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REVIEW

Biochemistry and pathophysiology of intravascular and intracellular lipolysis

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All organisms use fatty acids (FAs) for energy substrates and as precursors for membrane and signaling lipids. The most efficient way to transport and store FAs is in the form of triglycerides (TGs); however, TGs are not capable of traversing biological membranes and therefore need to be cleaved by TG hydrolases (“lipases”) before moving in or out of cells. This biochemical process is generally called “lipolysis.” Intravascular lipolysis degrades lipoprotein-associated TGs to FAs for their subsequent uptake by parenchymal cells, whereas intracellular lipolysis generates FAs and glycerol for their release (in the case of white adipose tissue) or use by cells (in the case of other tissues). Although the importance of lipolysis has been recognized for decades, many of the key proteins involved in lipolysis have been uncovered only recently. Important new developments include the discovery of glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1), the molecule that moves lipoprotein lipase from the interstitial spaces to the capillary lumen, and the discovery of adipose triglyceride lipase (ATGL) and comparative gene identification-58 (CGI-58) as crucial molecules in the hydrolysis of TGs within cells. This review summarizes current views of lipolysis and highlights the relevance of this process to human disease.

Fatty acids (FAs) are essential molecules with multiple biological functions; they are integral components of membrane lipids, efficient energy substrates, and potent second messengers. The limited water solubility of FAs and their relatively low critical micellar concentration cause them to form micelles in an aqueous environment. Micelle formation and the avid association of FAs with cellular membranes can adversely affect membrane and cell function. To prevent deleterious effects of high extracellular or intracellular FA concentrations, long chain FAs are “detoxified” by esterification to glycerol, a trivalent alcohol, forming relatively inert triglycerides

(TGs). A large fraction of FAs in TG-rich lipoproteins (TRLs; chylomicrons and very-low-density lipoproteins [VLDL]) and in cytoplasmic lipid droplets (LDs) are found in the form of TGs. In response to metabolic demand, TGs can be hydrolyzed to FAs and glycerol by a process called lipolysis, which involves the enzymatic activity of TG hydrolases (lipases).

The importance of lipolysis for virtually all organisms became clear with the realization that TGs cannot move across cell membranes without first being degraded by lipases. More than a century ago, it was observed that pancreatic juice contains a “fat-splitting” activity and that this activity is essential for the uptake of dietary fat by the intestine (Bernard 1856; Balser 1882; Whitehead 1909). Later, in the 1950s, it was shown that plasma TGs must be hydrolyzed intravascularly (Korn 1955a,b) to facilitate uptake of FAs and monoglycerides (MGs) by parenchymal cells (Fig. 1). Also, intracellular hydrolysis of the TGs stored in white adipose tissue (WAT) facilitates the release of FAs and glycerol from cells, a process that provides metabolic intermediates to tissues during fasting (Fig. 1; Vaughan et al. 1964).

Intravascular and cellular lipolysis has been studied for many decades, but the last few years have witnessed important new discoveries regarding lipolytic enzymes, enzyme mechanisms, and enzyme transport. This review summarizes these new results and discusses their importance for human disease (Table 1).

Lipolysis within blood vessels

Vertebrates have a complex and finely tuned system for delivering lipid nutrients to parenchymal cells. The central element of this system is the intravascular hydrolysis of TGs carried within the plasma lipoproteins (Havel 1977, 1980). Intestinal enterocytes package dietary lipids into chylomicrons, which enter the lymphatics and then quickly reach the bloodstream. Chylomicrons transport TGs to adipose tissue for storage and to vital tissues (e.g., the heart and skeletal muscle) for use as fuel. The liver secretes VLDL, which serves to redistribute TG to adipose tissue, heart, and muscle. Chylomicrons and VLDL are spherical particles containing a core of neutral lipids, mainly TGs; the surface of these particles contains polar lipids (e.g., phospholipids and free cholesterol), apolipo-

[*Keywords:* adipose triglyceride lipase; CGI-58; GPIHBP1; hormone-sensitive lipase; lipolysis; lipoprotein lipase; monoglyceride lipase]

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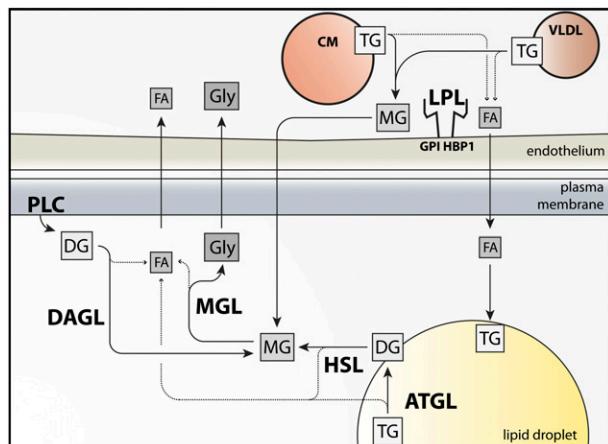


Figure 1. Schematic of intravascular lipolysis and intracellular lipolysis. Intravascular lipolysis: LPL hydrolyzes TGs in VLDLs and chylomicrons (CM) on the luminal face of capillaries, principally in adipose tissue and striated muscle. LPL is bound to the surface of capillaries by a glycosylphosphatidylinositol-anchored glycoprotein, GPIIIBP1. LPL products, FAs and MGs, traverse the endothelium and are taken up by the underlying parenchymal cells (adipocytes and myocytes). MGs are further catabolized by monoacylglycerol lipase (MGL), generating FAs and glycerol. LPL-generated FAs are re-esterified to TG or oxidized. Glycerol is resecreted and transported to the liver. Intracellular lipolysis: Hormonal stimulation of lipolysis activates ATGL and HSL, which hydrolyze TGs and diglycerides (DGs), respectively, in cellular LDs. MGs are hydrolyzed by MGL. Lipolytic FAs enter oxidative or biosynthetic pathways in most tissues. WAT releases FAs into the bloodstream, where they bind to albumin and eventually enter peripheral tissues. Hydrolysis of glycerolphospholipids by phospholipase C (PLC) and diacylglycerol lipase (DAGL) also generates MGs.

protein B (either apo-B48 or apo-B100), and several exchangeable apolipoproteins (e.g., apo-CI, apo-CII, apo-CIII, apo-E, apo-AI, apo-AII, apo-AIV, and apo-AV).

The large size of chylomicron (~100–1200 nm in diameter) and VLDL (30–80 nm) particles means that they have little capacity to move across capillaries; hence, the movement of lipids to parenchymal cells depends on hydrolysis of the TGs within these particles, a process that is carried out by lipoprotein lipase (LPL) along the luminal surface of capillary endothelial cells (Fig. 1; Brunzell and Deeb 2001). Intravascular lipolysis removes ~90% of the TGs from the particles (Bergman et al. 1971), generating remnant lipoproteins that are largely taken up and removed by hepatocytes. In the liver, the fenestrated capillaries allow remnant lipoproteins to interact directly with hepatocytes.

The recognition that plasma TGs undergo intravascular hydrolysis began with the discovery that fat particles in the blood are cleared more rapidly after an injection of heparin and that the clearing of opalescence continues after the plasma is placed in a test tube (Hahn 1943). Later, Korn (1955a,b) showed that the clearing factor was LPL, which converts the TGs in plasma to less turbid products (FAs and glycerol). In addition, given that heparin

is not capable by itself of reducing the turbidity of lipemic plasma, Korn (1955a,b) concluded that heparin must release LPL from tissues into the plasma. Within a few years, Havel and Gordon (1960) characterized a family in which three siblings had creamy plasma and showed that their post-heparin plasma was deficient in TG hydrolase activity. The three siblings were homozygous for LPL deficiency, the first example of an inherited disorder of plasma lipid metabolism (Havel 2010).

The importance of LPL in the processing of TRLs led to considerable excitement among physiologists, biochemists, and physicians. Even before the advent of molecular biology, several laboratories showed that intravascular lipolysis by LPL depends on a cofactor (later identified as apo-CII) that is carried on the surface of TRLs (Kinnunen et al. 1977; Bengtsson and Olivecrona 1979). The importance of LPL in lipolysis was underscored by Bensadoun and coworkers (Kompang et al. 1976), who purified the enzyme, generated antibodies, and showed that those antibodies, when injected into animals, prevented the lipolytic processing of TRLs.

LPL

The cDNA for LPL was cloned by several groups (Enerbäck et al. 1987; Kirchgessner et al. 1987; Wion et al. 1987). Full-length human LPL is 474 amino acids in length, 448 amino acids after removal of the signal peptide. The N-terminal portion of the mature protein (the first 312 amino acids) encodes the catalytic domain, while the C-terminal domain is required for binding TG substrates (Wong et al. 1994). Substrate binding requires the presence of three tryptophans in LPL's C terminus (Lookene et al. 1997a). When those residues are mutated, hydrolysis of triolein is markedly reduced, but tributyrin hydrolysis is minimally affected, indicating that soluble TGs with very short acyl chains can be processed without the lipid-binding sequences. The same tryptophans are also essential for LPL's ability to bind to TRLs and TG emulsion particles (Lookene et al. 1997a). Consistent with these findings, an LPL-specific monoclonal antibody, 5D2, which binds to the tryptophan-rich domain (Chang et al. 1998), blocks triolein but not tributyrin hydrolysis (Chang et al. 1998).

The fact that LPL could be released into the plasma by heparin (Korn 1955a,b) implied that LPL might contain positively charged heparin-binding sequences, and indeed, this was the case (Kirchgessner et al. 1987). A strong heparin-binding domain is located within the C terminus of the protein (residues 403–407) (Ma et al. 1994a; Sendak et al. 1998; Lookene et al. 2000), just a few residues downstream from the lipid-binding sequences; another is located between residues 292 and 304 (Hata et al. 1993).

LPL is secreted and enzymatically active as a homodimer (Iverius and Ostlund-Lindqvist 1976; Garfinkel et al. 1983). The ability of cells to produce and secrete LPL homodimers depends on a membrane protein of the endoplasmic reticulum (ER), lipase maturation factor 1 (LMF1) (Peterfy et al. 2007). In the absence of LMF1, LPL cannot form homodimers and is degraded intracellularly (Doolittle and Peterfy 2010). LPL homodimers are formed

Table 1. Diseases and phenotypes related to genes involved in lipolysis

Affected gene	Chromosomal localization	Disease name	Common phenotypes	Infrequent phenotypes
<i>LPL</i>	8p21.3	Familial chylomicronemia, LPL deficiency	Markedly elevated plasma TG levels, pancreatitis, eruptive xanthomas, lipemia retinalis, hepatosplenomegaly	Memory loss, dyspnea, atherosclerosis
<i>APOC2</i>	19q13.32	Familial chylomicronemia, apolipoprotein CII deficiency	Markedly elevated plasma TG levels, pancreatitis, eruptive xanthomas, lipemia retinalis, anemia; tends to be less severe and presents later in life than <i>LPL</i> deficiency	
<i>APOA5</i>	11q23.3	Hypertriglyceridemia, chylomicronemia	Variably elevated plasma TG levels	
<i>APOC3</i>	11q23.3	Apo-CIII deficiency	Heterozygous deficiency results in low plasma lipid levels, protection from coronary disease.	
<i>GPIHBP1</i>	8q24.3	Familial chylomicronemia, GPIHBP1 deficiency	Markedly elevated plasma TG levels, pancreatitis, eruptive xanthomas, lipemia retinalis	
<i>LIPC</i>	15q21.3	Hepatic lipase deficiency	Elevated levels of IDLs and HDL cholesterol; atherosclerosis	
<i>LMF1</i>	16p13.3	Combined lipase deficiency; lipase maturation factor 1 deficiency	Markedly elevated plasma TG levels, markedly reduced levels of LPL and HL in the postheparin plasma	
<i>LIPG</i>	18q21.1	Endothelial lipase deficiency	Elevated levels of HDL cholesterol	
<i>PNPLA2/ATGL</i>	11p15.5	Neutral lipid storage disease with myopathy (NLSDM)	Systemic TG accumulation, Jordans' anomaly (TG vacuoles in leukocytes), skeletal myopathy, cardiomyopathy	Hepatosteatorosis, diabetes
<i>ABDH5/CGI-58</i>	3p21	neutral lipid storage disease with ichthyosis (NLSDI); Chanarin-Dorfman syndrome	Systemic TG accumulation, Jordans' anomaly, ichthyosis, hepatosteatorosis	Growth retardation, small ears, mental retardation, hearing loss, cataracts, ectropion, splenomegaly
<i>LIPE/HSL</i>	19q13.2	HSL deficiency	Reduced adiposity	

by two monomers oriented in a head-to-tail fashion. When an expression vector containing two LPL cDNAs, arranged head-to-tail in a single ORF, is expressed in cultured cells, a catalytically active enzyme is produced (Wong et al. 1997); the "single-molecule LPL" has the same size as native LPL homodimers, as judged by density gradient ultracentrifugation. The LPL monomers probably act cooperatively to hydrolyze TGs, with the lipid-binding domain of one monomer providing substrates to the catalytic domain of the partner monomer. In support of this idea, transfection of cultured cells with two catalytically inactive LPL constructs—one with a mutation in the C-terminal lipid-binding motif and a second with a mutation in the N-terminal catalytic domain—results in the production of catalytically active LPL (Kobayashi et al. 2002).

LPL contains N-linked glycans at Asn 43 and Asn 359. Asn 43 is crucial for LPL secretion, while Asn 359 is less so (Semenkovich et al. 1990; Ben-Zeev et al. 1994; Busca et al. 1995). N-linked glycans may be crucial for the stability of LPL homodimers, but a variety of other sequences are required for stable homodimers (Mailly et al. 1997; Keiper et al. 2001). The sequences that participate di-

rectly in interactions between the two monomers are not known.

The rationale for LPL being a homodimer is not understood, but one possible explanation is that this structure facilitates regulation of LPL activity levels. The Olivecrona laboratory (Sukonina et al. 2006) showed that angiotensin-related protein 4 (ANGPTL4), a physiological inhibitor of LPL, reduces LPL activity by converting catalytically active homodimers to inactive monomers. In adipose tissue, ANGPTL4 plays a key role in changing LPL activity levels in response to metabolic cues. The homodimeric structure could also be important in other ways. It is possible, for example, that the two monomers serve distinct roles (i.e., that LPL is a functional heterodimer). In the case of another enzyme homodimer, cyclooxygenase, the binding of substrate by one monomer alters the structure and function of the partner monomer such that one monomer plays a catalytic role, while the partner monomer serves an allosteric role (Yuan et al. 2006, 2009). Whether LPL is a "functional heterodimer," in terms of either binding substrates or partner proteins, is unknown and needs investigation.

Without apo-CII, LPL is able to bind to lipoproteins, but catalytic activity is minimal (Olivecrona and Beisiegel 1997). Sequences within the C-terminal portion of apo-CII are essential for its interaction with LPL (Shen et al. 2010). Sequences within the N-terminal portion of LPL have been implicated in apo-CII binding (Davis et al. 1992), but C-terminal sequences also could play a role (Hill et al. 1998). The exact nature of apo-CII–LPL interactions and how apo-CII binding promotes enzymatic activity are incompletely understood.

Binding of LPL by endothelial cells

The fact that LPL is required for the processing of TRLs has been known for decades. Until recently, however, several elements of LPL physiology remained mysteries. One was LPL's binding site on the luminal face of capillaries. For years, dogma held that LPL was bound to capillary endothelial cells by electrostatic interactions between its heparin-binding motifs and negatively charged heparan sulfate proteoglycans (HSPGs) (Cryer 1989; Merkel et al. 2002). This view made some sense, given that LPL is readily released into the bloodstream by heparin, a low-molecular-weight sulfated glycosaminoglycan. Also, LPL binds to HSPGs *in vitro* (Klinger et al. 1985; Lookene et al. 1997b), and LPL binding to cultured cells can be reduced by reducing the sulfation of HSPGs or removing them enzymatically (Shimada et al. 1981; Hoogewerf et al. 1991). On the other hand, the "HSPG model" was never satisfying, mainly because it lacked biochemical specificity. HSPGs are produced by many cell types, and it was never clear why LPL would end up binding to HSPGs in the capillary lumen rather than to the HSPGs surrounding the cells where LPL is made (myocytes and adipocytes). Another nagging mystery was how LPL reached the capillary lumen. LPL is produced by myocytes and adipocytes and secreted into the interstitial spaces, yet its site of action is within the capillary lumen. One study suggested that the VLDL receptor might play a role in moving LPL to the capillary lumen (Obunike et al. 2001), but again, this explanation was not satisfying because VLDL receptor deficiency in mice has minimal effects on plasma lipid metabolism (Frykman et al. 1995).

Insights into both of these mysteries—LPL's binding site in capillaries and how LPL manages to reach the capillary lumen—came with the discovery of glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1), a GPI-anchored member of the lymphocyte antigen 6 (Ly6) family of proteins (Ioka et al. 2003; Beigneux et al. 2007). GPIHBP1's relevance to lipolysis was obvious with the development of *Gpihbp1* knockout mice (*Gpihbp1*^{-/-}), which manifest severe hypertriglyceridemia, even when fed a low-fat chow diet (Beigneux et al. 2007). Additional studies showed that GPIHBP1, when expressed on cultured cells, binds LPL avidly and that the bound LPL can be released with heparin (Beigneux et al. 2007). Also, GPIHBP1 is expressed at high levels in capillaries of heart and brown adipose tissue (BAT), two tissues that produce large amounts of

LPL (Beigneux et al. 2007; Davies et al. 2010). GPIHBP1 is absent from the capillaries of the brain, an organ that depends largely on glucose for fuel (Beigneux et al. 2007). It is also absent from the endothelial cells of venules, arterioles, and larger blood vessels (Davies et al. 2010).

GPIHBP1 contains two principal domains: an N-terminal acidic domain (highly enriched in aspartic and glutamic acids) and a cysteine-rich Ly6 domain (~80 amino acids in length) (Ioka et al. 2003; Beigneux et al. 2007). The Ly6 domain contains 10 cysteines, all arranged in a characteristic spacing pattern and all disulfide-linked, resulting in a three-fingered structural motif (Fletcher et al. 1994).

Mutation of the acidic domain impairs LPL binding (Gin et al. 2008). The Ly6 domain is equally important; mutation of any of the 10 cysteines markedly reduces GPIHBP1's ability to bind LPL (Beigneux et al. 2009c). Subsequent alanine-scanning mutagenesis studies uncovered 12 residues—most of which are in the "second finger" of the three-fingered motif—that are important for LPL binding (Beigneux et al. 2011). Whether those residues participate directly in LPL binding or are simply required for folding of the three-fingered structure is not clear. The Ly6 domain in mouse GPIHBP1 contains one N-linked glycosylation site, which is important for the trafficking of GPIHBP1 from the ER to the cell surface (Beigneux et al. 2008).

The discovery that GPIHBP1 domains are important for LPL binding prompted Beigneux et al. (2009c) to propose that LPL might contain two distinct GPIHBP1-binding domains. It makes sense that GPIHBP1's acidic domain might interact with one of LPL's heparin-binding domains, and in support of this idea, mutation of LPL's main C-terminal heparin-binding domain (residues 403–407) inhibits binding of LPL to GPIHBP1 (Gin et al. 2008). The portion of the LPL molecule that interacts with GPIHBP1's Ly6 domain has not been identified with certainty but likely includes sequences located further downstream (amino acids ~416–435). Mutating that region abolishes binding of human LPL to GPIHBP1 and does so without significant effects on heparin binding (Voss et al. 2011). Recent studies showed that the C terminus of LPL (residues 298–448), free of the N-terminal catalytic domain, binds avidly and specifically to GPIHBP1 (Gin et al. 2012).

Site-directed mutagenesis studies and immunochemical studies have yielded important insights regarding sequences relevant to LPL–GPIHBP1 interactions (Beigneux et al. 2009c; Beigneux et al. 2011; Voss et al. 2011; Gin et al. 2012); however, the residues that participate directly in these interactions are not known. Determining structures for GPIHBP1, LPL, and GPIHBP1–LPL complexes remains an important objective for the field.

The fact that GPIHBP1 binds LPL and is located in capillaries suggested that it might be a "platform for lipolysis" on the luminal side of capillary endothelial cells (Beigneux et al. 2007). Subsequent studies revealed that GPIHBP1 has a second and more intriguing function—picking up LPL from the interstitial spaces and shuttling it across capillaries to the capillary lumen (Davies et al.

2010). In *Gpihbp1*^{-/-} mice, LPL never reaches the luminal side of capillaries and remains mislocalized in the interstitial spaces surrounding parenchymal cells (Fig. 2) (Davies et al. 2010). GPIHBP1's transport function has been documented in both cultured cells and live mice. GPIHBP1-expressing endothelial cells, when cultured on a porous grid, transport both LPL and GPIHBP1-specific monoclonal antibodies from the basolateral to the apical side of cells (Davies et al. 2010). Also, when GPIHBP1-specific monoclonal antibodies are injected into the interstitium of skeletal muscle or BAT, they quickly associate with endothelial cells and move to the capillary lumen (Davies et al. 2010, 2012). GPIHBP1 and LPL movement across endothelial cells can be inhibited with dynasore and genistein, consistent with a vesicular transport process. By immunogold electron microscopy, GPIHBP1 and LPL can be found in invaginations in the plasma membrane of endothelial cells and in transcytotic vesicles (Davies et al. 2012).

The "mislocalized LPL" in the muscle and adipose tissue of GPIHBP1-deficient mice remains tightly bound in the interstitial spaces, presumably bound to HSPGs near the surface of myocytes and adipocytes (Davies et al. 2010). Even when GPIHBP1 is expressed normally, it seems likely that the LPL secreted by myocytes and adipocytes would bind first to HSPGs surrounding parenchymal cells. It is tempting to speculate that GPIHBP1's acidic domain may act as a lasso, weakening LPL–HSPG interactions and then promoting the binding of LPL to endothelial cells—with high affinity and lock-and-key specificity—by dual interactions with GPIHBP1's acidic and Ly6 domains. In this way, newly secreted LPL would be driven from the interstitial spaces to the surface of endothelial cells. Also, LPL is a homodimer and therefore could have two binding sites for GPIHBP1. The stoichiometry of LPL–GPIHBP1 binding has not been determined, but the binding of LPL by two GPIHBP1 molecules would presumably greatly increase the affinity of LPL binding to endothelial cells.

In addition to LPL, GPIHBP1 binds apo-AV (Beigneux et al. 2007; Gin et al. 2007, 2008, 2011), another heparin-

binding protein with a key role in plasma TG metabolism (Pennacchio et al. 2001, 2002). This interaction is mediated by interactions between apo-AV's heparin-binding motif and GPIHBP1's acidic domain (the binding does not appear to involve the Ly6 domain) (Gin et al. 2011). GPIHBP1 does not bind apo-B or apo-E, both of which contain strong heparin-binding domains (Gin et al. 2011).

The discovery of GPIHBP1 solved some lingering mysteries in lipolysis, but others remain. The molecular basis for LPL–GPIHBP1 interactions, how LPL is activated by apo-CII, and the mechanism for the inhibition of LPL activity by ANGPTL4 need to be elucidated. Also, no one understands mechanisms for the margination of TRLs along the surface of capillaries so that lipolysis can proceed. The prevailing view has been that TRLs bind to HSPGs on the endothelial cells (Cryer 1989; Merkel et al. 2002), but this idea needs testing. A second possibility is that GPIHBP1 (or GPIHBP1-bound LPL) is responsible for TRL margination. No one knows whether TRLs would stop along capillaries in the absence of GPIHBP1. Another mystery is how the products of lipolysis move across capillaries to parenchymal cells.

For adipose tissue and striated muscle, high levels of LPL and GPIHBP1 expression are closely matched (Beigneux et al. 2007), but there are two tissues where the levels of GPIHBP1 and LPL expression are quite different. First, GPIHBP1 transcripts are present in high levels in the lung, but there are only trace levels of LPL transcripts in the lung (Olafsen et al. 2010). The explanation for this discrepancy is not understood with certainty, but several lines of evidence have suggested that the GPIHBP1 in lung capillaries serves to scavenge LPL produced by other tissues (Olafsen et al. 2010). Thus, GPIHBP1 could serve to "sop up" any LPL that escapes from the interstitial spaces, preventing it from reaching the systemic circulation. Second, certain regions of the brain (for example, the hippocampus) produce substantial amounts of LPL transcripts (Goldberg et al. 1989; Ben-Zeev et al. 1990; Vilaro et al. 1990; Bessesen et al. 1993), but GPIHBP1 transcripts in the brain are extremely low (Beigneux et al. 2007). The production of LPL by neurons has significant effects on adiposity and body weight (Wang et al. 2011a), but the mechanisms are not clear. Given the absence of GPIHBP1 in brain capillaries, it seems possible that LPL in the brain functions in the interstitial spaces surrounding neurons and glia rather than having a role in intravascular lipolysis. More studies are required.

GPIHBP1 is expressed at a low level in the liver but is still easily detectable on endothelial cells by immunohistochemistry, where it presumably serves to capture LPL. *LPL* transcripts in the liver are low but easily detectable, and *LPL* transcript levels increase significantly on a high-cholesterol diet (Zhang et al. 2001). Under certain circumstances—for example, fibroblast growth factor 21 (FGF21) overexpression or the induction of torpor—a close relative of LPL, pancreatic lipase, is induced in the liver and presumably plays a role in providing free FAs to the cells of the liver (Inagaki et al. 2008). Pancreatic lipase expression has also been observed in adipose tissue in the setting of FGF1 deficiency (Jonker et al. 2012). These

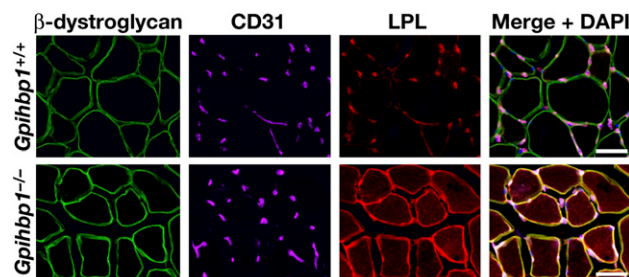


Figure 2. Confocal immunofluorescence microscopy showing that LPL is tightly bound within the interstitial spaces in skeletal muscle of *Gpihbp1*^{-/-} mice. Images show β -dystroglycan (a marker of skeletal myocytes) (green), CD31 (a marker of endothelial cells) (purple), and LPL (red) in muscle from a wild-type (*Gpihbp1*^{+/+}) mouse and a *Gpihbp1*^{-/-} mouse. The vast majority of the LPL in the skeletal muscle of the wild-type mouse is bound to capillaries. In the *Gpihbp1*^{-/-} mouse, the LPL is mislocalized to the interstitial spaces surrounding myocytes. (Reprinted from Davies et al. 2010, © 2010, with permission from Elsevier.)

observations are intriguing, but a link to GPIHBP1 seems unlikely because, unlike LPL, pancreatic lipase lacked the ability to bind to GPIHBP1 in either cell-free or cell-based binding assays (Jonker et al. 2012).

One final point about GPIHBP1 and LPL expression patterns deserves discussion: LPL is expressed in all vertebrates, but GPIHBP1 is found only in mammals (including the egg-laying platypus) (Beigneux et al. 2007, 2009a). GPIHBP1 presumably originated from another Ly6 gene by a gene duplication event, and there has been speculation that GPIHBP1's acidic domain came from another gene (Holmes and Cox 2012). The absence of GPIHBP1 in other vertebrates (e.g., birds and fish) poses intriguing questions (Young et al. 2011). Do the endothelial cells of those species have a distinct protein for shuttling LPL across capillaries? Is it possible that the LPL in those species functions within the interstitial spaces? Do these species transport TRLs outside of capillaries into the interstitial space where LPL exists rather than transporting LPL to the capillary lumen where TRLs exist? Answers to these questions are not known. In any case, it seems possible that the appearance of GPIHBP1 in mammals might somehow be related to a hallmark of mammals—nursing the young (Young et al. 2011). LPL is expressed at high levels in lactating mammary glands, and it seems possible that GPIHBP1 and intravascular lipolysis evolved to facilitate the movement of lipid nutrients from plasma TRLs to the mammary epithelium.

Hepatic lipase (HL) and endothelial lipase (EL)

LPL is not the only lipase with a role in intravascular lipolysis. Two other enzymes of the same family, HL and EL, participate in the remodeling of plasma lipoproteins. Like LPL, HL and EL are secreted as homodimers (Hill et al. 1997; Griffon et al. 2009), require LMF1 for secretion, and bind avidly to heparin (Peterfy et al. 2007; Ben-Zeev et al. 2010). In vivo, both are presumed to bind HSPGs and can be released from their binding sites with a bolus of heparin (Krauss et al. 1973; Fuki et al. 2003; Badellino et al. 2006). Neither HL nor EL binds to GPIHBP1 (Gin et al. 2011).

Human HL is ~40% identical to LPL at the amino acid level (Komaromy and Schotz 1987; Datta et al. 1988; Martin et al. 1988). Unlike LPL, it is not sensitive to inhibition by high concentrations of sodium chloride and is not activated by apo-CII. HL is expressed highly in hepatocytes and is located mainly at the surface of those cells and surrounding endothelial cells (Breedveld et al. 1997; Sanan et al. 1997). HL exhibits low TG hydrolase activity against chylomicron substrates and instead hydrolyzes TGs in chylomicron remnants, intermediate density lipoproteins (IDL), and TG-rich high-density lipoproteins (HDLs) (Hegele et al. 1993; Connelly 1999; Santamarina-Fojo et al. 2004). Inhibition of HL with specific antibodies interferes with the conversion of IDL to LDL and leads to an accumulation of remnant particles (Goldberg et al. 1982). HL variants associated with reduced enzymatic activity lead to higher HDL cholesterol levels (Cohen et al. 1994, 1999; Guerra et al. 1997; Vega et al.

1998). The basis for HL's lipoprotein substrate specificities has been investigated with LPL–HL chimeras and likely involves sequences in both the N-terminal and C-terminal portions of the protein (Davis et al. 1992; Dugi et al. 1995).

EL is made primarily by endothelial cells and is 44% identical to LPL and 41% identical to HL at the amino acid level (Jaye et al. 1999; Cohen 2003). EL is primarily a phospholipase A1, hydrolyzing phospholipids in HDL particles, which reduces HDL size and accelerates their removal from the plasma (Duong et al. 2003; Ishida et al. 2003; Jin et al. 2003a). Overexpression of EL in transgenic mice lowers HDL cholesterol levels, while knocking out the gene for EL has the opposite effects (Ishida et al. 2003; Jin et al. 2003a). The physiologic significance of EL-mediated changes in HDL levels is unclear, particularly since the altered HDL levels do not appear to affect the efficiency of reverse cholesterol transport in vivo (RJ Brown et al. 2010).

The specificities of HL and EL for different lipids and lipoproteins (Jaye et al. 1999; Duong et al. 2003; Griffon et al. 2006) and the consequences of HL and EL deficiencies for plasma lipoprotein levels have been studied in depth (Ishida et al. 2003; Jin et al. 2003a). Nevertheless, the physiologic purpose of both enzymes is less well defined than for LPL. One can confidently state that LPL plays a central role in processing dietary lipids so that they can move to parenchymal cells—a clear and undeniably important function that has been conserved through evolution. HL and EL affect the concentration of lipids and lipoproteins in the plasma, but there is no comparable clarity of physiologic purpose. It would appear that HL and EL fine-tune a complex system of lipoprotein processing and thereby affect the delivery of lipid nutrients to specific cell types. The consequences of the “fine tuning” of nutrient delivery are not necessarily trivial, particularly since genome-wide association studies have uncovered a link between the gene for HL and macular degeneration (Neale et al. 2010; Cipriani et al. 2012). EL is regulated by cytokines and could influence both the inflammatory pathway and changes in lipoprotein levels and properties during inflammation (Jin et al. 2003b; Yasuda et al. 2010). Interestingly, HL and EL protein sequences have changed much more rapidly in vertebrate evolution than LPL sequences (Holmes et al. 2011a,b,c).

LPL, HL, and EL have functions independent of catalysis. All interact with members of the LDL receptor family and HSPGs (Mulder et al. 1993; Merkel et al. 1998; Fuki et al. 2003; Dichek et al. 2004; Yasuda et al. 2007). In the case of LPL and HL, this “bridging” function is thought to promote the uptake and clearance of remnant lipoproteins.

Intracellular lipolysis

Lipolysis of TGs in cytoplasmic LDs (Fig. 1) fulfills two important functions. In WAT, lipolysis generates FAs and glycerol that are released into the blood for transport to other tissues; for example, cardiac muscle, skeletal muscle, liver, or BAT. This release of FAs and glycerol during fasting is unique to WAT; other tissues do not release the

products of TG hydrolysis and instead use them in a cell-autonomous manner for lipid synthesis or oxidation. The main enzymes for TG catabolism are the same in adipose and nonadipose tissues.

Adipose TG lipase (ATGL)

The initial step of TG hydrolysis is catalyzed by ATGL (Zechner et al. 2009). Surprisingly, the enzyme was only uncovered recently, in 2004 (Jenkins et al. 2004; Villena et al. 2004; Zimmermann et al. 2004). Previously, hormone-sensitive lipase (HSL) was considered the only neutral TG hydrolase in adipose and nonadipose tissues. Consequently, it came as a surprise when the targeted deletion of the *Hsl* gene in mice did not lead to TG accumulation and obesity (Osuga et al. 2000). Instead, HSL-deficient mice were lean and exhibited TG hydrolysis rates in WAT that were reduced by only 50% compared with wild-type WAT, arguing for the existence of at least one other neutral TG hydrolase. ATGL fulfilled the requirements for the “missing lipase.” ATGL cleaves TGs with high efficiency and specificity (Zimmermann et al. 2004; Eichmann et al. 2012). The preferred substrates for ATGL are saturated or unsaturated medium and long and very long chain esters in TGs.

Human ATGL is 506 amino acids in length. The N-terminal region of ATGL contains a patatin domain (186 amino acids) named after a related motif in patatin, the most abundant soluble protein in the potato tuber (Rydel et al. 2003). The human and the mouse genomes code for nine and eight patatin domain-containing proteins, respectively. In 2006, the gene family was named patatin-like phospholipase domain containing A 1–9 (PNPLA1–9), with ATGL being PNPLA2 (Wilson et al. 2006). ATGL and other patatin domain-containing proteins are found in all eukaryotes, including fungi, plants, and animals. Patatin-like proteins are also common in bacteria and may affect disease pathogenesis (Banerji and Flieger 2004). PNPLA1–9 act as TG hydrolases, phospholipases, retinyl esterases, and acyltransferases (Kienesberger et al. 2009b; Rajakumari and Daum 2010; Kumari et al. 2012). In mammals, ATGL (PNPLA2) is most closely related to PNPLA3 (Baulande et al. 2001). PNPLA3 exhibits TG hydrolase and acyltransferase activity (He et al. 2010; Huang et al. 2011; Kumari et al. 2012; Li et al. 2012) and has recently attracted major interest because a single amino acid sequence polymorphism (I148M) is strongly associated with hepatic steatosis. Individuals homozygous for the Met-148 allele exhibit increased susceptibility to alcoholic and nonalcoholic fatty liver disease (Romeo et al. 2008).

The structure of ATGL has not yet been determined, but sequence homologies with patatin domain proteins that have already been crystallized (Pat17 and cPLA2) suggest that the active site of ATGL is assembled around a catalytic dyad involving Ser 47 and Asp 166 (Rydel et al. 2003). Replacement of either of those residues with alanine leads to loss of enzymatic activity (Schweiger et al. 2008; Duncan et al. 2010). The nucleophilic Ser 47 is located within a GX SXG consensus sequence commonly found in

serine hydrolases. Structural modeling revealed that the active site is located within the patatin domain (amino acids 10–185). The patatin domain itself is embedded in a 250-amino-acid α - β - α sandwich structure in the N-terminal half of the protein. The C-terminal half of the protein consists of α -helical and loop regions with a presumed hydrophobic lipid-binding domain between amino acids 315 and 360. The functional importance of this region for LD binding was proven by the finding that ATGL lacking this region is catalytically active against artificial substrate emulsions but is unable to bind to LDs within cells (Schweiger et al. 2008; Duncan et al. 2010).

ATGL activity is regulated by multiple mechanisms on the transcriptional and post-transcriptional level (for review, see Lass et al. 2011). The most important post-translational mechanisms for ATGL regulation include its delivery to LDs by vesicular transport (Beller et al. 2008; Guo et al. 2008; Soni et al. 2009; Ellong et al. 2011) and its activation by comparative gene identification-58 (CGI-58, also named α/β hydrolase domain-containing 5, ABHD5) (Lass et al. 2006). CGI-58 was originally found by comparison between the human and the *Caenorhabditis elegans* proteome. Mutations in the *CGI-58* gene are causative for a rare human disease known as neutral lipid storage disease (NLS) with ichthyosis (NLSI) (discussed further below). Human CGI-58 is a 349-amino-acid protein that belongs to the large family of α/β hydrolase domain-containing proteins (Oberer et al. 2011). The α/β hydrolase domain of CGI-58 contains a pseudocatalytic triad consisting of Asn 155, His 329, and Asp 303. Asn 155 is situated within a GXNXG consensus sequence and apparently replaces the nucleophilic serine normally found in catalytically active serine hydrolases. Given the absence of that serine, it is not surprising that CGI-58 exhibits no measurable hydrolase activity against a variety of lipid esters.

The activation of TG hydrolases by protein cofactors is not unusual. As noted earlier, LPL requires apo-CII for efficient hydrolysis of TGs within TRLs, and pancreatic lipase requires colipase for the hydrolysis of dietary lipids. It is widely assumed that these cofactors change the properties of the lipid–water interphase; however, a detailed molecular mechanism for coactivation is lacking for any lipase, and it is quite possible that mechanisms are substantially different for different lipases. For ATGL activation, it is conceivable that CGI-58 affects substrate presentation, changes the conformation of ATGL, or is involved in product removal. Mutagenesis studies have demonstrated that both LD binding and ATGL binding are required for efficient ATGL activation by CGI-58 (Gruber et al. 2010). A tryptophan-rich stretch within the first 20 amino acids of CGI-58 mediates its binding to LDs. A naturally occurring splice variant of CGI-58 lacking this region is unable to activate ATGL (Yang et al. 2010a).

Elegant studies by Granneman et al. (2007, 2009) demonstrated that the activation step of ATGL is hormone-dependent. In nonstimulated cells, CGI-58 is unavailable for ATGL activation because it binds to perilipin-1. β -Adrenergic stimulation leads to perilipin-1 phosphory-

lation by protein kinase-A (PKA) and dissociation of CGI-58, allowing CGI-58 to bind to ATGL and activate its catalytic activity. Mutations in perilipin-1 that prevent CGI-58 binding lead to unrestrained lipolysis and partial lipodystrophy in humans (Gandotra et al. 2011). Importantly, CGI-58 also broadens the substrate specificity of ATGL (Eichmann et al. 2012). Generally, ATGL is specific for TG substrates and exhibits only weak diglyceride (DG) lipase, phospholipase, and transacylase activity (in which two DG molecules generate one TG and one MG molecule). In the hydrolysis of TGs, ATGL preferably cleaves fatty acyl esters at the *sn*-2 position of the glycerol backbone, resulting in the production of *sn*-1,3 DGs. This is unusual for TG lipases, which typically hydrolyze the ester bonds in the *sn*-1 or *sn*-3 positions. The specificity of ATGL for *sn*-2 position esters may indicate an evolutionary relationship to phospholipase A2 enzymes of the PNPLA family. Upon hormonal stimulation and enzyme activation by CGI-58, the substrate specificity extends to the *sn*-1 position of TGs (Eichmann et al. 2012). Thus, fully activated ATGL generates both *sn*-1,3 DGs and *sn*-2,3 DGs but no measurable amounts of *sn*-1,2 DGs.

In addition to its ability to activate ATGL, CGI-58 acts as an acyl-CoA lysophosphatidic acid acyltransferase (LPAAT) (Ghosh et al. 2008; Montero-Moran et al. 2009). Compared with classical LPAAT enzymes, the specific activity of CGI-58 is low, and the structural basis for the enzymatic activity remains obscure.

Recently, Liu and colleagues (Yang et al. 2010b) identified a peptide inhibitor of ATGL, which is encoded by the *G0/G1 switch gene 2* and called G0S2. Both human and murine G0S2 contain 103 amino acids. G0S2 was first discovered >20 years ago in cultured mononuclear cells during the cell cycle transition from G0 to G1 (Russell and Forsdyke 1991). The protein has been assigned diverse biological activities, including roles in cell cycle, cell proliferation, apoptosis, inflammation, and carcinogenesis (Heckmann et al. 2013). The best-studied function of G0S2, however, relates to its role in lipid metabolism (Yang et al. 2010b; Schweiger et al. 2012). G0S2 is expressed highly in WAT, BAT, and liver. Only very low levels of the protein can be detected in skeletal and cardiac muscle. In *in vitro* studies, G0S2 binds to the patatin domain of ATGL and suppresses ATGL hydrolytic activity independently of CGI-58. Consistent with its ability to inhibit ATGL, overexpression of G0S2 in cultured cells leads to an accumulation of TGs, whereas silencing of G0S2 causes TG depletion. Whether G0S2 regulates ATGL-mediated lipolysis *in vivo* is not known.

When ATGL was discovered, it was observed that the enzyme was phosphorylated (Zimmermann et al. 2004). Later, at least two phosphorylation sites were identified in murine ATGL: Ser 406 and Ser 430 (Bartz et al. 2007). Phosphorylation of Ser 406 increases the catalytic activity of ATGL in hormone-stimulated lipolysis; however, the protein kinase responsible for enzyme phosphorylation is controversial. Watt and colleagues (Mason et al. 2012; Pagnon et al. 2012) reported that PKA phosphorylates Ser 406, but Ahmadian et al. (2012) found that AMP-kinase was responsible for this modification.

HSL

Originally described in 1964 (Vaughan et al. 1964), HSL was long considered to be the only enzyme for the hydrolysis of cellular TG depots. As noted earlier, this view changed when Osuga et al. (2000) found that HSL-deficient mice are not obese and showed no signs of TG accumulation in either adipose or nonadipose tissues. Instead, HSL-deficient mouse tissues retained TG hydrolyase activity and accumulated large amounts of DG in multiple tissues (Haemmerle et al. 2002), suggesting that HSL was more important as a DG hydrolase than as a TG hydrolase. This conclusion was also consistent with the original finding that HSL hydrolyzed DG 10-fold more efficiently than TG (Vaughan et al. 1964). In addition to DG and TG, HSL also cleaves FA esters in MGs, cholesterol esters, and retinyl esters; the highest esterase activities are observed when short chain carboxylic esters are used as substrates. Thus, HSL possesses a broad substrate specificity (Holm et al. 2000). HSL has a preference for primary ester bonds in the *sn*-3 position of the glycerol backbone but can also hydrolyze *sn*-1 esters (Rodriguez et al. 2010). Accordingly, it hydrolyzes both DG stereoisomers generated by ATGL (*sn*-1,3 and *sn*-2,3 DGs) with high efficiency. In the absence of HSL, ATGL products (*sn*-1,3 and *sn*-2,3 DGs) accumulate in adipose and nonadipose tissues (Haemmerle et al. 2002; Eichmann et al. 2012). Despite massive DG accumulation, hyperactivation of conventional or novel protein kinase-C (PKC) isoenzymes has not been reported, and HSL knockouts do not develop insulin resistance (Mulder et al. 2003; Voshol et al. 2003; Park et al. 2005). These findings may be due to the fact that the most potent activators of PKCs among DG isoforms are *sn*-1,2 DGs (Boni and Rando 1985; Sanchez-Pinera et al. 1999), which are not formed in appreciable amounts during ATGL-mediated lipolysis (Eichmann et al. 2012). Thus, determination of total DG concentrations without knowledge of stereoisomer distribution and cellular localization may be inadequate to predict PKC activation and effects on insulin signaling. This conclusion may explain the inconsistent correlation between tissue DG concentrations and development of insulin resistance in various mouse models (Farese et al. 2012; Sun and Lazar 2013).

The absence of ATGL in mice reduces FA release from adipose tissue by ~70% (Haemmerle et al. 2006), and experiments with a highly specific HSL inhibitor showed that FAs released from ATGL-deficient adipose tissue result from TG (and DG) hydrolysis by HSL (Schweiger et al. 2006). Although these findings demonstrated that HSL is capable of hydrolyzing cellular TGs in WAT (in addition to DGs), it is not clear how important HSL-mediated TG hydrolysis is when ATGL is expressed normally. HSL-deficient mice exhibit an interesting adipose tissue phenotype with hypertrophic white and brown adipocytes but reduced total WAT mass (Osuga et al. 2000; Wang et al. 2001; Haemmerle et al. 2002). Adipose mass decreases with age and is virtually undetectable in mice >12 mo of age. WAT loss was attributed to reduced lipid synthesis as a result of defective peroxisome proliferator-activated

receptor γ (PPAR γ) signaling (Zimmermann et al. 2003). A crucial role of HSL in PPAR γ signaling was later confirmed (Shen et al. 2011) by suggesting that HSL-mediated lipolysis may provide FA and retinoic acid as ligands for PPAR γ and retinoic X receptor (RXR), respectively. Another reason for WAT loss in HSL-deficient mice may be cell death from increased inflammation, macrophage infiltration, and the formation of “crown-like structures” characterized by macrophages surrounding hypertrophic adipocytes (Cinti et al. 2005).

The importance of HSL in cholesterol ester and retinyl ester hydrolysis was also addressed in HSL-deficient mice. Interestingly, retinyl ester hydrolase activity was blunted in HSL-deficient WAT, leading to increased retinyl ester concentrations, decreased retinol and retinal levels, and increased “browning” of adipocytes, as judged by increased uncoupling protein-1 (UCP-1) expression (Strom et al. 2008, 2009). Similarly, HSL-deficient mice lack cholesterol ester hydrolase activity in various tissues and accumulate cholesterol esters (Sekiya et al. 2008; Obrowsky et al. 2012). Cholesterol ester and retinyl ester hydrolase activities may be important in steroidogenesis and retinoic acid formation, respectively (Kraemer et al. 2002; Strom et al. 2009). Lack of these activities in steroid hormone-producing tissues such as testes could underlie the defective spermiogenesis and sterility phenotype in male HSL-deficient mice (Vallet-Erdtmann et al. 2004).

The human gene for HSL codes for protein isoforms that differ in length between 775 to 1076 amino acids, a consequence of alternative splicing involving the first few exons of the gene (Laurin et al. 2000). Interestingly, HSL is unique in the genome of mammals with essentially no related homologous proteins. HSL is most prominently expressed in WAT and BAT, but lower levels can be detected in many nonadipose tissues. Although the structure of HSL has not been determined, mutagenesis studies have uncovered three functional domains (Holm et al. 2000). The N-terminal domain, comprising amino acids 1–300 of adipose HSL, is responsible for LD binding. The C-terminal domain harbors the catalytic triad (S-424, D-693, and H-723) within an α/β hydrolase fold. The nucleophilic serine is located within a GX SXG consensus sequence, which is typical for serine hydrolases. The third domain is a regulatory module located between amino acids 521 and 669, with at least five serine residues that can be phosphorylated (Holm 2003). In particular, the reversible phosphorylation of Ser 659 and Ser 660 regulates enzyme activity. The most important endocrine effectors of HSL are catecholamines, atrial natriuretic peptide, growth hormone, and insulin (Wang et al. 2008). Kinases involved in HSL phosphorylation include PKA, cGMP-activated kinase, AMP-activated kinase, extracellular signal-regulated kinase, glycogen synthase kinase-4, and Ca²⁺/calmodulin-dependent kinase. HSL dephosphorylation is catalyzed by protein phosphatase 2B (Holm 2003).

MG lipase (MGL)

The products of the ATGL and HSL reactions are *sn*-1 and *sn*-2 MGs. Additionally, the intravascular hydrolysis

of lipoprotein-associated TGs by LPL generates *sn*-3 MGs that enter adipocytes and myocytes (Morley and Kuksis 1972; Rogalska et al. 1993). Thus, at the step of MG hydrolysis, the pathways of intravascular and intracellular lipolysis converge. A third source of MGs derives from lipolysis of plasma membrane-associated glycerophospholipids by membrane-bound phospholipases C and DG lipases. The main enzyme responsible for the catabolism of MGs from all three sources is MGL, originally identified in 1964 (Vaughan et al. 1964). The protein contains 303 amino acids and belongs to the large group of α/β hydrolase fold hydrolases and esterases. The enzyme crystallizes as a homodimer with an apolar helix lid covering the active site (Bertrand et al. 2010; Labar et al. 2010). The active site contains a catalytic triad (Ser 122, Asp 239, and His 269) in which the nucleophilic serine is located within a GX SXG consensus sequence.

MGL is ubiquitously expressed, with the highest levels found in adipose tissue and testis. The *MGL* gene encodes various mRNA splice variants coding for proteins that are between 283 and 313 amino acids long. The enzyme localizes to the plasma membrane, ER, LDs, and cytoplasm. Compared with TG hydrolases, MGL has a much higher specific activity and does not exhibit significant substrate specificity, hydrolyzing all MG stereoisomers with similar efficiency (Tornqvist and Belfrage 1976). The physiological importance of MGL became evident when it was found to be the major enzyme in the catabolism of 2-arachidonylglycerol (2-AG), an important endocannabinoid regulating multiple aspects of metabolism and energy homeostasis (Dinh et al. 2002). 2-AG binds to G-protein-coupled cannabinoid receptor 1 (CBR-1) and CBR-2, affecting a large number of physiological processes, including motor function, pain, appetite, cognition, emotional behavior, and immunity (Di Marzo 2009). The classical pathway of 2-AG synthesis involves the conversion of phosphatidylinositols to DGs by phospholipase C and the subsequent hydrolysis of DGs to 2-AG by diacylglycerol lipase within the plasma membrane. Whether hydrolysis of LD-associated TGs by ATGL and HSL also contributes to 2-AG production and endocannabinoid signaling is unknown.

Lipolysis—three steps, three enzymes, or more?

The current concept of classical hormone-stimulated lipolysis by β -adrenergic agonists in adipocytes can be summarized as follows (Fig. 3). First, hormone (e.g., catecholamine) binding to the G_s-protein-coupled β -adrenergic receptors stimulates adenylate cyclase. Increased cAMP levels activate PKA, which phosphorylates perilipin-1 and HSL. Perilipin-1 phosphorylation facilitates ATGL activation by CGI-58 and the translocation of phosphorylated and activated HSL from the cytoplasm to LDs. Together, these enzymes hydrolyze TGs and DGs to MGs, which are subsequently converted to glycerol and FA by MGL. Hormonal stimulation of lipolysis activates FA and glycerol release from adipose tissue by >100-fold. ATGL, HSL, and MGL are responsible

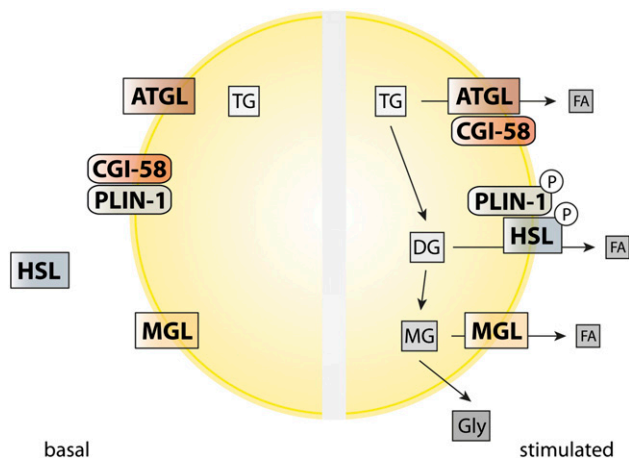


Figure 3. Lipolytic processing of LDs in adipose tissue under basal and hormone-stimulated conditions. In unstimulated adipocytes, TG hydrolysis is low because HSL and perilipin-1 are not phosphorylated. This results in the cytoplasmic localization of HSL and CGI-58 binding to perilipin-1 (PLIN-1). Consequently, CGI-58 is unavailable for ATGL activation. Hormonal stimulation results in a fully active lipolytic cascade with efficient TG hydrolysis. Activated PKA phosphorylates HSL and PLIN-1. This causes dissociation of the PLIN-1/CGI-58 complex and stimulation of ATGL by CGI-58. At the same time, HSL translocates to the LD, interacting with PLIN-1. The combination of ATGL and HSL generates DGs and, ultimately, FAs and glycerol (Gly).

for >90% of the total lipolytic activity in WAT (Schweiger et al. 2006).

Much less is known about enzymes and mechanisms that control lipolysis in nonadipose tissues. Although ATGL, HSL, and MGL are also observed in these tissues, their activities are much lower than in adipose tissue. Additionally, other TG hydrolases may also contribute to TG hydrolysis in liver, muscle, or macrophages (Quiroga and Lehner 2012). Many nonadipose tissues express perilipin-2 and perilipin-5 but not perilipin-1. Perilipin-2 and perilipin-5 regulate ATGL activity in the liver and cardiac muscle by restricting access of ATGL to LDs (Listenberger et al. 2007; Bell et al. 2008; Granneman et al. 2011; Wang et al. 2011b; Kuramoto et al. 2012). However, detailed mechanisms underlying ATGL activity in these tissues are not entirely clear and require more characterization. A number of other LD-binding proteins (e.g., pigment epithelium-derived factor) have been shown to affect lipolysis in adipose and nonadipose tissues (Chung et al. 2008; Borg et al. 2011), but again, mechanisms underlying their actions are unclear.

Lipolysis and disease

Considering the central role of lipases in lipid and energy metabolism, it is not surprising that they have proven to be relevant to human disease. Monogenetic deficiencies of LPL or ATGL lead to severe alterations in lipid metabolism (Table 1) and can be lethal if not treated properly. In addition, changes in intravascular and intracellular lipolysis affect numerous polygenic metabolic diseases such as atherosclerosis, obesity, and type 2 diabetes mellitus. Here,

we summarize recent studies in which altered lipolysis has been linked to human disease.

Intravascular lipolysis and disease

LPL deficiency

The loss of LPL activity leads to familial chylomicronemia syndrome, a syndrome characterized by creamy plasma and markedly elevated plasma TG levels (>1000 mg/dL) (Table 1; Havel and Gordon 1960). This disease is associated with a high risk of pancreatitis, a characteristic skin rash (eruptive xanthomas), and, occasionally, neurological manifestations (Brunzell and Deeb 2001). The absence of intravascular TRL processing is accompanied by reduced delivery of lipid nutrients to tissues, as demonstrated by deficiencies of essential FAs in adipose tissue (Ullrich et al. 2001; Weinstein et al. 2012) and breast milk (Steiner et al. 1985; Ginzinger et al. 1999). LPL-deficient mice die within a day of birth with hypoglycemia and plasma TG levels >20,000 mg/dL (Weinstock et al. 1995) but can be rescued by transient expression of LPL with an adenovirus (Strauss et al. 2001). The plasma TG levels in “rescued” *Lpl* knockout mice are quite high (>5,000 mg/dL), even on a low-fat chow diet. In mice, heterozygosity for LPL deficiency results in mildly elevated plasma TG levels (Weinstock et al. 1995). In humans, a single defective *LPL* allele often leads to mild or moderate hypertriglyceridemia (Miesenbock et al. 1993; Nordestgaard et al. 1997) but occasionally to severe hypertriglyceridemia, particularly during pregnancy (Ma et al. 1994b; Henderson et al. 1998).

For years, it was presumed that chylomicronemia did not predispose to atherosclerosis because the large size of TRLs prevented them from entering the arterial intima (Nordestgaard and Zilversmit 1988). However, some patients with chylomicronemia due to LPL deficiency have developed significant atherosclerosis (Benlian et al. 1996). This clinical observation in humans has been bolstered by the observation that rescued LPL-deficient mice (Zhang et al. 2008) and GPIHBP1-deficient mice (Weinstein et al. 2010) develop spontaneous atherosclerosis even on a low-fat chow diet.

LPL deficiency is associated with an absence of LPL activity in postheparin plasma (Havel and Gordon 1960). Over the past two decades, dozens of clinically significant LPL mutations have been described. Some abolish the production of LPL transcripts or lead to unstable transcripts; certain missense mutations prevent secretion of LPL from cells, others interfere with the stability of LPL homodimers, and others yield LPL homodimers that are stable yet catalytically inactive (Hayden et al. 1991). In recent years, new mechanisms of disease have been uncovered. For example, a pair of LPL missense mutations, C418Y and E421K, first identified in chylomicronemia patients (Henderson et al. 1996, 1998), do not affect LPL secretion or catalytic activity but abolish LPL's ability to bind to GPIHBP1 and be transported across endothelial cells to the capillary lumen (Fig. 4; Voss et al. 2011). Also, missense mutations at residues 409 and 410, long rec-

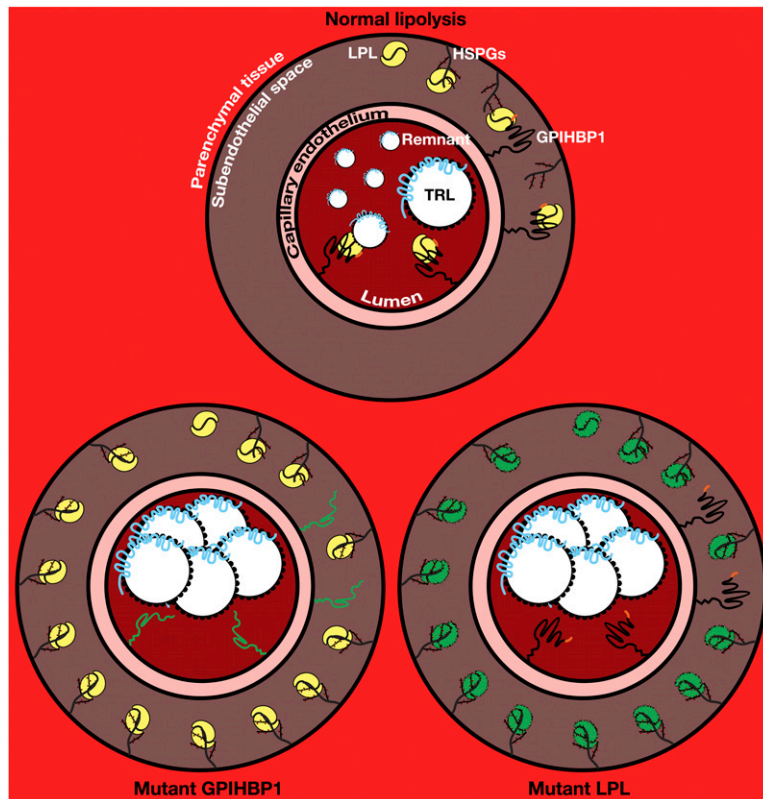


Figure 4. Schematic of a cross-section of a capillary depicting the location of GPIHBP1 and LPL and their role in the lipolytic processing of TRLs in health and disease. The *top* panel depicts a normal capillary illustrating the role of GPIHBP1 in capturing LPL in the interstitial space and moving it to the capillary lumen, where it hydrolyzes TGs in TRLs, converting them to smaller remnant lipoproteins. The *bottom left* panel depicts impaired delivery of LPL to the capillary lumen in the setting of a mutant GPIHBP1 (e.g., GPIHBP1-Q115P) (Beigneux et al. 2009b) lacking the ability to bind LPL. The *bottom right* panel depicts impaired delivery of LPL to the capillary lumen in the setting of an LPL mutant (e.g., LPL-C418Y) (Voss et al. 2011) that lacks the ability to bind GPIHBP1. When LPL does not reach the capillary lumen, there is a striking accumulation of TRLs in the plasma.

ognized to abolish LPL activity (Previato et al. 1992; Ginzinger et al. 1996), were recently shown to enhance LPL susceptibility to furin-mediated cleavage at residue 297 (Gin et al. 2012). Although the latter mutations were located in close proximity to LPL's GPIHBP1-binding domain, they did not appear to interfere with binding to GPIHBP1 (Gin et al. 2012).

Apo-CII deficiency

Homozygous loss of apo-CII also leads to familial chylomicronemia (Breckenridge et al. 1978), but these mutations are less common and tend to be less severe than LPL mutations (Table 1). Heterozygous apo-CII deficiency has no effect on lipid levels. A variety of nonsense, frameshift, and missense mutations have been uncovered (Connelly et al. 1987; Cox et al. 1988; Crecchio et al. 1990; Reina et al. 1992; Inadera et al. 1993; Tuzgol et al. 1994). Some of the missense mutations impair binding of apo-CII to TRLs and are associated with extremely low levels of apo-CII in the plasma. One of the missense mutations, Leu72Pro, underscored the importance of apo-CII's C terminus in LPL activation (Lam et al. 2006). The diagnosis of apo-CII deficiency can be suspected when low LPL activity levels in the postheparin plasma are normalized with apo-CII-containing plasma (Breckenridge et al. 1978). Transfusing apo-CII-deficient patients with donor plasma lowers plasma TG levels (Breckenridge et al. 1978).

LMF1 deficiency

Lmf1 was initially identified as the mutant gene (Peterfy et al. 2007) in a naturally occurring mutant strain of mice

("combined lipase deficiency" or *clb* mice) lacking both LPL and HL activity (Olivecrona et al. 1986; Langner et al. 1989). *LMF1* is also important for the secretion of EL (Benzeev et al. 2010). *LMF1* is critical for the formation and secretion of lipase homodimers (Peterfy et al. 2007). A human subject homozygous for a nonsense mutation in *LMF1* (Y439X) had markedly elevated plasma TG levels; postheparin LPL and HL levels were reduced by 91% and ~50%, respectively (Peterfy et al. 2007). A second homozygous nonsense mutation, W464X, was identified in another patient with severe hypertriglyceridemia; postheparin LPL activity in that patient was reduced by 76% (Cefalu et al. 2009). Like apo-CII deficiency, *LMF1* deficiency in humans is a recessive syndrome (Peterfy et al. 2007), and clinically significant mutations appear to be quite rare (Surendran et al. 2012).

GPIHBP1 deficiency

During the past few years, homozygous *GPIHBP1* mutations have been uncovered in patients with severe chylomicronemia (Table 1; Beigneux et al. 2009b; Franssen et al. 2010; Olivecrona et al. 2010; Charriere et al. 2011; Coca-Prieto et al. 2011; Rios et al. 2011). Most of the mutations described thus far are missense mutations within the Ly6 domain that interfere with the ability of GPIHBP1 to bind LPL. Impaired binding means that LPL cannot associate with endothelial cells and cannot reach the capillary lumen (Fig. 4). Many of the mutations involve conserved cysteines within the Ly6 domain (Franssen et al. 2010; Olivecrona et al. 2010; Charriere et al. 2011;

Coca-Prieto et al. 2011). That cysteine mutations would cause disease is not surprising, since these residues are required for producing the three-fingered structure of the Ly6 domain and are essential for LPL binding and transport across endothelial cells (Beigneux et al. 2009c, 2011).

Other GPIHBP1 missense mutations (for example, Q115P) have occurred in residues located near conserved cysteines (Beigneux et al. 2009b; Surendran et al. 2012). The Q115P mutation markedly impairs LPL binding (Beigneux et al. 2009b, 2011).

Recently, Charriere et al. (2011) identified a 35-year-old man with chylomicronemia and a homozygous G175R mutation. That mutation, located in GPIHBP1's C-terminal domain, reduces the amount of GPIHBP1 at the cell surface and likely interferes with the addition of the GPI anchor. Hobbs and Cohen (Rios et al. 2011) identified a homozygous 17.5-kb deletion that included the entire *GPIHBP1* gene in a family with chylomicronemia. Charriere et al. (2011) also identified a large deletion in a patient with chylomicronemia.

Humans with heterozygous *GPIHBP1* mutations appear to be normolipidemic (Franssen et al. 2010; Charriere et al. 2011; Rios et al. 2011). In mice, heterozygosity for the *Gpihbp1* knockout mutation lowers GPIHBP1 protein levels in tissues by 50% but has no effect on plasma lipid levels (Beigneux et al. 2007). Presumably, half-normal amounts of GPIHBP1 are sufficient to transport LPL to the capillary lumen.

In *Gpihbp1* knockout mice, an injection of heparin detaches LPL from its binding sites in the interstitial spaces, allowing the enzyme to enter the plasma (Beigneux et al. 2007; Weinstein et al. 2008). Once this occurs, the plasma TG levels fall (Weinstein et al. 2008). The situation is different in humans. At the doses of heparin that are given to humans, the amount of LPL that enters the plasma compartment is very low (Franssen et al. 2010; Olivecrona et al. 2010; Rios et al. 2011), and the effect on plasma TG levels is minimal or absent (Franssen et al. 2010; Rios et al. 2011).

Other LPL regulators

Mutations in LPL regulatory factors also alter plasma TG levels. Heterozygosity for a nonsense mutation in the gene for apo-CIII, a negative regulator of lipolysis, lowers plasma TG and cholesterol levels and is associated with reduced coronary artery calcification (Pollin et al. 2008). Defects in apo-AV lead to increased plasma TG levels and, occasionally, severe chylomicronemia (Grosskopf et al. 2005; Dorfmeister et al. 2008). Missense mutations in the gene for ANGPTL4, a lipase inhibitor (Yoshida et al. 2002; Koster et al. 2005), result in lower plasma TG levels (Romeo et al. 2007, 2009; Yin et al. 2009). Nonsense mutations in ANGPTL3, an inhibitor of both LPL and EL, lead to very low plasma lipid levels (Musunuru et al. 2010).

HL and EL deficiency

Mutations in HL and EL result in modest changes in plasma lipid levels, and given the variability in plasma lipid levels within human populations, these deficiencies

are unlikely to be diagnosed without genetic screening. Individuals with HL deficiency have increased levels of TGs in the HDL and IDL fractions and more remnant lipoproteins and appear to be more susceptible to coronary artery disease (Hegele et al. 1991, 1993; Brand et al. 1996; Connelly and Hegele 1998; Santamarina-Fojo et al. 2004). Subjects with an inactivating mutation in EL have higher HDL cholesterol levels (Edmondson et al. 2009). The latter finding raised considerable interest and suggested that EL inhibitors might be useful for increasing plasma HDL levels and reducing coronary disease risk (Jin et al. 2007; O'Connell et al. 2012). However, a large study has recently shown that an EL missense mutation that lowers EL activity and raises HDL cholesterol levels does not change susceptibility to coronary artery disease (Voight et al. 2012).

Intracellular lipolysis and disease

NLSD

NLSD is a rare nonlysosomal, autosomal-recessive lipid storage disorder (Table 1; Chanarin et al. 1975). Affected individuals accumulate TG-containing LDs in multiple tissues, including skin, skeletal muscle, heart, liver, the CNS, and blood leukocytes. The finding of lipid-filled vacuoles in leukocytes was first discovered by Jordans (1953) and is pathognomonic for the disease. More variable clinical features include liver steatosis and hepatomegaly, skeletal and cardiac myopathy, growth retardation, cataracts, hearing loss, and/or loss of mental acuity (Dorfman et al. 1974; Chanarin et al. 1975). The most obvious phenotype in a subset of NLSD patients is a severe skin defect known as nonbullous congenital ichthyosiform erythroderma (Dorfman et al. 1974; Chanarin et al. 1975), which is associated with a defect in the epidermal water barrier. Previously called Chanarin-Dorfman syndrome, this disease is now called NLSDI. Igal et al. (1997) categorized >40 patients with NLSD into two groups according to the presence or absence of ichthyosis and observed that NLSDI patients were more likely to develop liver steatosis, whereas the group without ichthyosis was more likely to develop skeletal and cardiac myopathy. The NLSD variant without ichthyosis is now called NLSD with myopathy (NLSDM). Mutations in the gene for ATGL (*PNPLA2*) cause NLSDM, whereas mutations in the gene for CGI-58 cause NLSDI.

ATGL deficiency and NLSDM

In 2007, Fischer's group (Fischer et al. 2007) reported that ATGL mutations cause NLSDM, and since then, 30 human cases of NLSDM have been recorded with at least 15 different mutations. Mutations include single-, di- and tetranucleotide deletions, nucleotide transversions, and splice site alterations (Schweiger et al. 2009). Aside from a single missense mutation in ATGL, all other mutations lead to premature stop codons due to frameshift or nonsense mutations. Interestingly, the clinical presentation varies among patients, and it is not clear whether the differences relate to the intrinsic properties of the mutant

protein or are due to gene–gene or gene–environment interactions. Generally, phenotypes in humans resemble those in ATGL-deficient mice but are less dramatic. Affected patients typically experience muscle weakness during their teenage years. By the third decade, patients often develop cardiac steatosis and dilated cardiomyopathy. This condition can be severe and often makes cardiac transplantation inevitable (Hirano et al. 2008).

Cardiac death in patients (and in the knockout mice) may not be due entirely to the accumulation of TG or the lack of energy substrates. The reason is that hearts of *Atgl* knockout mice exhibit a severe defect in mitochondrial oxidation of FAs and glucose, a consequence of defective PPAR α /PPAR γ coactivator 1 (PGC-1) signaling (Haemmerle et al. 2011). This metabolic defect leads to lipid deposition in the heart and cardiomyopathy. Treatment of ATGL-deficient mice with PPAR α agonists improves the metabolic defect, reverses cardiomyopathy, and prolongs life. ATGL activity is also important for PPAR α signaling in the liver and BAT (Sapiro et al. 2009; Ong et al. 2011; Ahmadian et al. 2012; Mottillo et al. 2012). The mechanism of how ATGL regulates PPAR α -mediated gene expression is not known, but since PPARs require lipid ligands for activation, it is conceivable that the ATGL reaction provides these ligands (or their precursors). Whether a similar mechanism is involved in the development of cardiomyopathy in patients with NLSMD and whether treating them with PPAR agonists would have beneficial effects remain to be investigated. LPL also regulates PPAR α signaling (Ziouzenkova et al. 2003). Transgenic mice overexpressing LPL in the heart exhibit increased PPAR α target gene expression and peroxisome proliferation.

CGI-58 deficiency and NLSDI

Homozygosity mapping, linkage disequilibrium analysis, and candidate gene sequencing showed that mutations in the gene for CGI-58 cause NLSDI (Lefevre et al. 2001). This finding predated the discovery of ATGL, and accordingly, the mechanism for lipid accumulation was initially mysterious. The discovery that CGI-58 activates the TG hydrolase activity of ATGL (Lass et al. 2006) eventually provided an explanation for the lipid accumulation phenotype. However, the ichthyosis phenotype was not readily explained because ATGL-deficient humans and mice exhibit no skin abnormalities. This suggested that CGI-58 has an ATGL-independent function in the skin (and possibly in other tissues as well). Of note, the skin defect in CGI-58-deficient mice was far more severe than in humans with NLSDI (Radner et al. 2010). *Cgi-58* knockout mice die soon after birth from water loss, a consequence of a severe defect in the permeability barrier of the epidermis. CGI-58 deficiency causes a marked reduction of epidermal acylceramides in mice and humans (Radner et al. 2010; Uchida et al. 2010). Since acylceramides are essential lipids in the formation of the corneocyte lipid envelope, their absence in CGI-58-deficient skin is most likely responsible for the epidermal barrier defect. How CGI-58 affects acylceramide synthesis is currently not clear.

HSL deficiency

A recent study uncovered two Amish subjects with homozygous loss of HSL due to a deletion mutation. According to a meeting abstract (Albert et al. 2011), these patients express no HSL protein, have a 50% reduction in adipocyte size, and accumulate DG in fat cells, reminiscent of findings in *Hsl* knockout mice (Wang et al. 2001; Haemmerle et al. 2002). Decreased fat mass in HSL-deficient mice is due to decreased PPAR γ activity, resulting in decreased lipogenesis (Zimmermann et al. 2003). In the future, it will be interesting to determine whether human HSL deficiency also affects PPAR γ -regulated lipid synthesis. Male *Hsl* knockout mice are also infertile (Osuga et al. 2000). Currently, no information exists on fertility in male HSL-deficient humans. However, a recent study reported an increased frequency of a single-nucleotide polymorphism in the human *HSL* gene in infertile males (Vatannejad et al. 2011), suggesting that genetic variation in HSL may be a risk factor for male infertility.

ATGL, CGI-58, HSL, and metabolic disease

A potential role of lipolysis in the development of obesity and insulin resistance in humans has been discussed extensively (for review, see Arner 2005; Jocken and Blaak 2008; Lafontan and Langin 2009; Kolditz and Langin 2010). TG accumulation in tissues is commonly, but not always, associated with the development of insulin resistance (Sun and Lazar 2013). Interestingly, despite neutral lipid accumulation in multiple tissues, no major alterations in glucose tolerance or insulin sensitivity have been reported in ATGL- and CGI-58-deficient humans (Kobayashi et al. 2008). The dissociation of TG storage and insulin resistance has also been observed in mice (Haemmerle et al. 2006; Kienesberger et al. 2009a; Hoy et al. 2011; Turpin et al. 2011), supporting the concept that TG accumulation per se is not sufficient to cause insulin resistance. In mice, ATGL also affects pancreatic insulin secretion, leading to reduced plasma insulin levels (Peyot et al. 2009). One study reported decreased plasma insulin levels in NLSMD patients (Akiyama et al. 2007), but additional studies of affected humans are needed to conclude that ATGL is necessary for normal insulin production.

Hepatic ATGL and CGI-58 expression levels have a pronounced effect on liver TG levels. While liver-specific knockouts of *Atgl* or *Cgi-58* cause severe hepatosteatosis, overexpression of ATGL results in low hepatic TG stores (Reid et al. 2008; JM Brown et al. 2010; Wu et al. 2011). These changes in ATGL expression and hepatic TG levels, however, do not seem to affect hepatic VLDL synthesis or plasma TG concentrations, suggesting that the ATGL reaction may not be important in providing FAs for VLDL assembly (Wu et al. 2011). Similarly, there are no apparent defects in plasma lipoprotein metabolism in patients with NLSMD or NLSDI (Akiyama et al. 2007; Fischer et al. 2007).

The severe defects in brown adipocyte function and thermogenesis in ATGL-deficient mice have highlighted the importance of lipolysis in these processes (Haemmerle

et al. 2006; Ahmadian et al. 2012). The presence and functional importance of brown adipocytes have also been demonstrated in humans (van Marken Lichtenbelt et al. 2009; Virtanen et al. 2009). To date, it is not known whether patients with NLSMD exhibit a BAT defect that affects thermogenesis.

MGL and disease

The discovery that 2-AG acts as an endocannabinoid signaling molecule ignited great interest in its synthesis pathways and its degradation by MGL. Thus far, mutations that inactivate MGL have not been reported in humans. However, experiments in mutant mice suggest that MGL could prove to be a target for treating various disorders. MGL deficiency in mice causes massive accumulation of MGs, specifically 2-AG, in multiple tissues (Chanda et al. 2010; Schlosburg et al. 2010; Taschler et al. 2011). In the brain, 2-AG levels increase >20-fold; however, chronic exposure to increased 2-AG concentrations leads to desensitization of endocannabinoid signaling (Chanda et al. 2010; Schlosburg et al. 2010), with no significant effects on food intake, energy expenditure, and other metabolic parameters. In contrast, acute treatment of mice with a MGL inhibitor provoked the expected cannabimimetic effects of analgesia, hypothermia, and hypomotility (Long et al. 2009). Conversely, when MGL activity was increased in the forebrain by transgenic overexpression, the animals were lean and had reduced adipose mass and improved glucose tolerance (Jung et al. 2012). Unexpectedly, the animals were hyperphagic and consumed this additional energy for thermogenesis. 2-AG acts in concert with another lipid mediator, anandamide (arachidonyl ethanolamide), in the activation of CBRs and endocannabinoid signaling. To induce analgesia in patients with chronic pain, it may be necessary to inhibit both MGL and FA amide hydrolase (FAAH), the main catabolic enzyme for anandamide.

MGL is not only important in inactivating 2-AG for endocannabinoid signaling, it also provides arachidonic acid for prostaglandin synthesis. Recently, Nomura et al. (2012) demonstrated that MGL deficiency leads to reduced arachidonic acid availability, reduced levels of neuroinflammatory prostaglandins in the brain, and neuroprotection in a mouse model of Parkinson's disease. Thus, inhibition of MGL could represent an anti-inflammatory treatment strategy.

MGL deficiency leads to MG accumulation in the liver, reduced plasma glycerol levels, decreased VLDL synthesis, and lower plasma TG concentrations (Taschler et al. 2011). Interestingly, MGL-deficient mice are more sensitive to insulin than wild-type mice, but the mechanism is currently unclear. One possibility involves the role of MGs as ligands for the G-protein-coupled receptor 119 (GPR119) (Hansen et al. 2012). This receptor acts as a fat sensor, with the highest levels of expression in the pancreas and the intestine. It is activated by a variety of oleic acid-containing lipids, including 2-oleylglycerol (2-OG), and regulates glucagon-like peptide-1 (GLP-1) and insulin secretion in enteroendocrine cells and pancreatic β cells.

2-OG is a major product of dietary fat hydrolysis by pancreatic lipase and induces GLP-1 secretion in intestinal cells through GPR119. This activity is also consistent with the finding that MGL overexpression in the small intestine reduces intestinal MG levels (including 2-OG), causing hyperphagia and obesity (Chon et al. 2012). In the pancreas, 2-OG and other MGs are products of both intravascular LPL activity and intracellular ATGL/HSL activity. All three lipases affect insulin secretion from pancreatic islet β cells (Roduit et al. 2001; Pappan et al. 2005; Peyot et al. 2009), and it is conceivable that, depending on the activity of MGL, the local MG concentration regulates pancreatic insulin secretion through GPR119.

Lipolysis in cancer and cancer cachexia

Metabolism in cancer cells has witnessed a revival in recent years (Vander Heiden et al. 2009). This includes renewed interest in lipid metabolism in cancer biology. In addition to numerous lipid signals and mediators that affect tumor cell proliferation, TG anabolic and catabolic pathways are instrumental in providing energy, membrane lipids, and other lipid intermediates for cancer cell growth (Menendez 2009). LPL expression by rapidly proliferating cancer cells could affect the delivery and uptake of lipid nutrients to those cells. Immunohistochemical studies have demonstrated the presence of LPL and CD36 (a FA transporter) in the majority of breast cancer, liposarcoma, and prostate cancer samples (Kuemmerle et al. 2011). Interestingly, LPL is frequently overexpressed in invasive cervical squamous cell carcinomas (Carter et al. 2012). Most impressively, patients with chronic lymphocytic leukemia (CLL) whose leukemia cells express high levels of LPL transcripts have a lower survival rate (Van Bockstaele et al. 2007; Maloum et al. 2009; Kaderi et al. 2011). One study indicated that high LPL transcript levels in CLL are associated with increased LPL protein production; however, enzymatic activity assays suggested that much of the LPL could be inactive (Mansouri et al. 2010). At this point, it is unclear whether LPL levels are simply a useful prognostic indicator for CLL or whether the high levels of LPL expression directly affect the behavior of the tumor cells. This topic needs further investigation.

Little is known about the role of intracellular lipases in carcinogenesis and tumor proliferation, but results in model organisms suggest a potential involvement. For example, in yeast (*Saccharomyces cerevisiae*), the ATGL ortholog Tgl4 participates in the regulation of cell cycle progression (Kurat et al. 2006). Tgl4 is activated by phosphorylation through the cyclin-dependent kinase Cdk1/Cdc28 (orthologous to mammalian Cdc2) at the G1/S transition and provides FAs during periods of high demand for membrane lipid synthesis. Deletion of *Tgl4* (together with *Tgl3*) abolishes TG hydrolysis and delays cell division.

Cravatt and colleagues (Nomura et al. 2010) found that MGL has potent protumorigenic activity in mice and that MGL expression is induced in many aggressive human

cancers. Interestingly, the tumor-promoting role of MGL appears to rely on both its metabolic function in providing FAs for cell membranes and its role as an endocannabinoid signaling antagonist (Nomura et al. 2011). However, not all studies agree on the role of MGL in cancer cell proliferation. One study found a tumor-promoting role for MGL in colorectal cancer (Ye et al. 2011), while another reported a tumor-suppressive role (Sun et al. 2013).

Although it is unknown whether ATGL/CGI-58 and HSL affect the development and proliferation of tumors, a crucial role for these proteins in cancer-associated cachexia was recently uncovered. Cachexia is defined as an unwanted loss of adipose tissue and muscle mass that cannot be corrected by dietary measures. It occurs in the end stages of many chronic diseases and is most commonly observed in cancer. Arner and colleagues (Agustsson et al. 2007; Ryden et al. 2008) noted that patients with cancer-associated cachexia exhibit increased lipolysis and FA release from adipose tissue. In a recent study, Das et al. (2011) found that ATGL deficiency in mice can prevent the loss of adipose tissue and muscle in animals with Lewis lung carcinoma, suggesting that intracellular lipolysis could play a central role in the physiology of cachexia. The mechanisms linking lipolysis with the pathogenesis of cachexia are currently under investigation, and many questions remain unanswered. For example, it is not known whether ATGL/HSL-catalyzed lipolysis is important in the pathogenesis of all forms of cachexia or only in cachexia associated with certain cancers. It will also be important to tease out the relative contributions of adipose or muscle lipolysis to the development of cachexia. Clarification of these issues will reveal whether ATGL and/or HSL are appropriate targets for preventing cachexia in humans.

Lipolysis and infectious disease

Given the conservation of LPL and GPIHBP1 in mammalian evolution, one might have imagined that endothelial cell pathogens would have evolved strategies to hijack these proteins and use them as vehicles for infecting endothelial cells or moving across capillaries. Thus far, however, no one has found evidence for these processes, but sooner or later, we suspect that examples will be uncovered. Certain meningococcal proteins are known to bind to heparin or negatively charged proteoglycans on the surface of cells (de Vries et al. 1998; Serruto et al. 2010). Similarly, the dengue fever virus is thought to infect endothelial cells by binding to negatively charged HSPGs (Dalrymple and Mackow 2011). Interestingly, the uptake of the dengue fever virus can be reduced with heparin. The major locus for mouse adenovirus susceptibility maps to a Ly6 gene locus containing *GPIHBP1* (Spindler et al. 2010), and the infection of some adenoviral strains can be inhibited with heparin (Dechecchi et al. 2001). Finally, red blood cells, when infected with different strains of *Plasmodium*, are thought to bind to HSPGs on endothelial cells (Vogt et al. 2003; Chotivanich et al. 2012). This binding can be inhibited with heparin. At this point,

whether any of these pathogens make use of GPIHBP1 as a binding site is unknown but certainly plausible.

In some cases, LPL could play a role in protecting the host from infection (Thomssen and Bonk 2002; Andreo et al. 2007; Shimizu et al. 2010; Maillard et al. 2011). Hepatitis C virus (HCV) is known to associate with plasma lipoproteins, and lipoprotein receptors could play a role in virus uptake by cells. Treatment of lipoproteins with catalytically active LPL reduces infectivity of the virus, likely by “tying up” the virus on the surface of cells and preventing productive infection within cells (Maillard et al. 2011).

Active lipid metabolism and intracellular LD turnover are also connected to the life cycle of various bacteria, viruses, and parasites. For example, *Mycobacterium tuberculosis*, an obligate intracellular bacterium, infects macrophages in the lung and uses host TGs as its main energy source (Neyrolles et al. 2006). The bacilli import FAs derived from host TGs, store them as TGs in intracellular lipid inclusions, and rehydrolyze them using their own lipases to meet metabolic demands. *Chlamydia trachomatis*, an intracellular pathogen that causes conjunctivitis, urethritis, and pelvic inflammatory disease, also depends on TG and cholesterol esters from host LDs. In contrast to *M. tuberculosis*, *Chlamydia* lacks proteins with homology with known TG hydrolases. Thus, it is assumed that TGs used by that organism are processed by host lipases such as ATGL. Bacterial proteins (e.g., Lda3) may facilitate this process by removing perilipins from the surface of LDs, thereby enabling access of lipases to TG substrates (Cocchiario et al. 2008).

Viruses have also been shown to use elements of host TG metabolism. The HCV life cycle depends on—and interferes with—host cell LD formation and degradation. A viral nucleocapsid protein named *core* translocates from the ER to the LD surface, which provides a platform for viral assembly (Boulant et al. 2007; Miyanari et al. 2007; Herker et al. 2010). This process relies on the TG-synthesizing enzyme acyl-CoA diacylglycerol acyltransferase-1 (DGAT1) (Herker et al. 2010). The absence of DGAT1 or LDs in hepatocytes leads to defective HCV assembly. The dependence of virus assembly on DGAT1 and LDs is also consistent with the observation that one of the major clinical manifestations of HCV infection is liver steatosis (Asselah et al. 2006). Recent data suggest that *core* causes LD accumulation by inhibiting intracellular TG hydrolysis and reducing TG catabolism (Harris et al. 2011). Dengue fever virus is closely related to HCV and displays a similar dependency on host cell LDs for viral replication and assembly. Moreover, dengue fever virus infection induces both host cell lipogenesis and autophagy for TG degradation (Heaton and Randall 2010; Heaton et al. 2010). The released FAs subsequently undergo mitochondrial β oxidation, and the resulting energy is used for viral RNA replication. Moreover, the degradation of LDs by autophagy may serve as an immune evasion strategy (Heaton and Randall 2010). Host LDs or lipid metabolites are also important for replication of rotavirus (Cheung et al. 2010), cytomegalovirus (Zhu et al. 2002), and influenza virus (Munger et al. 2008), but the role of

host lipolytic processes or lipases in these processes is insufficiently understood.

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