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REVIEW

SUBJECT COLLECTION: CELL BIOLOGY AND DISEASE

Lysosomal storage disorders – challenges, concepts and avenues for therapy: beyond rare diseases

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ABSTRACT

The pivotal role of lysosomes in cellular processes is increasingly appreciated. An understanding of the balanced interplay between the activity of acidic hydrolases, lysosomal membrane proteins and cytosolic proteins is required. Lysosomal storage diseases (LSDs) are characterized by disturbances in this network and by intralysosomal accumulation of substrates, often only in certain cell types. Even though our knowledge of these diseases has increased and therapies have been established, many aspects of the molecular pathology of LSDs remain obscure. This Review aims to discuss how lysosomal storage affects functions linked to lysosomes, such as membrane repair, autophagy, exocytosis, lipid homeostasis, signalling cascades and cell viability. Therapies must aim to correct lysosomal storage not only morphologically, but reverse its (patho)biochemical consequences. As different LSDs have different molecular causes, this requires custom tailoring of therapies. We will discuss the major advantages and drawbacks of current and possible future therapies for LSDs. Study of the pathological molecular mechanisms underlying these 'experiments of nature' often yields information that is relevant for other conditions found in the general population. Therefore, more common diseases may profit from a correction of impaired lysosomal function.

KEY WORDS: Lysosomal storage disease, Therapy, Lysophagy, Lysosomal positioning, Motility of lysosomes, Lysosomal exocytosis

Introduction

The study of lysosome positioning and acidification, inside-out signalling, autophagy, lysophagy and the capacity of lysosomes to fuse with other intracellular membranes have received a lot of attention in recent years. These studies have contributed to the elucidation of the multiple functions played by lysosomes within a cell (see Box 1). This variety of functions explains why the lack of lysosomal hydrolases, accessory proteins or some membrane proteins that cause lysosomal storage disorders (see Box 2) affects cellular processes far beyond the degradative function of lysosomes, such as exocytosis, autophagy and lipid homeostasis. It is also apparent that the extracellular environment, intracellular signalling pathways and inflammatory conditions modulate the development and progression of lysosomal diseases. It remains largely unclear how the onset of disease is linked to the degree of lysosomal storage and what sequence of pathological molecular events is required to affect cell and tissue functions. Despite considerable progress in the development of therapies for lysosomal storage diseases (LSDs), it is unknown which of the cellular changes caused by the storage dysfunction can be reversed and why not all the symptoms of a specific LSD can be efficiently corrected. This Review attempts to extent the discussion already presented in excellent recent reviews on this topic (see, for example, Ballabio and Gieselmann, 2009; Lim and Zoncu, 2016; Parenti et al., 2015a; Platt, 2018; Platt et al., 2018). We aim to critically summarize the current view on the cellular processes in LSDs and will discuss how knowledge of these rare disorders can possibly be applied to more common diseases.

Open questions regarding LSDs

Despite vast progress in the understanding of the pathophysiology of LSDs, several intriguing questions remain unsolved. One such enigma concerns the age of onset of the diseases, which can vary from childhood to late adulthood in many LSDs (Platt et al., 2018). Another question is how a particular disease-causing mutation leads to different courses of disease, considering that straightforward genotype–phenotype relations are rare in LSDs. Whereas homozygosity of null alleles often leads to relatively homogenous phenotypes, most LSDs are caused by autosomal recessive point mutations, in which residual protein activity is a poor predictor of disease course (Ferraz et al., 2014).

Phenotype variability among patients carrying the same mutation and even among monozygotic twins shows that other factors affect disease severity (Platt, 2018). To what extent genetic and epigenetic modifiers, infectious diseases, environmental and dietary factors account for these phenotypic disparities is still unclear (Platt, 2018). Murine disease models offer a valuable tool to reveal a genetic basis of phenotypic variability in LSDs. The lifespan of a particular LSD mouse model can vary depending on the inbred strain used (Klein et al., 2016; Parra et al., 2011). Through a genome-wide association study, Klein et al. discovered that inbred mouse strains with high levels of the B subunit of the NMDA glutamate receptor (NR2B, encoded by *Grin2b*) have shorter lives than other strains when Gaucher disease (GD) (see Box 2) is pharmacologically induced, indicating a role for glutamate in GD pathology (Klein et al., 2016). Additionally, other factors, such as excessive dietary lipid uptake, may also aggravate storage in LSDs, as was demonstrated in Fabry disease mice (Ferraz et al., 2016a). A lipid-rich diet can further cause the development of acquired forms of lysosomal (cholesterol and phospholipid) storage disease in the kidney, even in the absence of genetic mutations (Rampanelli et al., 2018).

Virtually every cell of the body possesses lysosomes, yet storage in these organelles can often vary even among neighbouring cells (Fig. 1A). A plethora of factors can contribute to the predisposition of a lysosome to become a storage organelle and the ability of cells to upregulate the lysosome–autophagy axis plays a key role in the process. The metabolic and signalling status of a cell is relayed via the microphthalmia family of transcription factors (MiTF/TFE) and determines the particular rate of lysosomal biogenesis, autophagy and exocytosis (Fig. 1B). For example, large myelinated sensory

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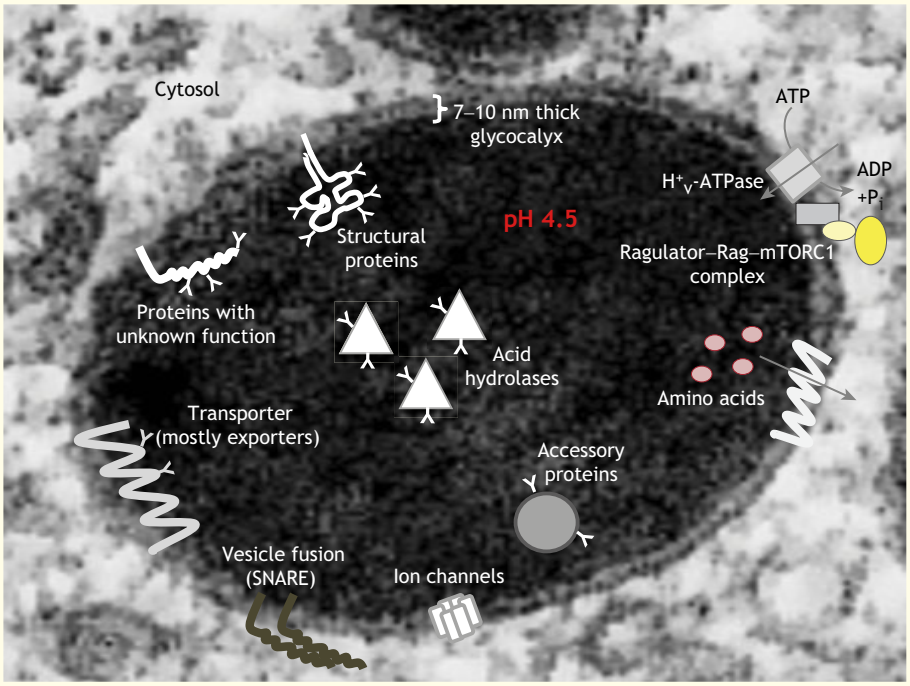
Box 1. The lysosome

Since its discovery and designation as a suicide bag or lytic body in the 1950s (De Duve et al., 1955), as a membrane-limited acidic organelle, the lysosome has raised increasing interest. About 60 specialized acid hydrolases are enriched in the lysosomal lumen (Saftig, 2006) (see box figure). The lysosomal membrane contains a high density and number of glycosylated membrane proteins possibly forming a 7- to 10-nm-thick glycocalyx-like layer (Saftig and Klumperman, 2009); it regulates transport across the membrane, acidification and membrane stability. The biogenesis of this compartment depends on both mannose-6 phosphate-dependent and -independent hydrolase delivery pathways. The biogenesis of lysosomes is also controlled by the transcription factor EB (TFEB) (Napolitano and Ballabio, 2016). TFEB is a member of the microphthalamia family of basic helix-loop-helix-leucine-zipper transcription factors (MiTF/TFE family) (Steingrímsson et al., 2004). Promoter studies revealed that many genes encoding for lysosomal proteins share a palindromic sequence, designated as 'coordinated lysosomal expression and regulation (CLEAR) elements' (Sardiello et al., 2009). TFEB binds to these sequences and triggers the expression of lysosomal genes, leading to an increased number of lysosomes and enhanced lysosomal hydrolase activities (Sardiello et al., 2009). In addition, TFEB not only leads to an increase in lysosomal exocytosis (Medina et al., 2011), but also enhances the degradation of autophagic substrates and the clearance of lipid droplets and mitochondria (Nezich et al., 2015; Settembre et al., 2011, 2013). Under nutrient-rich conditions, TFEB is phosphorylated at the lysosomal surface by the mTORC1 kinase, which means the transcription factor is retained within the cytosol. Recruitment of mTORC1 to the lysosomal surface involves v-ATPase, activation of the small Rag GTPases and activation of the kinase through the small GTPase Rheb. When cells are starved, mucolipin 1 (MCOLN1)-mediated Ca^{2+} release activates the phosphatase calcineurin, which leads to dephosphorylation of TFEB and its nuclear translocation (Medina et al., 2015). TFEB signalling therefore appears of pivotal importance to sense nutrients that are provided by lysosomal degradation and export; this, in turn, leads to a transcriptional response of lysosomal genes, which allows a cell to adapt to environmental metabolic demands (Napolitano and Ballabio, 2016).

The lysosomal compartment provides the tools for the enzymatic degradation of extracellular molecules. Many phagocytosed pathogens or intracellular molecules during autophagy end up in lysosomal degradation. In this way, lysosomes are at the centre of all these pathways and have to be reformed constantly. The lysosomal metabolism is tightly coupled to a cytosolic and nuclear signalling system thereby controlling cellular health and proliferation.



neurons accumulate storage material in large vacuoles, whereas smaller unmyelinated neurons induce lysosomal biogenesis; this may explain why these neurons present less storage and slower degeneration (Schultz et al., 2011; Zhou et al., 2010). Additionally, the rate of endocytosis and phagocytosis, as well as lysosomal hydrolase redundancy, influence the speed of turnover of cargo in lysosomes (Platt, 2018). Another factor that determines the development of abnormal storage accumulation is whether cells can use alternative strategies to dispose of the stored material. A prototypical example of such a mechanism is the formation of water-soluble glycosphingoid bases when glycosphingolipid-degrading glycosidases are deficient (Ferraz et al., 2016b).

An additional complicating factor in the study of LSDs is the fact that other molecules, besides the substrate of the deficient hydrolase or transporter, often accumulate within lysosomes. Because lysosomal hydrolases are involved in the stepwise degradation of macromolecules, their deficiencies can lead to a gradual build-up of upstream substrates of the same catabolic pathway (Walkley and Vanier, 2009). The accumulation and storage of secondary factors can also be a result of the inhibition of other lysosomal degradation pathways, such as the accumulation of gangliosides, which is a typical feature of the neurological LSDs Niemann–Pick type C (NPC) and mucopolysaccharidoses (MPS) (Walkley and Vanier, 2009). Moreover, increased substrate levels may drive lysosomal enzymes to form 'rare' metabolites. For example, in NPC, intralysosomal accumulation of cholesterol and glucosylceramide leads to the formation of glucosylated cholesterol (Marques et al., 2016), a metabolite that may play a role in pathology (Aerts et al., 2017; Franco et al., 2018). It is possible that a number of further metabolites arise that could contribute to disease progression.

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Box 2. Lysosomal storage disorders

Mutations in the genes encoding for lysosomal hydrolases, accessory proteins, membrane transporters or trafficking proteins may cause a LSD in man or animals. LSDs have an incidence of one in 7000 live births and are grouped depending on the substrate involved as lipid storage disorders (sphingolipidoses, gangliosidoses, leukodystrophies), mucopolysaccharidoses, glycoprotein storage disorders, mucolipidoses and cystinosis. LSDs are inherited in an autosomal recessive or, in some types, in an X-linked manner. Typical clinical symptoms include hepatosplenomegaly, pulmonary and cardiac problems, bone abnormalities, dementia, deafness, blindness and movement problems. Two-thirds of LSDs include neurological effects. Below, we briefly describe some of the most common LSDs.

Gaucher disease (GD). This is the most common LSD and caused by mutations in the *GBA* gene (locus 1q21), which encodes for the (lyso)glucosylceramide degrading enzyme β-glucocerebrosidase (EC 3.2.1.45). Type I GD is the chronic non-neurological and most common form of the disease, which is characterized by organomegaly, bone involvement and cytopenia. Types II and III have early onset and progressive brain involvement.

Fabry disease (FD). X-linked glycosphingolipidosis caused by deficiency of the lysosomal α-galactosidase A (EC 3.2.1.22), encoded by the *GLA* gene (Xq22.1), resulting in the intralysosomal accumulation of globotriaosylceramide (Gb3). FD is a multisystemic pathology characterized by specific renal, cardiovascular and neurological manifestations.

Krabbe disease (KD). Caused by mutations in the *GALC* gene (locus 14q31.3), encoding the enzyme galactocerebrosidase (E.C. 3.2.1.46). KD, also known as globoid-cell leukodystrophy, leads to the accumulation of undegraded galacto-lipids including psychosine; this causes the progressive demyelination of cells in the nervous system and ultimately cognitive and motor decline.

GM1 and GM2 gangliosidoses. These are caused by deficiencies in the enzymes acid β-galactosidase [EC 3.2.1.23 encoded by *GLB1* (3p22)] and β-hexosaminidase [EC 3.2.1.52, encoded by *HEXA* (15q23) and *HEXB* (5q13)], respectively, and characterized by the accumulation of gangliosides. GM1 and GM2 gangliosidoses present very severe neurological symptoms. GM2 gangliosidoses are also called Tay–Sachs or Sandohoff diseases, depending if the subunit A or B of hexosaminidase is deficient.

Niemann–Pick type C (NPC). Caused by deficiencies in the lysosomal cholesterol export machinery as a result from mutations in the *NPC1* (18q11.2) and *NPC2* (14q24.3) genes. NPC leads to intralysosomal cholesterol and sphingolipid accumulation resulting in severe neurological and visceral pathology.

Pompe disease. Also known as glycogen storage disease type II, this is caused by an accumulation of glycogen due to a deficiency in the lysosomal α-glucosidase (EC 3.2.1.3) encoded by the *GAA* gene (17q25.3). Patients are unable to degrade glycogen, which is stored in the lysosomes, particularly in muscle cells, thereby causing cardiac and respiratory failure.

Neuronal ceroid lipofuscinoses (NCLs). Group of 14 genetically heterogeneous diseases caused by mutations in genes encoding for lysosomal soluble and membrane proteins as well as one ER protein. NCLs have in common the accumulation of the autofluorescent pigment, ceroid lipofuscin, leading to neurodegeneration and blindness.

Mucopolysaccharidoses (MPSs). MPSs are divided in seven subtypes and are caused by deficiencies in the lysosomal enzymes necessary for the degradation of glycosaminoglycans (GAGs). Storage of GAGs affects the bone, skeletal tissue, cartilage and connective tissues, as well as the peripheral and central nervous system.

Mucolipidoses (MLs). These pathologies have the clinical and biochemical features of both MPSs and sphingolipidoses, being characterized by the accumulation of glycoproteins and glycolipids. ML type I (or sialidosis) is caused by a sialidase [EC 3.2.1.18, encoded by *NEU1* (6p21.33)] deficiency. MLs type II and III are caused by a deficiency in N-acetylglucosaminyl phosphotransferase [EC 2.7.8.17, encoded by *GNPTAB* (12q23.2)], responsible for phosphorylating mannose residues in newly synthetized glycoproteins. ML type IV is caused by mutations in the *MCOLN1* gene (locus 19p13.2-13.3), encoding a lysosomal membrane cation channel involved in Ca^{2+} signalling.

New players and mechanisms that might influence LSD progression

In the past few years, new 'players' have emerged in the field of lysosome biology that point to novel pathways and mechanisms that may strongly influence the ability of cells to cope with increasing lysosomal storage and so might help to shed new light on some of the unsolved mysteries surrounding LSDs.

Lysophagy

A dysfunctional lysosome is a typical hallmark of LSDs. However, lysosomes may still function to some degree in LSDs. It is likely that, at an early stage of lysosomal storage dysfunction, the affected organelle is cleared by lysophagy, an autophagy-related process that recognizes damaged lysosomes (Anding and Baehrecke, 2017). This process can be triggered experimentally by internalization of photochemicals, mineral crystals, bacteria or viral toxins, as well as uptake of β-amyloid or lysomotrophic compounds (Anding and Baehrecke, 2017). Internalization of these materials provokes the rupture of the lysosomal membrane, thereby activating lysophagy. How a ruptured lysosomal membrane is identified by the lysophagy machinery and whether and how quickly such a damaged lysosome causes the (selective) release of its luminal constituents are intriguing questions. The lysosome lumen contains high concentrations of hydrolytic enzymes that might be active upon release to the cytosol. Therefore, their cytosolic localization could potentially lead to uncontrolled degradation of cellular components (Boya and Kroemer, 2008). In LSDs, such as Niemann–Pick type A and GD, the lysosomal accumulation of undegraded lipid material – sphingomyelin and glucosylceramide, respectively – has been shown to cause the release of lysosomal cathepsin proteases into the cytosol (Gabandé-Rodríguez et al., 2014; Vitner et al., 2010), a sign of lysosome damage.

A process closely related to lysophagy is lysosomal membrane permeabilization (LMP) (recently reviewed in Wang et al., 2018). LMP has been linked to cell death processes where it may activate caspases through cathepsin-specific proteolytic activation of BH3 interacting-domain death agonist (Bid) and induction of mitochondrial membrane permeabilization followed by cytochrome *c* release (Repnik et al., 2014; Serrano-Puebla and Boya, 2016; Serrano-Puebla and Boya, 2018). Irrespective of the mode of induction of lysosome permeabilization, damaged lysosomes are quickly recognized by galectins and autophagic adaptors (Chauhan et al., 2016; Hung et al., 2013; Maejima et al., 2013), leading to the recruitment of ubiquitin ligases that ubiquitylate lysosomal membrane proteins, including lysosome-associated membrane protein 2 (LAMP2) (Yoshida et al., 2017). These tagged lysosomes are then incorporated into autolysosomes for degradation (Fig. 2). This quality control processes was uncovered 6 years ago (Hung et al., 2013; Maejima et al., 2013). Loss of lysosomal integrity and LMP have been shown to occur in NPC, MPS type 1, Mucolipidosis (ML) type 2 and neuronal ceroid lipofuscinosis (NCL) type 2 (see Box 2) (Amritraj et al., 2009; Kirkegaard et al., 2010; Kollmann et al., 2012; Micsenyi et al., 2013; Pereira et al., 2010). In this context, it is interesting to note that the heat shock protein chaperone 70 (HSP70)

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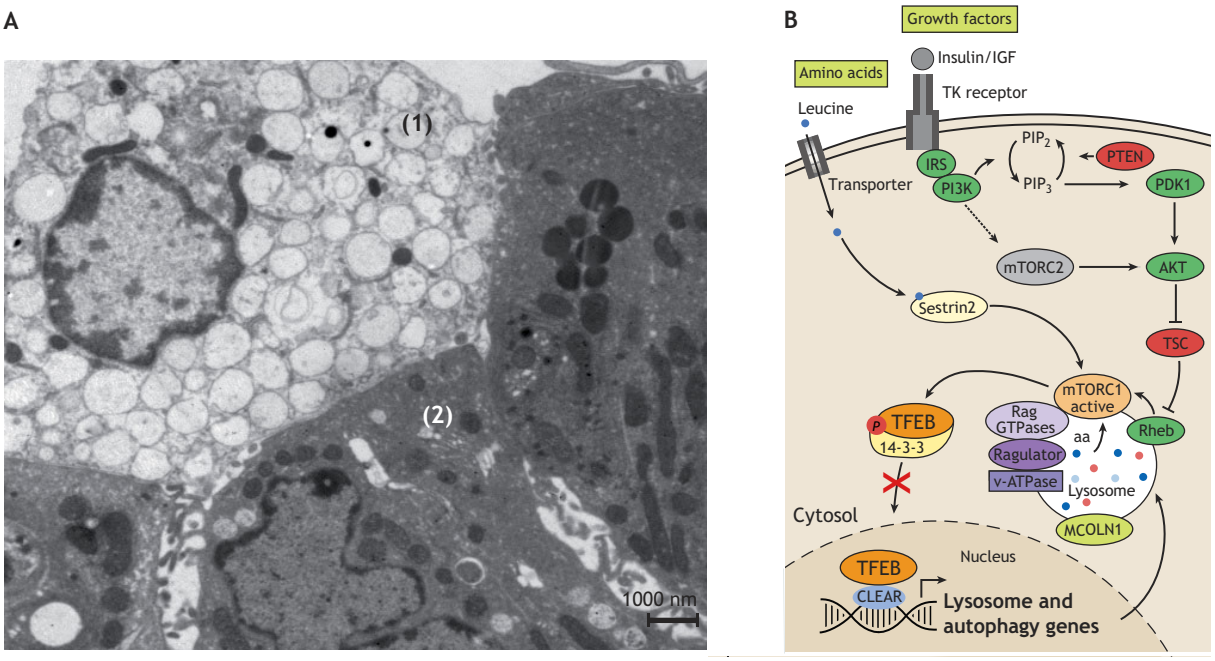

Fig. 1. Lysosomal storage and regulation of cellular metabolism by lysosomes. (A) Lysosomal storage in testicular macrophages of an α-mannosidase-deficient mouse (age 6 months) (1) as observed with electron microscopy. The lysosomes appear almost empty, because the storage material is water soluble; thus it is lost during the preparation for EM examination. The non-storing cells are androgen-synthesizing Leydig cells (2). Studies so far indicate that the storage burden in each particular cell type is, at least partially, dependent on the ability of the cell to induce lysosome biogenesis. Scale bar: 1000 nm. (B) Scheme showing the regulation of cellular metabolism by lysosomes. The translocation of TFEB to the nucleus leads to the transcription of lysosome and autophagy genes (CLEAR network; see Box 1). Phosphorylation of TFEB by mTORC1 results in its binding to 14-3-3 proteins and retention in the cytosol, thereby interrupting the transcription of the CLEAR network. The accumulation of amino acids (aa) in the lumen of lysosomes generates an activating signal that is transmitted to the Rag GTPases via the v-ATPase–Ragulator interaction. In this way, Rag GTPases recruit mTORC1 to the lysosomal surface. Under nutrient-rich conditions, the Ca^{2+} channel mucolipin 1 (MCOLN1) is inactive and mTORC1 remains active. Upon growth-factor stimulation, mTORC1 signalling is activated through the classical phosphoinositide 3-kinase (PI3K)–AKT pathway. Binding of insulin or insulin-like growth factor (IGF) to tyrosine kinase (TK) receptors at the cell surface leads to the phosphorylation of the insulin receptor substrate (IRS) proteins. Consequently, PI3K catalyses the phosphorylation of PIP_2 to phosphatidylinositol (3,4,5)-trisphosphate (PIP_3). The phosphatase and tensin homolog (PTEN) protein regulates PI3K signalling via the dephosphorylation of PIP_3. PIP_3 stimulates the recruitment and phosphorylation of the AKT proteins by 3′-phosphoinositide-dependent kinase 1 (PDK1; also known as PDPK1). mTORC2 also phosphorylates AKT proteins. Activated AKT promotes mTORC1 activity by inhibiting the activity of the tuberous sclerosis complex (TSC), thus activating Rheb, a potent mTORC1 activator. mTORC1 is also regulated by amino acid availability in a TSC-independent manner. The example of the leucine amino acid is depicted. Leucine enters the cytosol via amino acid transporters where it encounters the sensor sestrin 2, which then activates mTORC1.

family proteins apparently stabilize the lysosome membrane and prevents LMP-mediated cell death signalling (Ingemann and Kirkegaard, 2014). Induction of HSP70 function using small molecules, either through transcriptional activation or direct protein binding, is therefore regarded as a potentially therapeutic approach for LSDs (Brodsky and Chiosis, 2006).

ESCRT-mediated lysosome membrane repair

In an attempt to elucidate the early events following lysosomal membrane damage, Skowyra and co-workers recently described an unexpected role of the endosomal sorting complex required for transport (ESCRT) machinery in the repair of endosome/lysosome membranes (Skowyra et al., 2018). They observed an efficient and rapid recruitment of ESCRT proteins to the cytoplasmic side of the endosomes/lysosomes, as soon as small amounts of endolysosomal Ca^{2+} and proton release were observed, which likely occurs through small membrane lesions (Fig. 2). ESCRT-mediated repair, which occurred independently of lysophagy factors such as galectins, was able to restore the endolysosomal pH and the lysosomal hydrolase activity (Skowyra et al., 2018). In this context, it is interesting that in a *Caenorhabditis elegans* model of ML type IV (with deficiency of the TRPML1 channel), lysosome pathology and embryonic lethality of the *cup-5* (a TRPML1 orthologue) mutant could be rescued by reducing the expression of ESCRT proteins (Huynh et al., 2016). CUP-5 mediates a hypo-ubiquitylation of multidrug resistance-associated protein 4 (MRP-4), an ATB-binding cassette (ABC) transporter, possibly causing a pathologically increased MRP-4 transporter activity that leads to lysosomal defects and cell death in the worm. It will be interesting to see whether ESCRT-dependent membrane sealing (reviewed in Radulovic and Stenmark, 2018) is involved in mammalian LSDs, and whether lysophagy and ESCRT repair act in (regulated) concert during the development of lysosomal storage.

Lysosome mobility and subpopulations

Lysosomes move within a cell in a regulated manner (reviewed recently in Ba et al., 2018; Pu et al., 2016). Their motility leads to the formation of distinct lysosome populations that differ in intraluminal pH and degradative activities (Bright et al., 2016; Johnson et al., 2016). Lysosomes move in a bidirectional ‘stop-and-go’ manner controlled by microtubule-based motor proteins. Anterograde movement, towards the cell periphery, is governed by kinesin motors, while dynein motors mediate retrograde movement towards the perinuclear region (see reviews by Pu et al., 2016; Bonifacino and Neefjes, 2017; Cabukusta and Neefjes, 2018) (Fig. 2). In non-polarized cells, under steady-state conditions, the majority of endosomes/lysosomes are concentrated in the so-called ‘perinuclear cloud’ that surrounds the microtubule-organizing

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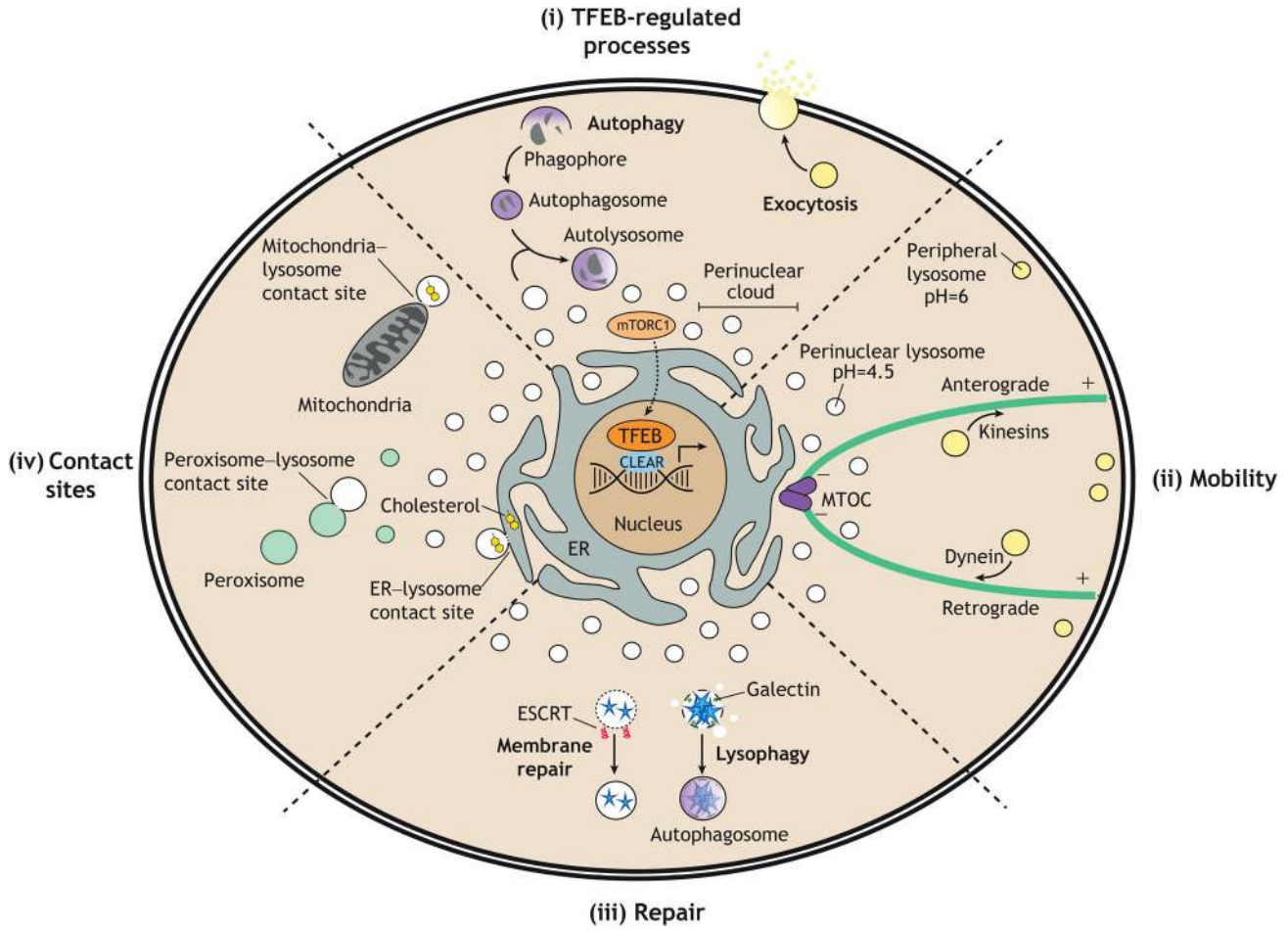

Fig. 2. Overview of the mechanisms regulating lysosome function: the master regulator TFEB and new players in the field. Scheme representing some of the main mechanisms regulating lysosome function. (i) Nearly a decade ago, TFEB was first described as the master regulator of lysosome biogenesis, autophagy and exocytosis (Sardiello et al., 2009). TFEB, in turn, is regulated by the activity of the mTORC1 kinase (see Fig. 1 for details). (ii) Under normal conditions, most lysosomes are located in the perinuclear cloud around the MTOC. These lysosomes have a lower pH than peripheral lysosomes. Movement of lysosomes from the perinuclear region to the periphery occurs along microtubules (green) – anterograde transport – is governed by kinesins and in the opposite direction – retrograde transport – by dynein. (iii) Damage to the lysosomal membrane caused by the accumulation of natural or synthetic material is repaired by the ESCRT machinery or, when the damage is too extensive, directs lysosomes for degradation via lysophagy. (iv) Lysosomes establish contact sites with other organelles, including peroxisomes, mitochondria and the ER. These contact sites are involved, among other processes, in the transport of cholesterol between organelles.

centre (MTOC) (Jongsma et al., 2016). These perinuclear lysosomes are highly acidic (pH 4.5–5.5), relatively immobile and represent the main sites in which substrates are metabolized (Bright et al., 2016; Johnson et al., 2016). In contrast, the less acidic (pH>5.5) peripheral lysosomes are more mobile and act as reservoirs for acid hydrolases (Bright et al., 2016) (Fig. 2). The relative abundance of these two lysosome pools will thus influence the degradative capacity of a cell. The intracellular positions of lysosomes also contribute to the regulation of mammalian target of rapamycin complex 1 (mTORC1) activity (Korolchuk et al., 2011). mTORC1 is a highly conserved serine/threonine kinase that responds to growth signals and nutrients, thereby regulating cell growth and division. mTORC1 regulates the balance between anabolic and catabolic processes at the lysosome, which acts as a major sensor and regulator (Fig. 1B) (Rabanal-Ruiz and Korolchuk, 2018; Settembre et al., 2013). Lysosomes tend to localize close to the plasma membrane when nutrients are available because mTORC1, as a key sensor of nutrient availability, is kept in proximity to signalling receptors at the cell surface (Betz and Hall, 2013). Nutrient removal leads to a more perinuclear localization as mTORC1 activity is suppressed; this allows for increased lysosomal fusion, autophagy and lysosomal activity (Fig. 1B, Box 1) (Korolchuk et al., 2011). The BLOC-1-related complex (BORC) is involved in this nutrient-dependent redistribution of lysosomes to the perinuclear region (Pu et al., 2017). Lyspersin, a BORC subunit, is specifically required to bind to LAMTOR, a subunit of the Ragulator complex (Filipek et al., 2017). This interaction depends on the availability of amino acids and also requires an association with the small GTPase Arl8 proteins and the kinesins KIF1B and KIF5B (Pu et al., 2017). Interestingly, as a transcription factor EB (TFEB)-regulated lysosomal membrane protein, TMEM55B (also known as PIP4P1) also controls the movement of lysosomes through an interaction with C-Jun-amino-terminal kinase-interacting protein 4 (JIP4; also known as SPAG9), which mediates a dynein-dependent transport of lysosomes (Willett et al., 2017).

The distribution of lysosomes is affected by various stimuli, and disturbances in this regulation have been associated with different pathologies. In LSDs, impaired hydrolysis and/or transport of molecules can directly affect the mobility and positioning of lysosomes (Lee et al., 2011; Pu et al., 2016). For instance, perinuclear clustering of lysosomes has been reported in different LSDs, such as NCL type 3 (Uusi-Rauva et al., 2012), NPC (Ko et al., 2001; Lebrand et al., 2002) and ML type IV (Li et al., 2016),

and is most likely the consequence of the cholesterol accumulation that is characteristic of many LSDs (Walkley and Vanier, 2009). Intralysosomal cholesterol accumulation constitutively activates the Ras-related protein Rab7 and Rab-interacting lysosomal protein (RILP)-dependent retrograde transport of lysosomes (Chen et al., 2008; Li et al., 2016; Rocha et al., 2009). This activation is mediated by the cholesterol sensor oxysterol-binding protein-related protein 1L (ORP1L), which, together with RILP, recruits the dynactin complex to the lysosome (Rocha et al., 2009).

Lysosome positioning is also essential for the maintenance of neuronal homeostasis, and it has a crucial role in cancer development and the immune response (see below). In neurons, lysosomes not only have to travel long distances owing to the extreme asymmetry of these cells and the length of axons and dendrites, but they must also cope with the task of degrading presynaptic proteins (reviewed in Ferguson, 2018). Accordingly, various psychiatric and neurological disorders are caused by variations or mutations in components of the lysosome-positioning machinery, including schizophrenia, amyotrophic lateral sclerosis, Charcot–Marie–Tooth disease and hereditary spastic paraplegia (Pu et al., 2016).

Lysosome-contact sites with other organelles

Movement of lysosomes also depends on contact with other organelles. Contact sites can influence motor recruitment and lysosome motility. For example, contact with the endoplasmic reticulum (ER) causes lysosomes to localize to the perinuclear area where fission and fusion between organelles take place (Bonifacino and Neefjes, 2017). Lysosome–ER contacts are morphologically and molecularly defined by the localized association of proteins and lipid transfer events (Cabukusta and Neefjes, 2018), and these are usually transient. Defects in lysosome–ER contacts have been linked to axonopathies and hereditary spastic paraplegia (Allison et al., 2017). For instance, the ESCRT protein IST1 and the ER-localized microtubule-severing enzyme spastin have been shown to interact at ER–endosome contact sites in supporting endosomal tubule fission (Allison et al., 2013). Spastin dysfunction or its absence causes defects in the mannose 6-phosphate receptor-dependent sorting of lysosomal hydrolases, leading to an increased number of very large lysosomes with abnormally dense membrane structures. ER–lysosome contacts are also involved in the uptake of cholesterol to the ER and they are typically formed by bridging proteins of the oxysterol-binding protein (OSBP) family at the lysosome side, and by members of the steroidogenic acute regulatory protein-related lipid-transfer (START) family of lipid transfer proteins at the ER (Ridgway and Zhao, 2018). The transfer of cholesterol can also occur from the ER through vesicle-associated membrane protein-associated proteins (VAPA and VAPB) to STARD3 on endosomes/lysosomes when endolysosomal cholesterol levels are low, thereby possibly facilitating intraluminal vesicle formation by providing building blocks for membrane formation (Wilhelm et al., 2017). In LSDs, these transport processes from and to the ER are likely to be altered, thereby contributing to an alteration in intracellular cholesterol (and lipid) homeostasis. NPC is a prototypical example of such a LSD with an impaired cholesterol transport from endosomes to the ER (Vance and Karten, 2014).

Similarly, cholesterol can also be transferred from lysosomes to peroxisomes, suggesting that peroxisomal functions directly contribute to lysosomal lipid homeostasis (Chu et al., 2015). Contact sites between lysosomes and peroxisomes require the presence of NPC1, synaptotagmin VII and phosphatidylinositol 4,5-bisphosphate (PIP_2). When peroxisomes are dysfunctional, as observed in peroxisomal disorders (Waterham et al., 2016), cholesterol accumulates in late endosomes (Chu et al., 2015). Furthermore, peroxisome dysfunction has been shown to cause the secondary storage of lysosomal gangliosides, resulting in impaired ganglioside metabolism in myelin (Kleinecke et al., 2017). How much peroxisome function is affected in LSDs is not well understood. It has been reported, however, that peroxisomal β-oxidation and catalase activity are decreased in NPC1-deficient mouse brain and liver (Schedin et al., 1997), suggesting that peroxisomal disturbances are early manifestations and an important factor in the development of NPC disease.

There are also contact sites between mitochondria and lysosomes that affect their function and dynamics. Such contact sites are observed by electron microscopy and depend on GTP-bound lysosomal Rab7 proteins (which has Rab7a and Rab7b forms) (Wong et al., 2018). However, it remains to be seen whether these contact sites, which have been postulated to be involved in metabolic exchanges (Wong et al., 2018), are altered in LSDs. Mitochondria and lysosomes may also be linked through the ER (Annunziata et al., 2018). If this is indeed the case, different degrees of communication between the three organelles could possibly explain the extent of lysosomal storage. For example, in NPC, an increase in lysosome–mitochondria contact sites owing to the upregulation of STARD3 in lysosomes leads to secondary accumulation of lipids, including cholesterol, in mitochondria (Balboa et al., 2017). This causes defects in antioxidant quality control and mitochondrial dysfunction (Torres et al., 2017). In the case of GM1 gangliosidosis, accumulation of GM1 ganglioside alters the composition of mitochondria-associated ER membranes (Sano et al., 2009). It also overloads mitochondria with ER-derived Ca^{2+}, resulting in a mitochondrial membrane permeabilization that leads to an activated apoptotic pathway (Annunziata et al., 2018; Sano et al., 2009). In conclusion, contact sites formed by lysosomes with different organelles may also affect the functions of these compartments. It is therefore not surprising that, in LSDs, dysfunction of mitochondria, peroxisomes and the ER can be observed.

Beyond storage – other lysosome functions affected in LSDs

One of the main difficulties of studying LSDs is distinguishing the direct consequences of the protein deficiency from secondary effects caused by the dysfunction of the lysosome–autophagy machinery. In this section, we aim to summarize the various physiological functions that may be affected by a dysfunctional lysosomal compartment as a result of LSDs.

Immune response

Many LSDs are associated with immune abnormalities including autoimmune phenomena (reviewed in Rigante et al., 2017; Simonaro, 2016). The autophagy–lysosome system is crucial for infection and immunity, in particular for processing of the major histocompatibility complex class II (MHC-II) and its presentation to $CD4^+$ T cells (Münz, 2012). In addition, intact lysosomes are required for the digestion of phagocytosed bacteria and the subsequent release of antigenic peptides that bind to MHC-II (Pu et al., 2016). Lysosomes in mature dendritic cells are also important for the transport of peptide-loaded MHC-II molecules to the plasma membrane (Chow et al., 2002; Michelet et al., 2015; Vyas et al., 2007) and for the killing of virally infected or tumorous cells by cytotoxic T lymphocytes and natural killer cells (Pu et al., 2016). Hence, defects in the lysosome machinery can increase the susceptibility to certain infections, as demonstrated for mycobacteria infections (Berg et al., 2016; Kong et al., 2018).

Similarly, GD patients are more susceptible to bacterial infections because their phagocytes have dysfunctional lysosomes and, consequently, an impaired capacity to kill the ingested bacteria (Maródi et al., 1995), and NPC mice accumulate lipid-filled dysfunctional macrophages in the lungs (Deutsch et al., 2016). These findings highlight the threat lysosomal storage dysfunction represents to the critical scavenging function of macrophages.

Other roles of lysosomes in immunity include the control of inflammasome-mediated release of cytokines and the regulation of sphingolipid metabolism (Simonaro, 2016). In GD, for example, accumulation of the glycosphingolipid glucosylceramide results in increased expression of CD1d and MHC-II in monocytes (Balreira et al., 2005) and triggers the activation of the C5a complement pathway, which aggravates the pathological cascade in GD by stimulating the production of the already accumulated glycosphingolipid substrate (Pandey et al., 2017, 2018). Similar immunological imbalances occur in other LSDs (Gadola et al., 2006) and they may contribute to the observed clinical heterogeneity of these diseases.

Exocytosis

Lysosomes can fuse with the plasma membrane and release their contents into the extracellular space, for instance during plasma membrane repair after wounding (Andrews and Corrotte, 2018). This pathway appears to be an appealing option for the cell to dispose of lysosomal waste that accumulates in LSDs. Lysosome exocytosis occurs in a stepwise fashion, beginning with a Ca^{2+}-independent recruitment of lysosomes to the cytosolic leaflet of the plasma membrane (Andrews, 2000). A subsequent local Ca^{2+} elevation – most likely due to activation of the lysosomal Ca^{2+} channel mucolipin type 1 (MCOLN1) – triggers fusion of the lysosome with the plasma membrane followed by release of the lysosomal luminal constituents into the extracellular space (Andrews, 2000; Jaiswal et al., 2002; Tucker et al., 2004). The discovery that lysosome exocytosis is in part controlled by TFEB-mediated lysosome biogenesis, which leads to an increased fusion-competent pool of lysosomes close to the plasma membrane, has made this pathway an attractive approach to treat LSDs (Medina et al., 2011). TFEB belongs to the MiTF/TFE family of transcription factors, described as master regulators of lysosomal biogenesis and autophagy (Sardiello et al., 2009). Indeed, targeting TFEB was found to be effective in Pompe disease, which comprises an acid α-glucosidase deficiency. Here, TFEB overexpression in muscle cells (Spampanato et al., 2013) and in a murine model of Pompe disease (Gatto et al., 2017; Spampanato et al., 2013) reduced the glycogen load, possibly due to exocytosis of storage lysosomes and increased the autophagic flux. A more-detailed analysis revealed that, in Pompe disease, autolysosomes can also be exocytosed after TFEB overexpression, thereby contributing to the removal of the glycogen burden and autophagic build-up (Feeney et al., 2013). However, it is currently unknown whether increased TFEB expression could result in unwanted side effects, for instance by dysregulating cell proliferation control. TFEB has also been implicated in promoting tumorigenesis (Haq and Fisher, 2011; Kauffman et al., 2014), including in melanoma, renal cell carcinoma, alveolar soft part sarcoma and pancreatic ductal adenocarcinoma (Argani et al., 2001; Perera and Bardeesy, 2015; Ramphal et al., 2006). Indeed, when TFEB is overexpressed in mouse kidney, the animals develop kidney cancer, most likely due to a hyperactivated WNT pathway (Calcagnì et al., 2016). TFEB was also recently implicated in the control of myelination in the central nervous system (CNS) by stimulation of a programmed cell death pathway and elimination of premyelinating oligodendrocytes (Sun et al., 2018). It will also be important to investigate whether a release of lysosomal waste into the extracellular space is well tolerated and/or gives rise to inflammation or specific tissue dysfunctions.

Cholesterol homeostasis

An accumulation of cholesterol in lysosomes is an early hallmark of many LSDs. Impairment of the lysosomal cholesterol export pathway, which is mediated by NPC1 and NPC2 proteins, but can also be induced by subtle alterations in lysosome trafficking, can lead to a build-up of cholesterol in the organelle (Glaros et al., 2005; Luo et al., 2017; Puri et al., 1999). Cholesterol usually enters lysosomes through the low density lipoprotein (LDL) receptor by receptor-mediated endocytosis (Goldstein and Brown, 2015), and is transferred to other intracellular destinations through contact sites with ER, mitochondria or peroxisomes (Thelen and Zoncu, 2017). In addition to NPC1 and NPC2, LAMP proteins also bind to cholesterol handed over by NPC2, and so likely act as a reservoir for cholesterol to be exported by NPC1 (Li and Pfeffer, 2016). Lysosomal cholesterol also binds to the SLC38A9 amino acid transporter and activates mTORC1 in an amino-acid-independent manner (Castellano et al., 2017). In contrast NPC1, which also interacts with SLC38A9, removes cholesterol from the lysosomal lumen and inactivates mTORC1 (Castellano et al., 2017). In this context, studies in yeast are of interest. For instance, sterol transport proteins (Ltc/Lam) were identified in membrane contact sites at the vacuole and plasma membrane, and found to regulate TORC1 signalling (Murley et al., 2017). Overall, these discoveries directly link sterol metabolism and cell growth control (Castellano et al., 2017). Despite these insights, considerable research efforts are still required to understand the full extent of the regulation and the factors involved in cholesterol transport from lysosomes.

Nutrient sensing by lysosomes

One of the most intriguing features of lysosomal storage is that it differentially affects crucial cellular pathways that are associated with the control of cell death, differentiation and proliferation (Ballabio and Gieselmann, 2009). Storage substrates can directly modulate the function and localization of cellular receptors, as shown for MPS, Hurler syndrome (the most severe form of MPS type I) and NPC disease. For example, they can activate Toll-like receptors, impair insulin signalling, and modulate FGF-2, BMP-4 and WNT signalling (Fiorenza et al., 2018). Furthermore, the activity of AMP-activated protein kinase (AMPK), which can be localized to the cytosolic side of the lysosomal membrane and is regulated by the v-ATPase complex upon glucose starvation, and the mTOR complexes are linked to the hydrolytic function of lysosomes, and their signalling is thus often disturbed in LSDs (Fig. 1B) (Carroll and Dunlop, 2017). For example, the lysosomal storage defects in Pompe and NPC disease cause a reduction in the activity of mTOR (Lim et al., 2017; Xu et al., 2010). mTOR responds to the availability of amino acids, which recruits mTORC1 to the lysosomal surface, its site of activation (Bar-Peled and Sabatini, 2014). In this pathway, leucine is bound to its cytosolic sensor sestrin 2, which activates mTORC1 (Wolfson et al., 2016). Consequently, restoration of normal mTORC1 activity through leucine feeding or short hairpin RNA (shRNA)-AAV-mediated knockdown of tuberous sclerosis complex (TSC), an inhibitor of mTORC1, leads to an improvement of these pathologies (Lim et al., 2018; Shemesh et al., 2014; Yanagisawa et al., 2017). TSC knockdown activates mTORC1 and reduces autophagy, but also

upregulates phospholipase A2 (PLA2). Both processes possibly contribute to the therapeutic benefit (Lim et al., 2018). However, even though mTORC1 inactivation has been suggested to be a biochemical hallmark of LSDs, such as Pompe and NPC disease (Lim et al., 2017; Xu et al., 2010), there are contradictory reports showing that mTORC1 activation actually causes the skeletal disease phenotype observed in MPS (Bartolomeo et al., 2017). This indicates that dysregulation of this central cellular pathway may affect the cellular pathology in LSDs in a tissue-dependent manner.

How far can therapies go?

Some excellent recent reviews cover the current therapeutic approaches to treat LSDs (Beck, 2018; Ferreira and Gahl, 2017; Platt, 2018; Platt et al., 2018). Therefore, below, we will only briefly introduce the different types of therapies and discuss their potential use.

Currently explored therapeutic avenues

Bone marrow transplantation (BMT) was the most used approach before alternative treatment options were available. The rationale is that transplanted healthy donor cells will contribute to the tissue macrophage populations and become permanent sources of enzyme (Biffi, 2017). This approach was particularly aimed at treating patients with severe CNS effects (Biffi, 2017). However, there are some risks associated to BMT and the therapeutic benefits are not always clear, with the exception of Hurler patients, who benefit considerably more from the treatment compared to patients with other LSDs (Aldenhoven et al., 2015).

At the moment, enzyme replacement therapy (ERT) remains the most established type of therapy for several different LSDs, namely Gaucher, Fabry, Pompe and Wolman disease, α-mannosidosis, NCL type 2, and MPS type I, II, IV, VI and VII (Platt et al., 2018). ERT has proved rather effective in the treatment of GD type I (Gary et al., 2018) and Wolman disease (Aguisanda et al., 2017). However, the beneficial effects are only partial in other LSDs owing to several drawbacks, including the formation of neutralizing antibodies. Unfortunately, defects in lysosome membrane proteins cannot be overcome by ERT. Furthermore, the blood–brain barrier (BBB) is a major hurdle in bringing the therapeutic enzyme to the CNS, which is affected in two-thirds of all LSDs. However, the recent approval for intraventricular injection with Cerliponase Alfa for the treatment of CNL2 opens up the possibility of expanding ERT to other LSDs with neurological involvement (Schulz et al., 2018).

An alternative approach of substrate reduction therapy (SRT) was initially devised and approved by the European Medicines Agency (EMA) with the aim of reducing the production of the accumulated substrate by inhibiting its synthesis. SRT drugs have the advantage that they can be delivered orally and are designed to cross the BBB. Clinical evaluation of SRT with brain-permeable drugs, such as the glucosylceramide synthase inhibitors Ibiglustat and Miglustat for neuronopathic glycosphingolipidoses are still ongoing (ClinicalTrials.gov identifier: NCT02843035 and NCT02520934). In the case of NPC, recent studies have shown that some of the benefits observed with the EMA-approved drug Miglustat may not be directly ascribed to SRT, but rather to the off-target inhibition of GBA2, possibly through the reduction of toxic sphingosine levels (Marques et al., 2015; Mistry et al., 2014; Nietupski et al., 2012).

Gene therapy, unlike the other approaches above, has the potential to cure LSDs by correcting the primary genetic defect. Encouraging results have been obtained in pre-clinical trials with animal models (Rastall and Amalfitano, 2015) and in clinical trials with Metachromatic Leukodystrophy (MLD) patients that were treated with hematopoietic stem cell transplantation (HSCT) (Biffi et al., 2013; Groeschel et al., 2016). Most recently the unprecedented correction of a lysosomal transmembrane enzyme deficiency via a novel AAV-TT serotype has also been reported in MPS IIIC mice (Tordo et al., 2018). Disappointingly, only limited effects have been observed in MPS and MLD patients that underwent gene therapy with adeno-associated viral vectors delivered to the brain (Beck, 2018). For example, this therapy was unable to halt brain atrophy in MPS IIIA patients (Tardieu et al., 2014). The ongoing clinical trials might elucidate the long-term safety and efficacy of these approaches. It is, however, clear that a 'one-gene-fits-all' therapy cannot be applied for the different LSDs.

Another therapeutic approach is the use of small-molecule pharmacological chaperones (PCs) to increase the stability of proteins that are misfolded due to missense mutations, thereby partially rescuing their enzymatic activity. PCs are easy to administer and have the potential to reach the CNS. Nonetheless pre-clinical and clinical trials have shown major limitations, which are related to the fact that only some of the mutations are responsive to PC treatment and owing to the risk associated with most of these compounds acting as active-site competitive inhibitors of the target enzyme (Mohamed et al., 2017; Parenti et al., 2015b).

TFEB gained particular attention recently as it induces the expression of many lysosomal genes and so can contribute to the clearance of pathogenic proteins. The disaccharide trehalose, a natural sugar and a known inducer of TFEB, has proven therapeutic effects in several pre-clinical LSD models (Lotfi et al., 2018; Palmieri et al., 2017; Seranova et al., 2017).

Can tackling lysosomal dysfunction be an approach to treat other more common disorders?

The intralysosomal accumulation of lipids and proteins occurs not only in LSDs, but also in many common human pathologies, such as cancer, neurodegeneration, and even ageing. The study of LSDs can therefore contribute to a better understanding of these conditions, and therapeutic approaches targeting rare LSDs might be adapted to these other pathologies as discussed below.

Cardiovascular diseases

The autophagy-lysosome system plays a crucial role in the development of atherosclerotic plaques (Razani et al., 2012). In particular, macrophages in atherosclerotic plaques heavily rely on this system to clear deposited lipids and apoptotic cells. In early atherosclerotic plaques, macrophages take up oxidized low-density lipoproteins (oxLDL) in a non-regulated manner through their scavenger receptors. Over time, oxLDL uptake blocks the normal handling of cholesterol in the endolysosomal system, causing lysosomal engorgement owing to further accumulation of cholesteryl ester and the formation of cholesterol crystals (Sheedy et al., 2013). This in turn leads to increased lysosomal pH and an impairment of the activities of various lysosomal lipases and proteases, through yet unclear mechanisms (Emanuel et al., 2014). The progressive lysosomal dysfunction ultimately causes a form of lipidosis that is very similar to the one observed in NPC and other LSDs. Accordingly, disruption of autophagy in macrophages can accelerate plaque formation by exacerbating the accumulation of cholesterol crystals (Sergin et al., 2015). In the final stages of plaque development, accumulation of these crystals could cause lysosomal rupture and elicit a pro-inflammatory response (IL-1β cytokine secretion), thereby aggravating the development of atherosclerosis (Razani et al., 2012) (Fig. 3). These parallels between atherosclerosis and LSDs have led to suggestions of boosting

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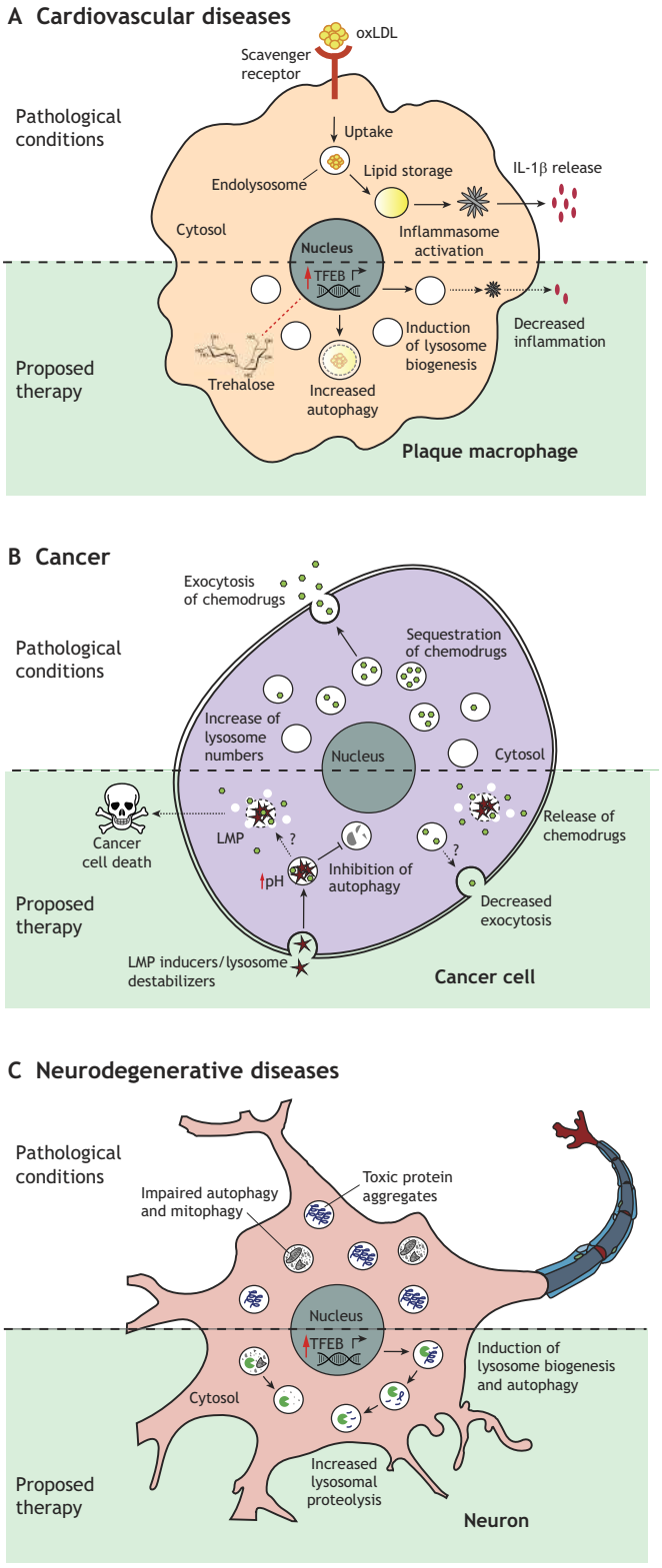

Fig. 3. Can treatment of LSDs pave the way for other diseases? (A) In cardiovascular diseases (CVDs), plaque macrophages accumulate lipid in lysosomes (via oxLDL uptake), impairing lysosome function and triggering inflammasome activation (secretion of pro-inflammatory IL-1β). Treatment of macrophages with trehalose, an activator of TFEB, stimulates TFEB-mediated transcription of lysosome and autophagy genes. In this way, storage is cleared through an increase in autophagy and inflammation is reduced. (B) Cancer cells have increased number of lysosomes which sequester chemodrugs and release them via exocytosis. Lysosome destabilizers and LMP inducers such as hydroxychloroquine (HCQ) cause an elevation of lysosomal pH and inhibit autophagy, and may represent a clinical avenue to fight cancer. These drugs are also suggested to cause the release of chemodrugs and decrease their exocytosis from cancer cells, as well as triggering LMP-mediated cancer cell death. (C) Common hallmarks of neurodegenerative diseases are the accumulation of toxic protein aggregates (e.g. α-synuclein) and impaired autophagy/mitophagy in neurons. Increasing lysosome biogenesis in these cells through TFEB induction may represent a therapeutic approach that would act by boosting autophagy and proteolysis of these protein aggregates and/or damaged organelles.

lysosomal biogenesis in macrophages by upregulation of TFEB as a therapeutic avenue for atherosclerosis (Evans et al., 2018; Sergin et al., 2017) (Fig. 3). Trehalose was indeed shown to have atheroprotective effects seemingly through the induction of autophagic clearance of polyubiquitylated proteins and decrease of IL-1β secretion in plaque macrophages (Sergin et al., 2017).

Diabetes

The ganglioside GM3 is a primary or secondary storage product in many LSDs, and, owing to its role in the modulation of insulin sensitivity and energy homeostasis (Aerts et al., 2011), its storage can reduce insulin signalling, as was demonstrated in GD (Langeveld et al., 2008). In cells and tissues of patients and animal models of diabetes, alterations in lysosome function, such as intralysosomal phospholipid accumulation and autophagy insufficiency, contribute to the etiology of the disease (Sims-Robinson et al., 2016; Yamamoto et al., 2017; Yasuda-Yamahara et al., 2015). Specifically, β-cells under starvation degrade secretory insulin granules in a protein kinase D-dependent manner after their recruitment to lysosomes (Goginashvili et al., 2015). Proinsulin- and insulin-containing granules are degraded by lysosomal hydrolases, most likely preventing unwanted insulin release. This triggers the recruitment and activation of mTOR followed by suppression of macroautophagy (Goginashvili et al., 2015). It is yet to be proven whether such an autophagy-independent mechanism of insulin granule degradation by lysosomes is also relevant in patients suffering from diabetes. Therefore, lysosome and autophagy functions are also important in insulin-producing cells, and targeting their degradative role in pancreatic β-cells could be an attractive therapeutic approach for diabetes.

Cancer

The autophagy-lysosome machinery is essential for cancer cell proliferation, metabolism and adaptation to environment stress. In many types of cancer, lysosome biogenesis is increased, which allows the cancer cells to maintain homeostasis during proliferation and to survive under stress conditions (Dielschneider et al., 2017; Kroemer and Jäättelä, 2005). Additionally, lysosomes play an important role in the resistance to chemotherapeutic drugs by either sequestering these compounds or facilitating their exocytosis (Dielschneider et al., 2017; Kroemer and Jäättelä, 2005) (Fig. 3). During oncogenic transformation, lysosomes often undergo transformations with regard to their number, morphology, luminal pH, hydrolase content and intracellular distribution (Kroemer and Jäättelä, 2005; Pu et al., 2016). In addition, alterations in lysosomal sphingolipid metabolism are another trait of many cancers (Dielschneider et al., 2017). This reliance on the lysosome-autophagy system makes cancer cells particularly susceptible to LMP and, consequently, lysosome-associated cell death pathways. Among the agents currently being investigated for their ability to target the lysosomal machinery of cancer cells are LMP-inducing lysosomotropic compounds (e.g. hydroxychloroquine) (Fig. 3),

v-ATPase inhibitors, acid-sphingomyelinase modulators, cathepsin protease inhibitors and HSP70 inhibitors (Piao and Amaravadi, 2016). However, most of these compounds have only been tested in pre-clinical trials (Piao and Amaravadi, 2016), with the exception of hydroxychloroquine (HCQ), which is currently being tested in clinical trials and proposed to work through the inhibition of autophagy (Rebecca and Amaravadi, 2016). HCQ is suggested to function by inhibiting the lysosomal v-ATPase; this increases lysosome pH and inhibits autophagy (Chude and Amaravadi, 2017).

Conversely, additional insights into cancer biology might also be gained from studying LSDs. GD type I is a prime example of how a lysosome deficiency can contribute to the development of malignancies. GD patients show increased susceptibility to monoclonal and polyclonal gammopathies due to the production of antibodies directed against accumulating lysosphingolipids (Nair et al., 2016; Pastores and Hughes, 2017; Pavlova et al., 2013). Because increased levels of lysosphingolipids are not exclusive to GD, it is possible that patients with other LSDs may also be more prone to develop malignancies due to the production of antibodies against these lipids (Aerts et al., 2017).

Neurodegenerative diseases

There is no doubt that an impairment of the lysosomal system is involved in many neurodegenerative processes. For example, malfunction of lysosomal proteins, such as CLN3, cathepsins and progranulin, leads to severe childhood neurodegeneration in NCL patients (Paushter et al., 2018; Stoka et al., 2016). In LSDs, the nervous system is particularly sensitive to the lysosomal dysfunction (Onyenwoke and Brenman, 2015). Owing to their postmitotic character, neurons encounter greater difficulties in eliminating unwanted and damaged organelles than dividing cells. Furthermore, alterations in the dendritic and axonal sorting of lysosomes are closely linked to neurodegenerative processes (Yang et al., 2013). For example, the impaired degradative capacity of lysosomes, reduced autophagy flow, altered lipid composition and different subcellular localization of lysosomes in neurons are all examples of lysosomal dysfunctions in common neurodegenerative diseases, such as Alzheimer's disease (Nixon, 2017), Parkinson's disease (Blanz and Saftig, 2016) and frontotemporal disorders (Götzl et al., 2016) (Fig. 3). It should be noted that the inhibition of autophagy owing to mutations in genes encoding for autophagy-relevant proteins (such as EPG5) is associated with neurological phenotypes as observed in patients suffering from Vici syndrome where EPG5 is missing and autophagosome–lysosome fusion is impaired (Ebrahimi-Fakhari et al., 2016).

Carriers or patients suffering from GD type I are more prone to Parkinson's disease (Goker-Alpan et al., 2008). Conversely, many Parkinson's disease patients exhibit a decreased activity of β-glucocerebrosidase, an accumulation of glucosylceramide and of related lipids, all of which may stabilize the neurotoxic α-synuclein (Sidransky and Lopez, 2012). This, in turn, further decreases β-glucocerebrosidase activity and transport of the enzyme from the ER to lysosomes, thereby contributing to neuronal cell death and Parkinson's disease progression (Blanz and Saftig, 2016).

From a therapeutic point of view, strategies to increase the activity of lysosomal β-glucocerebrosidase, for instance by improving the ER–lysosome transport through the LIMP-2 (also known as SCARB2) pathway, could be promising (Zunke et al., 2016). Furthermore, in LSDs, impaired lysosomal protein degradation can result in the presynaptic sequestration of α-synuclein, which contributes to the neurodegeneration observed in these diseases (Sambri et al., 2017).

Finally, increasing the expression of progranulin (PGRN) in frontotemporal dementia turned out to be a promising therapeutic option in mouse models (Arrant et al., 2017). In one study, trehalose was found to increase the endogenous levels of PGRN and exhibited neuroprotective effects in cell-based assays and in PGRN-haploinsufficient mice (Holler et al., 2016) (Fig. 3). However, a major problem in all types of therapies aimed at modulating lysosomal function in neurodegenerative diseases as well as in LSDs with neuronal involvement remains the transport of a drug and/or the storage material across the BBB (Begley et al., 2008).

Conclusions and perspectives

Despite the progress made in understanding the lysosomal compartment and the different diseases caused by mutations or deficiencies in lysosomal proteins, we still cannot fully explain the individual pathologies. Since lysosome function is tightly linked to autophagy and phagocytosis, there is also a need to better understand the abnormalities in these pathways in LSD cells. Furthermore, the inappropriate storage caused by deficiencies of acid hydrolases or specific transporters is only one aspect of disease pathology, and the exact molecular mechanisms of LSDs can only be fully appreciated if we consider all (altered) cellular functions affected. Minor alterations in the activities of the lysosomal compartment may not only account for some of the alterations seen in common human diseases, but also be relevant for physiological processes, such as ageing, immune function and the regulation of cell death and proliferation. In terms of available and future therapeutic approaches, we will need to appreciate that many interventions may only be partially effective, and combination therapies and suitable therapeutic windows likely will have to be determined to circumvent any unwanted side effects when targeting lysosomal diseases.

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Competing interests

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