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Lipid Droplets and Very Low Density Lipoproteins; Their Relation to Insulin Resistance

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1. Introduction

1.1 Organization of the lipid droplet

Lipid droplets are organelles involved in the storage of neutral lipids, such as triglycerides or cholesterol esters. These molecules are neither soluble in water nor in the amphipathic monolayers that build up intracellular membranes, and are therefore stored in a separate hydrophobic “oil phase”, which is the core of the lipid droplet. Since this is a general process, the ability to form lipid droplets is preserved throughout evolution and is present in most mammalian cells (Martin and Parton, 2006; Murphy and Vance, 1999; Olofsson et al., 2008; Olofsson et al., 2009).

The core of the lipid droplets is surrounded by a monolayer of amphipathic lipids, such as phospholipids and unesterified cholesterol (Martin and Parton, 2006; Olofsson et al., 2008; Olofsson et al., 2009). The monolayer is also associated with a number of different proteins, of which the best described and quantitatively most important are the PAT domain proteins (Dalen et al., 2007; Londos et al., 1999) (reviewed in (Brasaemle, 2007)), named after the first discovered members of the family i.e. perilipin, adipocyte differentiation-related protein (ADRP) and tail interacting protein 47 (TIP47). They are characterized by an amino-terminal PAT domain with a high degree of homology between the family members. Recent additions to the list of known PAT proteins include lipid storage droplet protein 5 (LSDP5; also known as OXPAT), myocardial lipid droplet protein (MLDP; also known as PAT-1) (Dalen et al., 2007; Wolins et al., 2006) and S3-12 (Dalen et al., 2004; Wolins et al., 2003).

1.1.1 Perilipin

Perilipin, which is mainly expressed in adipocytes and steriogenic cells (Londos et al., 1995), exists in three isoforms (perilipin A, B and C), which are formed from a single gene through

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alternative splicing (Lu et al., 2001). Perilipin A is by far the most abundant and well-investigated isoform (Londos et al., 1999).

Perilipin has an important dual role in the turnover of triglycerides in lipid droplets. It protects against triglyceride degradation when expressed in cells that lack natural expression of the protein (Brasaemle et al., 2000). Moreover, perilipin A-knockout mice show a substantial increase in basal lipolysis and reduction in adipose mass, and are resistant to diet-induced obesity (Martinez-Botas et al., 2000; Tansey et al., 2001). Perilipin also promotes triglyceride degradation: β -adrenergic stimulation does not promote lipolysis in perilipin A-knockout mice, and cells derived from these mice fail to show translocation of hormone-sensitive lipase (HSL) to the lipid droplet (Martinez-Botas et al., 2000; Tansey et al., 2001) (reviewed in (Londos et al., 2005)). A proposed model, based on these and more direct results (Granneman et al., 2007), states that concomitant phosphorylation of perilipin and HSL results in translocation of HSL to the lipid droplet where it catalyzes the hydrolysis of triglycerides (Granneman et al., 2007).

Perilipin also has an important role in the activation of adipose triglyceride lipase (ATGL), which catalyzes the first step in the degradation of triglycerides. Perilipin A interacts with CGI-58, the activator of ATGL (Lass et al., 2006). Phosphorylation of perilipin A promotes its dissociation from CGI-58, which will then associate with ATGL on lipid droplets to allow lipolysis (Granneman et al., 2007; Miyoshi et al., 2007).

1.1.2 ADRP

ADRP seems to play a central role in the assembly of lipid droplets even in perilipin-expressing cells such as the adipocyte. It is expressed in increasing amounts early in adipocyte differentiation, but is replaced by perilipin at later stages (Brasaemle et al., 1997).

In contrast to perilipin, ADRP is expressed ubiquitously (Brasaemle et al., 1997). The expression is highly related to the amount of neutral lipids in the cell (Heid et al., 1998), and overexpression of ADRP results in an increased formation of droplets (Imamura et al., 2002; Magnusson et al., 2006; Wang et al., 2003). The regulation of ADRP levels in the cell is complex. It is regulated at the transcriptional level by peroxisome proliferator-activated receptor α (PPAR α) (Dalen et al., 2006; Edvardsson et al., 2006; Targett-Adams et al., 2003), but also through post-translational degradation by the proteasomal system (Masuda et al., 2006; Xu et al., 2005), which occurs when there are low levels of lipids in the cell. Thus, accumulation of intracellular triglycerides appears to stabilize ADRP and prevents it from being sorted to degradation.

1.1.3 TIP47

TIP47 was initially described as a ubiquitously expressed cytosolic and endosomal 47 kDa protein involved in the intracellular transport of mannose 6-phosphate receptors between the trans-Golgi and endosomes (Diaz and Pfeffer, 1998; Krise et al., 2000). TIP47 is believed to act as an effector for the Rab9 protein in this process, causing budding of vesicles directed to lysosomes (Carroll et al., 2001). TIP47 is also present on lipid droplets (Wolins et al., 2001). In contrast to ADRP, which is always associated with droplets and is degraded in the absence of neutral lipid, cytosolic TIP47 is shifted to lipid droplets in the presence of increased levels of fatty acids (Wolins et al., 2001).

1.1.4 LSDP5 (OXPAT)

LSDP5 is mainly expressed in tissues with high rates of β -oxidation, such as muscle, heart, liver, and brown adipose tissue (Wolins et al., 2006). Overexpression of LSDP5 in cultured

cells results in a substantial increase in the accumulation of triglycerides in response to fatty acid treatment (Wolins et al., 2006), which might be explained by a decrease in both basal and stimulated lipolysis (Dalen et al., 2007). Thus, LSDP5 seems to protect the triglyceride core of lipid droplets from degradation in a similar manner to perilipin. LSDP5 is transcriptionally regulated by PPAR α in striated muscle and liver, and by PPAR γ in white adipose tissue (Dalen et al., 2007; Wolins et al., 2006; Yamaguchi et al., 2006).

1.1.5 S3-12

S3-12 is mainly expressed in white adipose tissue, and it shares only a weak sequence homology with the PAT proteins (Wolins et al., 2003). S3-12 expression is transcriptionally regulated by PPAR γ (Dalen et al., 2004).

1.1.6 Other lipid droplet-associated proteins

Several other proteins have also been described on lipid droplets (Brasaemle et al., 2004; Cermelli et al., 2006; Liu et al., 2004). They are involved in processes such as sorting/transport (e.g. RABs, ARFs, SNARE proteins and motor proteins), lipid biosynthesis [e.g. acyl-CoA synthetase, diacylglycerol acyltransferase (DGAT), acyl-CoA synthase and lanosterol synthetase] and lipid turnover [e.g. ATGL and its co-activator CGI-58, HSL, and cytosolic phospholipase A₂ (cPLA₂)] (reviewed in (Olofsson et al., 2009).

Caveolin and vimentin have been proposed to be present on lipid droplets (Brasaemle et al., 2004; Franke et al., 1987; Liu et al., 2004), but their function is not understood. One suggestion is that the presence of caveolin reflects an involvement of caveolin-rich plasma membranes in the assembly of lipid droplets (Ost et al., 2005). Caveolin has also been linked to triglyceride lipolysis in the droplets (reviewed in (Martin and Parton, 2006)). There are several other lipid droplet-associated proteins with functions that are yet to be elucidated.

1.2 Assembly of lipid droplets

Lipid droplets are formed from microsomal membranes (Brown, 2001). The main driving force in the assembly process is the formation of triglycerides (Marchesan et al., 2003; Stone et al., 2009) and all stimuli that promote triglyceride biosynthesis will therefore also promote the formation of lipid droplets. Other factors important for the assembly process include phospholipase D₁ (PLD₁) (Andersson et al., 2006; Marchesan et al., 2003), which catalyzes the formation of phosphatidic acid, a lipid that is essential for lipid droplet assembly (Andersson et al., 2006; Marchesan et al., 2003). PLD₁ contains a pleckstrin homology (PH) domain that is targeted by phosphatidylinositol (4,5) bisphosphate (PI(4,5) P₂), which is essential for PLD₁ activity (McDermott et al., 2004; Powner and Wakelam, 2002). Additional targets for PI(4,5)P₂ that have been identified as important for lipid droplet formation include ARF1 (and proteins involved in the regulation of its activity) (Guo et al., 2008) and cPLA₂ (Gubern et al., 2008).

We have shown that lipid droplet formation also requires extracellular regulated kinase 2 (ERK2), which phosphorylates the motor protein dynein and thereby sorts it to lipid droplets (Andersson et al., 2006). The lipid droplets are then able to contact microtubules and are thus transported towards the center of the cell (Bostrom et al., 2005). Movement in both directions has been demonstrated (Bostrom et al., 2005; Welte et al., 1998). Our results clearly show that dynein is essential for lipid droplet fusion (see below), but also indicate that dynein is involved in the initial formation of the droplet (Andersson et al., 2006). The

details of this latter process have not been elucidated, but one possibility is that dynein provides a “pull force” that is necessary for the budding of droplets from the microsomal membrane.

The mechanism for the creation of cytosolic lipid droplets from the ER is not fully elucidated. One mechanism that was proposed several years ago (but without substantial experimental evidence) suggests that, upon formation, triglycerides are 'oiled out' between the leaflets of the microsomal membranes to form a lens that will become the core of the primordial lipid droplet. The rationale behind this model is that whereas the triglyceride precursors (diglycerides and acylCoA) are highly soluble in the cytosolic leaflet of the microsomal membrane, triglycerides have limited solubility in this leaflet and are therefore forced into the hydrophobic part of the membrane (Figure 1) (Brown, 2001; Olofsson et al., 2008).

Fig. 1. Lipid droplets are formed from microsomal membranes. The assembly is driven by triglyceride formation from diglycerides, which is catalyzed by DGAT. The assembly process also requires PLD₁ and the formation of phosphatidic acid and ERK2. ERK2 phosphorylates dynein, which is then sorted onto droplets allowing them to migrate on microtubules.

1.3 Growth of lipid droplets

Newly synthesized lipid droplets are only 0.2 μm in diameter (Brown, 2001). However, mature lipid droplets are much larger (1-20 μm in diameter), indicating that they are able to grow after their formation. DGAT, which catalyzes the conversion of diglycerides to triglycerides, and the ongoing biosynthesis of triglycerides are essential for this process. It has been suggested that the surface of lipid droplets contains DGAT2, and thus the droplets may acquire triglycerides by direct biosynthesis (Kuerschner et al., 2008). However, because DGAT2 is known to span a bilayer twice (Stone et al., 2006), substantial adaptation of the enzyme would be required if it were to fit into the monolayer surface of the lipid droplet.

We demonstrated that lipid droplets can grow by fusion (Figure 2), and that approximately 15% of all droplets are engaged in the fusion process at a given time (Bostrom et al., 2005). The importance of this process, however, cannot be completely understood until we establish methods to follow the smallest lipid droplets by time lapse studies. Our very preliminary observations indicate that the fusion rate is highest among these primordial droplets. An interesting implication of fusion is that it likely involves droplets at all stages, and thus the larger droplets could have a relatively rapid connection with the DGAT2-dependent formation of the primordial lipid droplets in the microsomal membrane (Figure 3)

In addition to its dependence on dynein (Andersson et al., 2006; Bostrom et al., 2005), we have shown that lipid droplet fusion also involves the SNARE proteins synaptosomal-associated protein of 23 kDa (SNAP23), syntaxin-5 and vesicle-associated protein 4 (VAMP4) (Bostrom et al., 2007) and proteins involved in their regulation, namely the ATPase N-ethylmaleimide-sensitive factor (NSF) and α -soluble NSF adaptor protein (α -SNAP) (Bostrom et al., 2007). Recent results demonstrate that the ARF-like GTPase ARFRP1 is involved in determining the size of the droplets by sorting SNAP23 to lipid droplets (Hommel et al., 2010).

The role of the SNARE proteins, NSF and α -SNAP in fusion processes has primarily been investigated in the fusion between transport vesicles and target membranes. Central to this process is the formation of a four-helix bundle between α -helical domains present in the SNAREs (SNARE domains), which forces the membranes together promoting their fusion. A detailed molecular model of this process has recently been proposed (Giraudo et al., 2009; Sudhof and Rothman, 2009). The stable four-helix bundle present after the completed fusion is unwound by NSF and α -SNAP (for reviews, see (Hong, 2005; Jahn and Scheller, 2006; Malsam et al., 2008; Sudhof and Rothman, 2009)).

It is important to note that the presence of SNARE proteins on lipid droplets and the described fusion process open up the possibility for interactions with other organelles. Thus, fusion between a lipid droplet and the outer monolayer of the bilayer around a peroxisome may theoretically result in a structure very similar to that suggested to be formed between these two organelles (Binns et al., 2006). Further investigation is required to determine whether fusion accounts for the relatively tight interaction between lipid droplets and other organelles such as mitochondria (Shaw et al., 2008), peroxisomes (Binns et al., 2006) and the endoplasmic reticulum (ER) (Ozeki et al., 2005).

1.4 Lipid droplets and insulin resistance

Systematic insulin resistance is highly related to ectopic lipid accumulation, i.e. the accumulation of triglycerides in non-adipocytes such as liver, skeletal muscle and macrophages. Here, we focus on skeletal muscle, which is the tissue with the highest insulin-dependent consumption of glucose and thus of major importance in the development of insulin resistance.

Fig. 2. The migration of lipid droplets on microtubules is important for the fusion between the droplets. This fusion is catalyzed by the SNARE proteins SNAP23, syntaxin-5 and VAMP4. (A) A schematic view of the fusion process. (B) A time lapse study of the fusion between two droplets. The process was viewed by confocal microscopy and three dimensional structures of the droplets were constructed as described in (Andersson et al., 2006).

Figure 3. The fusion process allows small droplets to fuse with larger droplets. The primordial droplets formed by triglyceride biosynthesis in the microsomal membrane can fuse with larger “old” droplets and thus provide these droplets with newly synthesized triglycerides.

The strong correlation between lipid droplet accumulation in skeletal muscle and insulin resistance was for many years used as evidence that such accumulation causes insulin resistance. However, endurance-trained athletes also accumulate triglycerides in their skeletal muscle but are extremely insulin sensitive. This “athletes paradox” (Goodpaster et al., 2001; van Loon and Goodpaster, 2006) was one of the indications that the accumulation of triglycerides per se was not the problem but rather products of triglycerides such as fatty acids. Indeed, the accumulation of triglycerides in droplets has been regarded to be the result of a surplus of fatty acids in the cell. Moreover, it has been proposed that insulin resistance and inflammation are prevented by forcing fatty acids into droplets by increasing the levels of DGAT (Koliwad et al., 2010).

Several products of fatty acids have been linked to the development of insulin resistance, including partially oxidized fatty acids (Koves et al., 2008), ceramides (reviewed in (Summers, 2006)) and diglycerides (reviewed in (Samuel et al., 2010)). The mechanism behind the influence of the two first is not known in detail, but diglycerides are known to impair insulin signaling through activation of protein kinase C θ (PKC θ). PKC θ phosphorylates insulin receptor substrate I, thus preventing the phosphorylation involved in the insulin signal for details, see (Samuel et al., 2010).

Fatty acids can also directly influence the insulin-dependent recruitment of the glucose transporter 4 (GLUT4) to the plasma membrane though their influence on SNAP23 (Bostrom et al., 2007). As described above, SNAP23 is a SNARE protein that is involved in lipid droplet fusion, but it also plays a central role in insulin-dependent glucose uptake in skeletal muscle and adipose tissue. SNAP23 together with syntaxin-4 form a target SNARE complex, which interacts with the vesicle SNARE VAMP2 on GLUT4-specific vesicles (GSV) and thus allows GSV to fuse with the plasma membrane upon insulin stimulation. GLUT4 is thereby directed to the plasma membrane, thus increasing the glucose uptake.

We demonstrated first in cells that fatty acids displace SNAP23 from the plasma membrane (and the fusion of GSV) to the interior of the cell, resulting in insulin resistance (Bostrom et al., 2007). We translated these results into humans by studying skeletal muscle biopsies from patients with type 2 diabetes and lean and obese controls (Bostrom et al., 2010). In agreement with our results in cells, we observed that triglyceride accumulation in human skeletal muscle is accompanied by both insulin resistance and redistribution of SNAP23 from the plasma membrane to the interior of the cell (Bostrom et al., 2010).

1.5 Lipid droplets in hypoxia/ischemia

Both human macrophages and heart muscle cells that are exposed to hypoxia accumulate lipid droplets. In both cell types, lack of oxygen results in a decrease in the oxidation of fatty acids, an increase in glycolysis and lactate production and increased triglyceride biosynthesis. Thus, the accumulation of lipid droplets seems to be part of a mechanism that adapts the metabolism to minimize oxygen consumption.

Macrophages are exposed to hypoxia in both atherosclerotic lesions (Bjornheden et al., 1999) and adipose tissue (Donath and Shoelson, 2011; Trayhurn et al., 2008; Ye, 2009). Thus, the described mechanism may be of importance for creating lipid-loaded macrophages (foam cells) in atherosclerotic lesions and in the adipose tissue of obese individuals. It is well known that cholesterol from low-density lipoproteins (LDL) contributes to the lipid droplet formation in macrophages in the arterial wall. The mechanism involving modified LDL and scavenger

receptor(s) has been described in detail elsewhere (see for example (Greaves and Gordon, 2005). However, it should be noted that macrophages from atherosclerotic lesions contain high levels of triglycerides (Mattsson et al., 1993). Adipose tissue hypoxia results in macrophage recruitment and has a role in the inflammation seen in the adipose tissue during insulin resistance/type 2 diabetes (Donath and Shoelson, 2011; Trayhurn et al., 2008; Ye, 2009).

We have shown that accumulation of lipid droplets in hypoxic macrophages promotes the formation and secretion of eicosanoids and chemokines by recruiting cPLA₂ to the lipid droplet surface (Bostrom et al submitted). cPLA₂ catalyzes the production of arachidonic acid, which is the precursor of eicosanoids. Thus, triglyceride accumulation in hypoxic macrophages induces inflammation. By contrast, triglyceride accumulation caused by increased expression of DGAT1 in macrophages prevents insulin resistance and inflammation (Koliwad et al., 2010). This difference suggests that the triglyceride storage seen in hypoxia may be accompanied by a surplus of lipotoxic fatty acids, ceramides and diglycerides that have not been metabolized. Because DGAT1 promotes the conversion of diglycerides to triglycerides, increased levels of DGAT1 will likely promote the conversion of lipotoxic lipids to a hydrophobic, inert lipid that is safely stored in lipid droplets.

We have also shown that the hypoxia/ischemia-induced accumulation of triglyceride-containing lipid droplets in heart muscle cells is completely dependent on the VLDL receptor, which promotes the endocytosis of triglyceride-rich lipoproteins (Perman et al., 2011). Hypoxia-induced VLDL receptor expression is dependent on hypoxia-inducible factor 1 α through its interaction with a hypoxia-responsive element in the promoter of the VLDL receptor (Perman et al., 2011). We also observed an increased accumulation of lipid droplets and a parallel increase in expression of the VLDL receptor in biopsies from ischemic left ventricle from human hearts compared with biopsies from non-ischemic left ventricles (Perman et al., 2011).

The VLDL receptor induced accumulation of lipid droplets during hypoxia/ischemia is accompanied by increases of both ER stress (which is at least partly caused by increased formation of long chain ceramides) and apoptosis in mouse hearts (Perman et al., 2011). Importantly, VLDL receptor knockout mice have improved survival in response to an acute myocardial infarction than wildtype mice (Perman et al., 2011). Thus, the VLDL receptor and the accumulation of lipid droplets seen in hypoxia/ischemia are potential targets for treatment against early death following an acute myocardial infarction.

2. The secretion of triglycerides

Triglycerides are mostly secreted from the intestine and liver as triglyceride-rich lipoproteins, which have an organization that is very similar to the lipid droplets. Thus, they consist of a core of the neutral lipids surrounded by a monolayer of phospholipids, cholesterol and proteins (known as apolipoproteins). The primary apolipoprotein is apoB, which is required for the formation of lipoproteins. It exists in two forms: apoB48 on chylomicrons (the lipoproteins formed in the intestine); and apoB100 on very low-density lipoproteins (VLDL; the lipoproteins formed in the liver). Here we focus on the formation of VLDL.

The secretory pathway

As for other secretory proteins, apoB is synthesized on ribosomes attached to the surface of the ER (Figure 4) and the 'nascent' polypeptide is translocated through a channel

(reviewed in (Johnson and Haigh, 2000; Johnson and van Waes, 1999)) to the lumen of the ER, where it is folded into its correct structure with the help of chaperone proteins. When folded correctly, the secretory proteins are sorted into exit sites to leave the ER by transport vesicles. Failure to fold results in retention in the ER and retraction through the membrane channel followed by sorting to proteasomal degradation (Ellgaard and Helenius, 2001; Ellgaard and Helenius, 2003; Ellgaard et al., 1999; Johnson and Haigh, 2000; Johnson and van Waes, 1999; Kostova and Wolf, 2003; Lippincott-Schwartz et al., 2000).

Fig. 4. The formation of VLDL1 and VLDL2. ApoB is formed on ribosomes attached to the ER and translocated to the lumen of the ER. During this translocation, the protein is lipidated by the microsomal triglyceride transfer protein (MTP) to form pre-VLDL. If this lipidation is inadequate, apoB is sorted back to the cytosol to be degraded by proteasomes. By post-translational lipidation, the pre-VLDL forms VLDL2, which is allowed to leave ER through exit sites. Pre-VLDL that is not converted to VLDL2 will be sorted to degradation (most likely by autophagocytosis). VLDL2 is translocated through the secretory pathway and is either secreted or converted to VLDL1 in the Golgi apparatus by bulk lipidation, a process that is highly dependent on the amount of triglycerides that is stored in the cell.

The vesicles that bud off from the ER exit sites form the ER Golgi intermediate compartment (ERGIC), which is involved in protein sorting. ER-specific proteins are returned to the ER from the ERGIC and are thereby prevented from entering the later part of the secretory pathway. The ERGIC matures into cis-Golgi, which undergoes 'cisternal maturation' to form the medial- and trans-Golgi apparatus. During this maturation, proteins that will be secreted are transferred through the Golgi stack. Finally, the proteins are transported from

the trans-Golgi to the plasma membrane for secretion (reviewed in (Elsner et al., 2003; Kartberg et al., 2005)).

2.1 The assembly of VLDL

The assembly of VLDL involves three types of particles: a primordial lipoprotein (pre-VLDL), a triglyceride-poor form of VLDL (VLDL2) and a triglyceride-rich atherogenic form of VLDL (VLDL1) (Stillemark-Billton et al., 2005).

2.1.1 The primordial lipoprotein

The assembly process starts when the growing apoB100 is cotranslationally lipidated by MTP in the lumen of the ER (Figure 4), resulting in the formation of a dense, partially lipidated form of apoB100 that is retained in the cell (Boström et al., 1988; Stillemark-Billton et al., 2005). This product, which we refer to as primordial lipoprotein (or pre-VLDL), is a precursor to VLDL2 and VLDL1.

The appearance of the apoB100 primordial lipoprotein is highly dependent on the C-terminal region of apoB100 (Stillemark-Billton et al., 2005). Moreover, the particle is highly associated with chaperone protein such as binding proteins (BiP) and protein disulfide isomerase (PDI). A potential explanation is that regions in the C-terminal of apoB100 sense the degree of lipidation and anchor the partially lipidated particle to chaperones, which retain the particle in the ER. Once the level of lipidation is sufficient to allow apoB100 to fit on the particle and the C-terminal to fold correctly, the chaperones dissociate and the particle can transfer out of the ER. Thus, the primordial lipoprotein is either retained in the cell and degraded (if not sufficiently lipidated) or further lipidated to form VLDL2 (Figure 4) (Olofsson and Asp, 2005; Olofsson et al., 1999; Olofsson et al., 2000; Stillemark-Billton et al., 2005).

2.1.2 VLDL2

VLDL2 formation is highly dependent on the length of apoB, and truncated forms of apoB result in the formation of denser particles (Stillemark et al., 2000). Indeed, there is an inverse relation between the density of the lipoproteins formed and the length of apoB. *Bona fide* VLDL2 is only formed with apoB100. The lipoprotein formed by apoB48 (which is produced only in the intestine in humans but in both the intestine and liver in mice) has the same density as high-density lipoprotein (HDL) (Stillemark-Billton et al., 2005). However, despite having the same density as apoB100 pre-VLDL (which is retained in the cell unless further lipidated), the dense lipoprotein formed by apoB48 is secreted and behaves in the same way as a VLDL2 particle formed by apoB100. We therefore propose that it is a VLDL2 analog. Thus, both *bona fide* VLDL2 and VLDL2 analogs can be either secreted or further lipidated to form VLDL1 (Fig 4).

2.1.3 VLDL1

VLDL1 is formed from VLDL2 by a second type of lipidation in which the VLDL2 particle receives a bulk load of lipids in the Golgi apparatus (Stillemark-Billton et al., 2005). We have detected a precursor-product relationship between VLDL2 and VLDL1 both in cell cultures (Stillemark-Billton et al., 2005) and turnover experiments in humans (Adiels et al., 2007).

In contrast to the formation of VLDL2, apoB only needs to have a minimum size of apoB48 to allow the conversion to VLDL1 (Stillemark-Billton et al., 2005). We have recently demonstrated that the sequence close to the C-terminal of apoB48 is essential for the VLDL1 formation. We have identified a protein (BAP31) that interacts with this sequence and promotes the formation of VLDL1 (Beck et al. Manuscript in revision).

The formation of VLDL1 is dependent on the GTPase ARF1, a protein that is required in the anterograde transport from ERGIC to cis-Golgi (Asp et al., 2000). This is consistent with results showing that VLDL1 formation occurs in the Golgi apparatus (Stillemark et al., 2000), and indicates that the formation of VLDL1 requires a transfer of apoB100 from the ER to the Golgi apparatus (Figure 4). Thus, one would expect a time delay of approximately 15 min between the biosynthesis of apoB100 and the major addition of lipids to form the VLDL1 particle. Indeed, in turnover studies in humans, we confirmed the presence of two steps in the assembly of VLDL1 with a 15 min difference between the secretion of newly formed apoB100 and newly formed triglycerides (Adiels et al., 2005b).

It has been suggested that the formation of lipid droplets in the lumen of the secretory pathway plays a central role in VLDL assembly, i.e. lipid droplets fuse with apoB to form VLDL (Alexander et al., 1976). This is an interesting hypothesis that still remains to be tested, particularly in terms of elucidating the mechanism by which a luminal lipid droplet is formed and how it fuses with VLDL2. The proposed mechanism may link the assembly of the core of VLDL1 to the process by which the core of a cytosolic lipid droplet is assembled. It has been proposed that the assembly of a droplet starts in the hydrophobic portion of the microsomal membrane with the formation of a triglyceride lens, which is then released into the cytosol. A triglyceride lens may also bud into the lumen of the secretory pathway, thereby giving rise to a luminal droplet that becomes the core of VLDL. This hypothesis remains to be tested experimentally (Brown, 2001; Murphy and Vance, 1999; Olofsson et al., 1987).

Several authors have demonstrated that fatty acids used for the biosynthesis of VLDL triglycerides are derived from triglycerides stored in cytosolic lipid droplets (Gibbons et al., 2000; Salter et al., 1998; Wiggins and Gibbons, 1992), and that enzymes involved in the release of such fatty acids have an influence on the formation of VLDL (Dolinsky et al., 2004a; Dolinsky et al., 2004b; Gilham et al., 2003; Lehner and Vance, 1999; Trickett et al., 2001).

2.2 VLDL assembly in type 2 diabetes

A major factor in the development of the dyslipoproteinemia seen in type 2 diabetes is the increased secretion of VLDL1 (Taskinen, 2003). This secretion has important implications for the formation of small dense LDL and the low levels of HDL. Below, we will discuss possible mechanisms for the increased secretion of VLDL1 during type 2 diabetes.

Using stable isotope techniques, we and others (Adiels et al., 2006; Fabbrini et al., 2009; Fabbrini et al., 2008) have repeatedly shown a relationship between liver fat content and secretion of VLDL particles. Thus, the major determinant for the secretion of VLDL1 is the amount of triglycerides in the liver. An accumulation of ectopic triglycerides in the liver is a major event in the development of insulin resistance/type 2 diabetes. Thus, lipids in the liver link type 2 diabetes to increased secretion of VLDL1.

Another factor of importance is insulin. Although insulin inhibits the assembly of VLDL1 in individuals with low liver lipid levels, insulin does not have a similar effect in patients with

high liver lipid levels (Adiels et al., 2007). These findings are in agreement with lipid accumulation in the liver being the most important regulator of VLDL1 assembly.

Several possibilities to explain why insulin inhibits VLDL1 formation have been summarized previously (Taskinen, 2003). One potential reason is that insulin inhibits lipolysis in adipose tissue and thereby decreases the inflow of fatty acids to the liver. Support for an influence on the lipolysis in the adipose tissue was obtained from studies using nicotinic acid analogs (reviewed in (Taskinen, 2003)).

Insulin is also known to promote the formation of lipid droplets (Andersson et al., 2006). Thus, it is possible that insulin diverts triglycerides from the bulk lipidation of VLDL2 to the formation of lipid droplets. Indeed, we have observed other situations where promoting the formation of lipid droplets inhibits VLDL1 assembly. For example, increased levels of ADRP in the cell result in increased storage of neutral lipids in lipid droplets and reduces their entry into the assembly pathway (Magnusson et al., 2006). Such a manipulation results in decreased VLDL1 production, despite increased levels of triglycerides in the cell. In addition, increasing the rate of fusion between droplets results in decreased VLDL secretion and an increased number of droplets in the liver cell (Li et al., 2005).

2.3 ApoB100 degradation

It has long been known that apoB100 undergoes intracellular degradation (reviewed in (Davidson and Shelness, 2000; Olofsson et al., 1999; Shelness and Sellers, 2001)). The degradation is dramatically reduced when the supply of fatty acids (and the biosynthesis of triglycerides) is increased (Borén et al., 1993; Boström et al., 1986) and it is known that post-translational degradation is important for the regulation of the secreted apoB. The intracellular degradation of apoB100 occurs at three different levels (Fisher and Ginsberg, 2002; Fisher et al., 2001): (i) close to the biosynthesis of apoB (co- or post-translationally) by a mechanism that involves retraction of the apoB molecule from the lumen of the ER to the cytosol (through the same channel as it entered during its biosynthesis), ubiquitination and subsequent proteasomal degradation (Fisher et al., 2001; Liang et al., 2000; Mitchell et al., 1998; Pariyarath et al., 2001); (ii) post-translationally by an unknown mechanism that seems to occur in a compartment separate from the rough ER, and is referred to as post-ER presecretory proteolysis (PERPP) (Fisher et al., 2001); (iii) by reuptake from the unstirred water layer around the outside of the plasma membrane (Williams et al., 1990) via the LDL receptor. The LDL receptor has been shown to have an important role in regulation of the secretion of apoB100-containing lipoproteins (Horton et al., 1999; Twisk et al., 2000).

Interestingly, the PERPP has been linked to the autophagocytic pathway (Pan et al., 2008). Contrary to post-translational degradation which targets proteins, the autophagocytic pathway allows the degradation of particles, such as pre-VLDL and VLDL.

The intracellular degradation of apoB seems to be a consequence of a failure to form the correct particle. To avoid degradation, apoB100 needs to form pre-VLDL during translation and the pre-VLDL must be converted to VLDL2 (see above: The primordial lipoprotein). Both steps are dependent on the amount of lipids that are loaded on to apoB. The formation of VLDL1 is not necessary for apoB100 secretion but allows increased secretion of triglycerides from the liver.

2.4 The turnover of VLDL in the circulation

Lipid changes in metabolic diseases such as insulin resistance, the metabolic syndrome and type 2 diabetes, commonly known as diabetic dyslipidemia, consist of elevated triglycerides,

low HDL cholesterol and formation of small dense LDL. The formation of small dense LDL may occur without an increase in total LDL cholesterol, but is often connected to an increase in total apoB100.

The secreted apoB100 lipoproteins are hydrolyzed in the circulation. Because protein has a higher density than lipids, removal of the core lipids will result in the formation of smaller and denser particles. In a sequential order, hydrolysis of VLDL1 will result in first VLDL2, then intermediate-density lipoprotein (IDL) and finally LDL. The initial steps are carried out by lipoprotein lipase (LPL), which is present at the luminal side of endothelial cells in peripheral tissues such as adipose tissue, skeletal muscle and the heart. The liberated fatty acids are then taken up by different mechanisms in the target tissue (including the CD36 receptor-mediated pathway), and are re-esterified for storage or used as energy through mitochondrial oxidation. LPL has several modulators in the circulation, such as apoC-II and apoC-III, which enhance and inhibit lipolysis, respectively. New evidence also suggests that apoA-V, angiopoietin-like proteins 3 and 4, lipase maturation factor 1 and glycosylphosphatidylinositol-anchored HDL binding protein 1 (GPIHBP1) may be important for LPL function (Dallinga-Thie et al., 2010). The later steps in the removal of triglycerides are carried out by hepatic lipase. Of importance for the formation of the end product i.e. LDL is also the cholesterol ester transfer protein (CETP) (Chapman et al., 2010). IDL and LDL are removed from the circulation by the LDL receptor uptake or heparin sulphate proteoglycan mechanisms in the liver.

The triglyceride content of circulating VLDL1 has been estimated to be ~10500 molecules per particle (i.e. per apoB100 molecule), whereas VLDL2, IDL and LDL have ~3500, ~1200 and ~180-280 molecules per particle (Kumpula et al., 2008). Thus, although only 10% of the total apoB100 are in the VLDL1 and VLDL2 fractions, the majority of triglycerides are in the VLDL1 fraction and, to a lesser extent, the VLDL2 fraction (Hiukka et al., 2005). The cholesteryl ester content of lipoprotein particles increases with increasing density: VLDL1, VLDL2, IDL and LDL have ~500, ~950, ~1400 and ~1000-1500 molecules of cholesterol ester per particle (Kumpula et al., 2008). This compositional change reflects the action of cholesterol ester transfer protein, which transports cholesterol esters from HDL and LDL to VLDL particles in exchange for triglycerides (Chapman et al., 2010). This transport is increased when triglyceride levels are increased and thus type 2 diabetic subjects have lower relative amount of triglycerides in VLDL1 but higher relative amount of cholesterol esters in VLDL1 and VLDL2 compared with control subjects (Hiukka et al., 2005).

2.5 *In vivo* studies of VLDL secretion and turnover in humans

Circulating levels of apoB100, triglycerides and cholesterol are thus dependent on many different mechanisms: the rate of secretion of apoB100 and triglycerides as VLDL1 and VLDL2 particles, the rate of lipolysis by LPL and hepatic lipases (and the impact of regulating molecules on these enzymes) and the rate of removal from the circulation by uptake mechanisms. To fully understand the contribution of these mechanisms to the final plasma concentration, in particular how these different processes contribute to the development of dyslipidemia, it is necessary to quantify these within humans.

Today, most studies indirectly calculate the rates of these processes using stable isotope labeling techniques, either by *in vivo* labeling of protein content using labeled amino acids as precursors or labeling of triglycerides using labeled glycerol as precursor or by *ex vivo*

labeling (Magkos and Sidossis, 2004). The methods differ in the choice of molecules to study (i.e. triglycerides or apoB100) and consequently in the choice of tracer molecules, but also in the choice of detail (i.e. VLDL, VLDL1 and VLDL2, or VLDL, IDL and LDL) and in the modeling approach.

Our approach is a combined experiment where the kinetics of both apoB100 and triglycerides are determined in VLDL1 and VLDL2 using a combined model (Adiels et al., 2005b). Briefly, stable isotope labeled leucine and glycerol are simultaneously injected as a bolus and blood is drawn repeatedly for 10 hours. Enrichment of leucine is measured free in plasma as well as in apoB100 protein from VLDL1 and VLDL2 particles separated by ultracentrifugation. Enrichment of glycerol is measured in the triglyceride content of the VLDL1 and VLDL2 particles. Enrichment is measured using sensitive gas-chromatograph/mass-spectrometry equipment. The time series data are used as input in a mathematical model in which the different rates of transfer and synthesis can be calculated.

The kinetics of apoB100 and triglycerides have been well studied in type 2 diabetes. Most studies have revealed an increased secretion of VLDL (Cummings et al., 1995; Kissebah et al., 1982; Ouguerram et al., 2003; Sorensen et al., 2011) and VLDL1 (Adiels et al., 2005a; Taskinen et al., 1990). Several studies have also shown impaired suppression of VLDL secretion by insulin in type 2 diabetes (Adiels et al., 2007; Lewis et al., 1993; Malmstrom et al., 1997; Sorensen et al., 2011). Some studies also suggest that diabetic subjects have slower clearance of VLDL particles (Duvillard et al., 2000; Kissebah et al., 1982; Taskinen et al., 1986) but these results are less conclusive, which may reflect the importance of other factors such as genetic background and the progress of diabetes.

3. Acknowledgement

This work was supported by grants from the Swedish Research Council, the Swedish Foundation for Strategic Research, the Swedish Heart and Lung Foundation, Söderbergs Foundation, the Swedish Diabetes association, and the EU projects LipidomicNet. .

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Role of the Adipocyte in Development of Type 2 Diabetes

Edited by Dr. Colleen Croniger

ISBN 978-953-307-598-3

Hard cover, 372 pages

Publisher InTech

Published online 22, September, 2011

Published in print edition September, 2011

Adipocytes are important in the body for maintaining proper energy balance by storing excess energy as triglycerides. However, efforts of the last decade have identified several molecules that are secreted from adipocytes, such as leptin, which are involved in signaling between tissues and organs. These adipokines are important in overall regulation of energy metabolism and can regulate body composition as well as glucose homeostasis. Excess lipid storage in tissues other than adipose can result in development of diabetes and nonalcoholic fatty liver disease (NAFLD). In this book we review the role of adipocytes in development of insulin resistance, type 2 diabetes and NAFLD. Because type 2 diabetes has been suggested to be a disease of inflammation we included several chapters on the mechanism of inflammation modulating organ injury. Finally, we conclude with a review on exercise and nutrient regulation for the treatment of type 2 diabetes and its co-morbidities.

How to reference

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Sven-Olof Olofsson, Linda Andersson, Jeanna Perman, Mikael Rutberg, Lilliana Håversen, Li Lu, Emma Lu, Reza Mobini, Marcus Ståhlman, Susanna Myhre, Christina Olsson, Rosie Perkins, Thomas Larsson, Jan Borén and Martin Adiels (2011). Lipid Droplets and Very Low Density Lipoproteins; Their Relation to Insulin Resistance, Role of the Adipocyte in Development of Type 2 Diabetes, Dr. Colleen Croniger (Ed.), ISBN: 978-953-307-598-3, InTech, Available from: <http://www.intechopen.com/books/role-of-the-adipocyte-in-development-of-type-2-diabetes/lipid-droplets-and-very-low-density-lipoproteins-their-relation-to-insulin-resistance>

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