient mice, and since CD36 is ubiquitous, it is necessary to work with mice depleted in CD36 in a tissue specific manner. This could be implemented by generating specific deletions in the different cells types that express CD36 (epithelial, enteroendocrine, immune and endothelial) in order to evaluate the actual intestinal contribution to the suspected alterations. To date, only the contribution of CD36 from endothelial cells is known, and studies in epithelial cells are still in progress. Depending on the obtained results, intestinal CD36 could eventually constitute a therapeutic target for the treatment of obesity and / or MetS, conditions which are known to be associated with CD36 dysfunction. For instance, treatment with strong, and non-absorbable (to avoid systemic effects) CD36 agonists could be considered. Since CD36 is causally involved in HF diet-induced insulin resistance and contractile dysfunction of heart and muscles [142,143], the non-absorbable condition would be necessary to ensure an intestinal specific effect and avoid diseases in other tissues [155,156]. The effects of dietary lipids depending on quality have not been addressed in this review [125]. Data suggest that saturated and unsaturated lipids have differing effects on the

intestine (including microbiota) [75,125] and that CD36 might have preferential ligands [14] and so its functions might be differently modulated. Further studies on this subject could help to clarify nutritional lipid recommendations. This review focused on excess dietary lipids, which brings to light the disorders observed in obesity and Mets, but the issue of excess carbohydrates also has to be considered. Indeed, western diets are generally too rich in both, and carbohydrates can also affect CD36 function *via* increases in postprandial insulin blood levels.

## **CRedit authorship contribution statement**

LJL: Conceptualization, Writing - review & editing, Figures formatting, Validation; SM: Conceptualization and Figures formatting; AT: Writing - review & editing, Bibliography formatting; IN: Supervision, Conceptualization, Writing - original draft, Writing - review & editing, Validation;

## **Declaration of interest**

The authors have no conflicts of interest.

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