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Lipophagy at a glance

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ABSTRACT

Lipophagy is a central cellular process for providing the cell with a readily utilized, high energy source of neutral lipids. Since its discovery over a decade ago, we are just starting to understand the molecular components that drive lipophagy, how it is activated in response to nutrient availability, and its potential as a therapeutic target in disease. In this Cell Science at a Glance article and the accompanying poster, we first provide a brief overview of the different structural and enzymatic proteins that comprise the lipid droplet (LD) proteome and reside within the limiting phospholipid monolayer of this complex organelle. We then highlight key players in the catabolic breakdown of LDs during the functionally linked lipolysis and lipophagy processes. Finally, we discuss what is currently known about macro- and micro-lipophagy based on findings in yeast, mammalian and other model systems, and how impairment of these important functions can lead to disease states.

KEY WORDS: Autophagy, Lipid droplet, Lipolysis, Lipophagy, Metabolism

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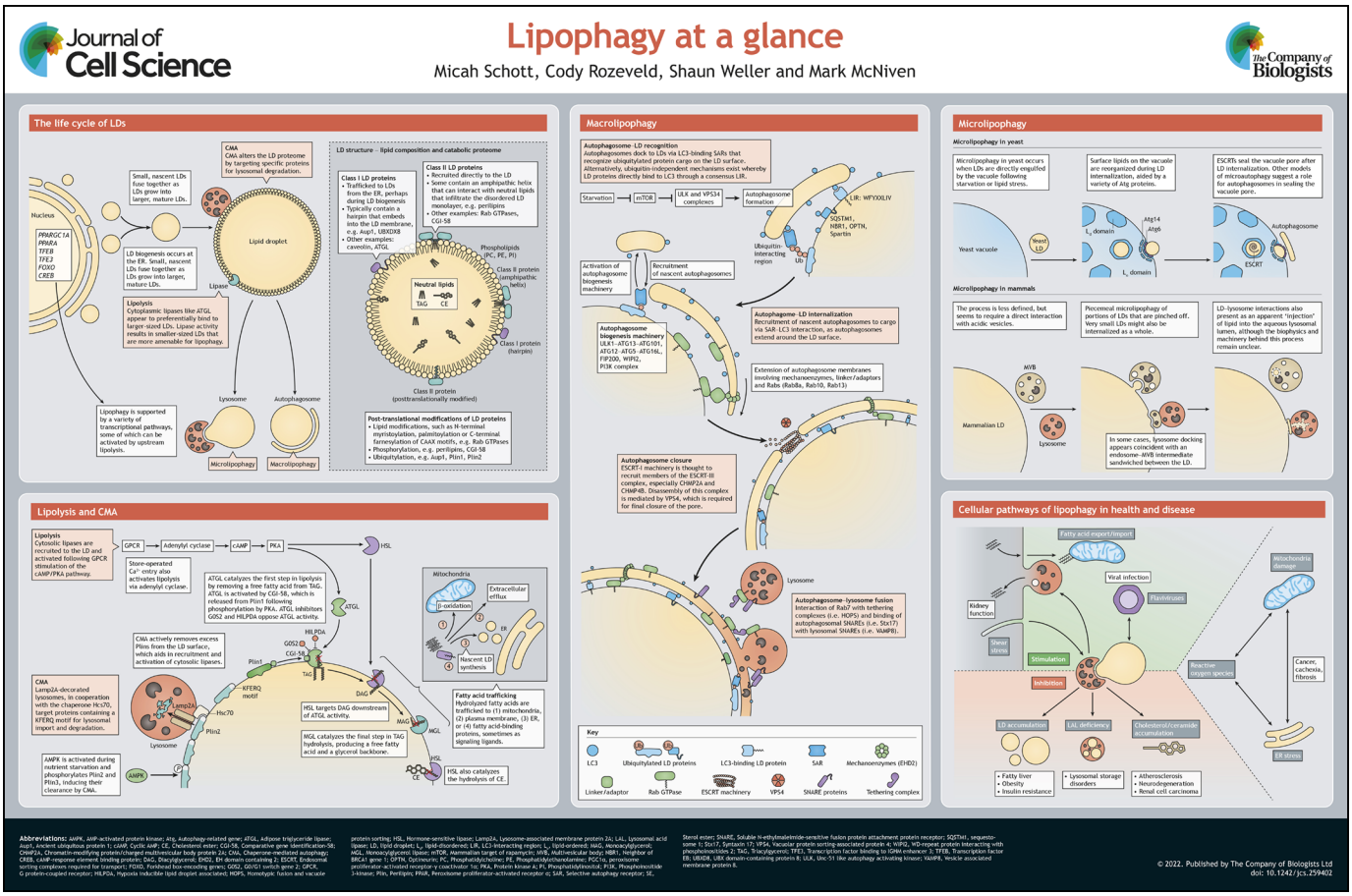
Introduction

Lipid droplets (LDs) play important roles in numerous cell types across virtually all species. Beyond serving as energy-rich lipid reservoirs for the breakdown of fatty acids by β-oxidation, cells use LDs to protect against lipid stress by converting cytotoxic free fatty acids (FFAs) into inert neutral lipids, such as triacylglycerol (TAG) and cholesterol ester (CE) (Olzmann and Carvalho, 2019). FFAs in the cytoplasm are quickly trafficked to the endoplasmic reticulum (ER), where their conversion into neutral lipids is facilitated by a series of neutral-lipid synthesis enzymes (Jackson, 2019). TAG and CE accumulate between the two leaflets of the ER bilayer, and extrude into the cytoplasm as small nascent LDs surrounded by a



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phospholipid monolayer composed mainly of phosphatidylcholine (PC), phosphatidylethanolamine (PE) and phosphaditylinositol (PI), with varying fatty acid chains that influence LD membrane biophysics (Arisawa et al., 2013). Phospholipids on the LD monolayer are packed at lower density than that of bilayers and exhibit randomly disordered movement that allows for transient exposures of the neutral lipid core, influencing protein localization to the LD surface (Chorlay et al., 2021; Prevost et al., 2018; Thiam et al., 2013).

During LD biogenesis, localization of LD-resident proteins to the phospholipid monolayer requires unique binding domains and trafficking pathways. Class I proteins, which often possess a short hairpin motif that embeds within the phospholipid monolayer, traffic through the ERTOLD (ER to LD) pathway (Olarte et al., 2021). Examples of catabolic Class I LD proteins include the autophagosome receptor ancient ubiquitous protein 1 (Aup1) (see poster). Class II proteins are recruited to the LD from the cytoplasm through the CYTOLD (cytoplasm to LD) pathway and contain variable domains for LD localization (Olarte et al., 2021). For example, members of the perilipin family (Plin1 to Plin5) possess an amphipathic helix that embeds within the phospholipid monolayer and can interact with neutral lipids within the LD core. Other Class II proteins include members of the Rab family of small GTPases, which play diverse roles in LD homeostasis, including LD–LD fusion, subcellular trafficking and lipophagy (Dejgaard and Presley, 2021). Rab GTPases are prenylated at their C-terminal CAAX domain, which acts as an anchor to the LD (Schroeder et al., 2014). Other post-translational modifications of LD proteins include phosphorylation, which aids in trafficking and activation of cytosolic lipases (Egan et al., 1992; Granneman et al., 2009; Lass et al., 2006; Sahu-Osen et al., 2015; Xie et al., 2014), and ubiquitylation, which can regulate protein degradation (Roberts and Olzmann, 2020; Stevenson et al., 2016) as well as lipophagy (Robichaud et al., 2021; Yan et al., 2019; Zhang et al., 2018).

Lipophagy is the autophagic degradation of lipid droplets and has been widely demonstrated in mammalian cells, as well as plants, yeast and algae (Zienkiewicz and Zienkiewicz, 2020). Moreover, it is now appreciated that distinct subtypes of lipophagy exist. Macrolipophagy is a form of selective autophagy that utilizes autophagosomes to target and engulf LDs for subsequent degradation upon fusion with lysosomes (see poster) (Singh et al., 2009). Microlipophagy is a distinct form of lipophagy whereby LDs directly interact with lysosomes or lysosome-like organelles, such as the yeast vacuole (see poster). Microlipophagy is not thought to require the targeting of LDs to the autophagosome; however, several studies in yeast implicate a genetic requirement for core autophagy proteins in this process, although the molecular mechanism is unclear (discussed further below). Lysosomal acid lipase (LAL; also known as LIPA) resides within the lysosomal lumen and functions as the principal enzyme for lipid catabolism for both macro- and micro-lipophagy, degrading TAG and CE within the acidic environment (Zhang, 2018).

Lipophagy can be stimulated by nutrient deprivation and is transcriptionally controlled by factors that support lysosomal and mitochondrial biogenesis (see poster). In addition, other LD catabolic pathways serve as important upstream mediators of lipophagy, including chaperone-mediated autophagy (CMA) and cytosolic lipolysis.

Upstream mediators of lipophagy – CMA and lipolysis

CMA is a proteolytic pathway that targets specific proteins for degradation within lysosomes (Kaushik and Cuervo, 2018). During this process, proteins harboring a unique pentapeptide motif (KFERQ) are selectively bound by the chaperone Hsc70 (also known as HSPA8), which then docks to the cytoplasmic tail of the lysosomal transmembrane protein Lamp2A (an isoform of Lamp2). Lamp2A assembles into a large, multimeric translocation complex through which cargo proteins traverse into the lysosomal lumen for degradation (see poster). CMA is intimately linked to LD homeostasis, as CMA inhibition causes defective LD catabolism and the abnormal accumulation of lipids (steatosis). CMA may be stimulated by AMP-activated protein kinase (AMPK) to degrade LD-resident Plin2, as well as Plin3 and Plin5 (Kaushik and Cuervo, 2015, 2016; Ma et al., 2020). Clearance of these proteins from the LD surface promotes the recruitment of cytosolic lipases for lipolysis (Kaushik and Cuervo, 2015). Thus, CMA deficiency inhibits LD catabolism by lipolysis and leads to cellular steatosis. In addition, CMA deficiency also prevents LC3B (also known as MAP1LC3B) recruitment to the LD and reduces LAL levels, thereby restricting the cellular capacity to degrade LDs by lipophagy (Kaushik and Cuervo, 2015; Qiao et al., 2021).

Cytosolic lipolysis is initiated by the cAMP-protein kinase A (PKA) pathway upon activation of adenylyl cyclase by β-adrenergic receptor [a G protein-coupled receptor (GPCR)], or by store-operated Ca^{2+} entry (Maus et al., 2017; Zechner et al., 2017). Lipolysis relies on cytoplasmic lipases, such as adipose triglyceride lipase (ATGL; also known as PNPLA2), hormone-sensitive lipase (HSL; also known as LIPE) and monoglyceride lipase (MGL; also known as MGLL), that operate sequentially to degrade TAG within the LD core (see poster). Lipolytic stimulation not only serves to recruit cytosolic lipases to the LD surface, but also to increase lipase activity by regulating the binding of lipase to its cofactors. ATGL, for example, binds to its coactivator CGI-58 (also known as ABHD5) following PKA activation, while being simultaneously shielded from inhibitory cofactors, such as G0S2 and HILPDA (Yang and Mottillo, 2020) (see poster). ATGL and HSL also contain LC3-interacting regions (LIRs) that play a role in their LD recruitment and activation, highlighting crosstalk between lipolysis and the autophagy machinery (Martinez-Lopez et al., 2016). Upon activation, lipolysis preferentially targets and reduces larger-sized LDs, and FFA byproducts can be transported to the plasma membrane, mitochondria or ER, where they are re-esterified into small, nascent LDs (Paar et al., 2012; Schott et al., 2017). The small LDs resulting from re-esterification at the ER are more readily engulfed by autophagosomes and lysosomes, such that lipolysis acts as an important upstream pathway prior to lipophagy (Schott et al., 2019). In addition, lipolysis stimulates lipophagy by releasing fatty acid byproducts that serve as signaling ligands to activate peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α)- and/or peroxisome proliferator-activated receptor α (PPARα)-dependent transcription of lipophagic genes (Sathyanarayan et al., 2017).

Macrolipophagy is a subtype of selective autophagy

Macrolipophagy is a type of selective autophagy whereby LDs are enveloped by autophagosomes and delivered to lysosomes for degradation (Shin, 2020). While autophagosome engulfment is thought to be restricted to smaller-sized LDs, piecemeal macrolipohagy of larger LDs has also been described (Schott et al., 2019; Singh et al., 2009). Macrolipohagy involves many of the components involved in selective autophagy, a process by which organelles, proteins and other cargoes are specifically targeted for delivery to lysosomes. We therefore first provide a brief introduction to selective autophagy, focusing on the processes that apply to

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macrolipophagy, before further discussing recent molecular insights into macrolipophagy.

During selective autophagy, cargo recognition is mediated by various selective autophagy receptors (SARs); these localize to specific target cargoes and recruit autophagosomes by way of LIRs that bind to Atg8 family proteins (LC3s and GABARAPs) decorating the autophagic membrane (Lamark and Johansen, 2021) (see poster). Soluble SARs bind ubiquiylated proteins on the target of interest, whereas membrane-bound SARs directly bind to their specific cargoes (Lamark and Johansen, 2021). In addition to serving as a physical link between autophagosomes and cargo, SARs can also stimulate the formation of additional nascent autophagic membranes to complete the engulfment process (Turco et al., 2019; Vargas et al., 2019). After their initiation, autophagosomes extend to completely engulf their cargo until final closure of the autophagosome pore is required. This process involves components of the endosomal sorting complex required for transport (ESCRT) family of proteins, particularly the ESCRT-I subunit VPS37A, the ESCRT-III subunit CHMP2A and the hexameric AAA ATPase VPS4A (Takahashi et al., 2018; Takahashi et al., 2019) (see poster). Following autophagosome closure around its cargo, fusion with lysosomes is necessary to deliver hydrolytic enzymes responsible for cargo degradation; this is mediated by Rab7 (herein referring to Rab7a), SNARE proteins localized to autophagosomes and lysosomes, as well as the tethering complex homotypic fusion and protein sorting (HOPS) (Tian et al., 2021).

Autophagic catabolism of LDs was first described to occur in liver hepatocytes, and this is when the process was termed macrolipophagy (Singh et al., 2009). Since then, there has been intense interest in defining LD-resident lipophagy receptors that link autophagosomes to LDs during macrolipophagy. A recent, unbiased screen of macrophage LDs revealed several putative macrolipophagy receptors, including SQSTM1 (also known as p62), NBR1 and optineurin, all of which are well-known SARs for other cargoes (Robichaud et al., 2021). These findings support previous studies indicating a lipophagic role for SQSTM1 in hepatocytes (Wang et al., 2017) and myocytes (Lam et al., 2016). However, while the above studies suggest that SARs, such as SQSTM1, NBR1 and optneurin, may include LDs in their cadre of autophagic cargoes, knowledge of receptors that are exclusive to macrolipophagy are lacking. The hereditary spastic paraplegia protein spartin has also been implicated in LD-autophagosome targeting. Spartin localizes to LDs and increases ubiquitylation of LD surface proteins by activating the E3 ligase AIP4 (also known as ITCH), leading to triglyceride accumulation (Hooper et al., 2010). More recently, spartin was reported as a bona fide lipophagy receptor that interacts with LC3A and LC3C, connecting autophagosomes to the LD surface (Chung et al., 2021 preprint). Whether spartin serves as a receptor exclusively for macrolipohagy is not absolutely clear, but it might represent a promising target for developing lipophagy-specific therapeutics in the future.

In addition to via lipophagy receptors, LDs are targeted to autophagosomes by the vesicle trafficking machinery, including several members of the Rab family of small GTPases, which are known for trafficking distinct vesicle subpopulations within cells. Rab7 in hepatocytes has been shown to be activated during autophagy stimulation by starvation, thereby promoting LD fusion with autophagic vesicles (Schroeder et al., 2015). A subsequent study further revealed that hepatocellular Rab7 activity is impaired by chronic alcohol consumption, resulting in increased LD accumulation owing to reduced lipophagy (Schulze et al., 2017). Rab7 can also be activated by β-adrenergic stimuli for lipophagy in adipocytes. (Lizaso et al., 2013). Another lipophagy regulator is Rab10, which forms a trimeric complex with the endocytic adaptor EHBP1 and the membrane-deforming mechanoenzyme EHD2. This Rab10–EHBP1–EHD2 complex recruits autophagosomes to the LD and appears to provide mechanical extension of autophagic membranes around the LD for engulfment (Li et al., 2016) (see poster). Rab10 also cooperates with the large GTPase dynamin-2 to aid in the maturation of lipo-autophagosomes through a mechanism involving tubulation, scission and recycling of autolysosomal membranes (Li et al., 2020; Schulze et al., 2013). In hepatic stellate cells (HSCs), Rab25 is required for autophagic turnover of LDs during cell activation (Zhang et al., 2017). This is stimulated by mitochondrial production of reactive oxygen species (ROS), which increases Rab25 expression to drive lipophagy (Zhang et al., 2017). Finally, Rab40 has also been implicated in lipophagy in *Drosophila* through a mechanism involving its activation by TBC1D22 at the Golgi (Duan et al., 2021).

Microlipophagy

Microautophagy is a ubiquitous process in which cellular organelles are directly consumed by the lysosome without an initial targeting by autophagosomes. Many cellular organelles are targeted by this process, including the ER, peroxisomes, mitochondria and the nucleus (Li et al., 2012; Oku and Sakai, 2018; Schuck, 2020). The microautophagy of LDs has been observed in several yeast models and is involved in regulating energy production during starvation, but it also serves as a quality control mechanism for degrading misfolded proteins that accumulate on the LD surface (van Zutphen et al., 2014; Vevea et al., 2015). The exceptional size of the yeast lysosome, or vacuole (1–2 µm), has aided in the study of its dynamics and lipid segregation during LD catabolism. Under conditions of starvation or lipid stress, surface lipids on the yeast vacuole partition into hexagonal patterns representing liquid ordered sterol-rich domains (L_o) that serve as sites of LD docking and engulfment during microlipophagy (Seo et al., 2017; Wang et al., 2014) (see poster). The mechanisms for yeast microlipophagy are somewhat specific to the conditions used, but several studies seem to indicate a requirement for the ESCRT machinery and nuclear pore complex (NPC) proteins that transport sterols to form L_o domains, as well as select members of the core autophagic machinery (Liao et al., 2021; Oku et al., 2017; Tsuji et al., 2017). In addition, a recent study has shown that microlipophagy can occur independently of the formation of L_o domains during ER stress, during which the vacuole becomes fragmented and imports LDs in an ESCRT-dependent manner (Garcia et al., 2021).

The exact makeup of proteins utilized for microlipophagy and the biomechanics of this process remain enigmatic. Moreover, how the vacuole bilayer engulfs and/or fuses with the phospholipid monolayer of LDs is unclear. Oku and Sakai provide a helpful framework to think about this question of LD fusion with lipid bilayers, which is applicable to yeast and mammalian cells (Oku and Sakai, 2018). This includes membrane protrusion from the vacuolar/lysosomal surface mediated by Vac8 and Atg18 proteins (type 1) versus a reciprocal process of membrane invagination driven by ESCRT assembly from lysosomes and endosomes (types 2 and 3, respectively) (Oku and Sakai, 2018). More recently, a conceptual extension of these models suggests that either membrane fission or fusion processes are required for lipophagy (Schuck, 2020). Fission-type microlipophagy may drive invagination and fission of endosome/lysosome membranes requiring ESCRT

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function. In contrast, fusion-type microlipophagy could produce invaginations that are sealed by fusion with a phagophore-like cap. The latter model is intriguing as it could explain the requirement for core autophagy proteins reported in some instances of microlipophagy (Seo et al., 2017; van Zutphen et al., 2014; Wang et al., 2014).

The recent discovery of microlipophagy in liver hepatocytes (Schulze et al., 2020) provides a new twist to findings in yeast models, especially given that the size of the lysosome relative to LDs is reversed compared to the size of the vacuole relative to LDs [i.e. in most mammalian cells, the lysosome is rather small (0.5 µm), while the LD can exceed several microns in diameter]. Despite this size differential, the models described above can still apply, although questions about organelle docking and membrane deformation remain. An attractive aspect of a microlipophagy process in hepatocytes is the perceived simplicity and speed of this function in an organ that is required to store and catabolize LDs quickly in response to 4–8 h cycles of feeding and fasting. The mechanisms of targeted docking between the two organelles are unclear, although ultrastructural analyses suggest an endosome and/or multivesicular body (MVB)-like intermediate between the lysosome and the LD (Schulze et al., 2020). Whether this membranous 'cushion' aids in docking and fusion needs to be tested. Finally, while the authors of this study describe a LD piecemeal engulfment into lysosomes, it also appears that LD hydrophobic contents are injected directly into the lysosomal lumen (Schulze et al., 2020) (see poster). Both processes would appear to require a need for a force-generating apparatus, although they occur in the absence of core autophagy proteins such as Atg5. Whether there is a role for contractile proteins such as actin, myosin or membrane-deforming mechanoenzymes such as the large ATPase EDH2 in microlipophagy remains to be determined.

Implications of lipophagy in human disease

Precise regulation of lipophagy is critical for the maintenance of lipid and metabolic homeostasis across multiple cell types and tissues. Disruption of this lipophagic balance has been implicated in human health and disease. Indeed, several lines of evidence now suggest that either stimulation or inhibition of lipophagy plays a central role in tissue physiology (Haidar et al., 2021; Kounakis et al., 2019; Liu et al., 2020; Shin, 2020; Zhou et al., 2019).

Stimulation of lipophagy generally plays a preventative role in diseases related to aberrant lipid storage. However, in some contexts, lipophagy can propagate disease pathology. Perhaps the clearest example of this phenomenon is the infection by various *Flavioridae* family members, where lipid metabolism is hijacked to promote viral replication (Cloherty et al., 2020). Dengue virus stimulates lipophagy through Aup1 to increase LD-autophagosome association following infection (Zhang et al., 2018) (see poster). The precise mechanism linking Aup1 to lipophagy warrants further investigation, but it appears to require the acyltransferase activity of Aup1, which is governed by deubiquitylation (Zhang et al., 2018).

Lipophagy stimulation results in excessive levels of free fatty acids within lysosomes. Recently, it was shown that lipid-filled lysosomes fuse with the plasma membrane for export into the extracellular milieu, which is predicted to alter systemic lipid homeostasis and intercellular signaling (Cui et al., 2021). Excess fatty acids can also disrupt intracellular homeostasis downstream of augmented lipophagy. β-oxidation of excessive free fatty acids by mitochondria can produce detrimental ROS and mitochondrial damage (Mukhopadhyay et al., 2017; Zhao et al., 2020). These high levels of cellular fatty acids can also lead to lipid-induced ER stress and ROS-associated damage (Mukhopadhyay et al., 2017). The combined impacts of mitochondrial damage, ER stress and ROS generation create a multifaceted array of damage downstream of excessive cellular lipophagy that may contribute to cancer progression, fibrosis, and further dysregulation of lipid homeostasis (Kounakis et al., 2019; Maan et al., 2018; Zhou et al., 2019).

Inhibition of lipophagy leads to LD accumulation, which can worsen disease pathology. This is thought to be a major driver of metabolic liver diseases, such as non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) and alcohol-associated liver disease (AALD) (Carotti et al., 2020; Schulze et al., 2017; Yang et al., 2019). Obesity and insulin resistance are also coincident with lipophagy inhibition in non-liver tissues, such as adipose and muscle (Zhou et al., 2019) (see poster). Diminished lipophagy in macrophages has been implicated in atherosclerosis, leading to intracellular lipid accumulation and foam cell formation (Liu et al., 2020; Ouimet et al., 2011; Robichaud et al., 2021). Lipophagy also maintains kidney function, as fluid flow transmits pro-lipophagy signals via the primary cilium of kidney epithelial cells, thereby providing energy to maintain osmotic balance (Miceli et al., 2020). Therefore, it is likely that lipophagy perturbations may lead to the development of chronic kidney disease, particularly where dysregulated urinary flow is prevalent (Miceli et al., 2020).

In diseases of the central nervous system, evidence of diminished lipophagy is also beginning to emerge (Haidar et al., 2021). For example, Huntington's disease has been linked to reduced autophagic cargo recognition that leads to LD accumulation in neurons (Martinez-Vicente et al., 2010). The protein huntingtin (HTT) itself functions as a selective autophagy receptor (Rui et al., 2015), strengthening its possible role in lipophagy. In Troyer syndrome, a form of hereditary spastic paraplegia affecting muscle and neurons, loss of function mutations in the *SPG20* gene, which encodes spartin, leads to increased LD accumulation in mice (Renvoise et al., 2012). Other studies show that spartin functions in LD catabolism as a lipophagy receptor, further supporting a protective role for lipophagy against neurodegernative disease (Chung et al., 2021 preprint; Eastman et al., 2009; Hooper et al., 2010).

Conclusions and future perspectives

Despite its substantial importance in cellular function and health, our understanding of lipophagy remains rudimentary, with many exciting opportunities for future research. This includes a better understanding of the various lipophagy receptors and tethering proteins present at contact sites between LDs and lipophagic vesicles (Drizyte-Miller et al., 2020). Furthermore, the organelle-associated machinery that drives the fusion of the LD phospholipid monolayer with the unit membrane of MVBs and lysosomes is poorly defined. Additional important insights include defining how LD-associated proteins regulate lipophagy. For example, the roles of the many Rab GTPases, which have been identified as being present on the LD surface via several proteomic studies, remain unclear (Bersuker et al., 2018; Brasaemle et al., 2004; Zhang et al., 2011). Given the role of Rab GTPases in membrane trafficking (Borchers et al., 2021), it is plausible that these factors drive the targeting, docking and subsequent fusion of LDs with degradative compartments.

Another important area of study is crosstalk between lipophagy and other LD catabolic pathways. CMA has been shown to remove LD proteins that promote lipolysis, but the function of CMA in promoting lipophagy is unclear. Further questions include how do

autophagosomes and lysosomes preferentially recognize small LDs that are generated by lipolysis? Does the composition of LD neutral lipids and membrane phospholipids influence catabolism by CMA, lipolysis, or lipophagy? These and other issues ensure an exciting future for lipophagy research in the context of metabolic disease.

Competing interests
The authors declare no competing or financial interests.

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