Lysosomal Storage Diseases—Regulating Neurodegeneration

Libertas Academica
FREEDOM TO RESEARCH

Supplementary Issue: Molecular and Cellular Mechanisms of Neurodegeneration

Rob U. Onyenwoke[1] and Jay E. Brenman[2,3]

[1]Department of Pharmaceutical Science, Biomanufacturing Research Institute and Technology Enterprise (BRITE), North Carolina Central University, Durham, NC, USA. [2]Department of Cell Biology and Physiology, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. [3]Neuroscience Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.

ABSTRACT: Autophagy is a complex pathway regulated by numerous signaling events that recycles macromolecules and can be perturbed in lysosomal storage diseases (LSDs). The concept of LSDs, which are characterized by aberrant, excessive storage of cellular material in lysosomes, developed following the discovery of an enzyme deficiency as the cause of Pompe disease in 1963. Great strides have since been made in better understanding the biology of LSDs. Defective lysosomal storage typically occurs in many cell types, but the nervous system, including the central nervous system and peripheral nervous system, is particularly vulnerable to LSDs, being affected in two-thirds of LSDs. This review provides a summary of some of the better characterized LSDs and the pathways affected in these disorders.

KEYWORDS: autophagy, lysosomal storage disease, mucolipidosis, mucopolysaccharidosis, sphingolipidosis

SUPPLEMENT: Molecular and Cellular Mechanisms of Neurodegeneration

CITATION: Onyenwoke and Brenman. Lysosomal Storage Diseases—Regulating Neurodegeneration. *Journal of Experimental Neuroscience* 2015:9(S2) 81–91 doi:10.4137/JEN.S25475.

TYPE: Review

RECEIVED: September 4, 2015. **RESUBMITTED:** November 11, 2015. **ACCEPTED FOR PUBLICATION:** November 16, 2015.

ACADEMIC EDITOR: Lora Watts, Editor in Chief

PEER REVIEW: Four peer reviewers contributed to the peer review report. Reviewers' reports totaled 998 words, excluding any confidential comments to the academic editor.

FUNDING: This study was supported by the National Institute of Health (grant number NS080108 to JEB). The authors confirm that the funder had no influence over the study design, content of the article, or selection of this journal.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

COPYRIGHT: © the authors, publisher and licensee Libertas Academica Limited. This is an open-access article distributed under the terms of the Creative Commons CC-BY-NC 3.0 License.

CORRESPONDENCE: ronyenwo@nccu.edu

Paper subject to independent expert single-blind peer review. All editorial decisions made by independent academic editor. Upon submission manuscript was subject to anti-plagiarism scanning. Prior to publication all authors have given signed confirmation of agreement to article publication and compliance with all applicable ethical and legal requirements, including the accuracy of author and contributor information, disclosure of competing interests and funding sources, compliance with ethical requirements relating to human and animal study participants, and compliance with any copyright requirements of third parties. This journal is a member of the Committee on Publication Ethics (COPE).

Published by Libertas Academica. Learn more about this journal.

Introduction

Cellular homeostasis is essentially a balancing act between anabolic and catabolic processes. Eukaryotic cells primarily use two distinct mechanisms for large-scale degradation of macromolecules and intracellular organelles: proteasomal degradation and autophagy. However, only autophagy, which can be further subdivided into macroautophagy, microautophagy, and chaperone-mediated autophagy, has the capacity to degrade entire organelles.[1] Here, we focus on macroautophagy, hereafter termed simply as autophagy, and its important physiological role in human health and in neurodegeneration, including lysosomal storage diseases (LSDs). We also discuss the possibility of autophagic regulation by various signaling pathways (eg, extracellular signal-regulated kinase [ERK], microtubule-associated protein kinase [MAPK], Akt, target of rapamycin [TOR], and AMP-activated protein kinase [AMPK]) and other mechanisms (eg, Ca^{2+} levels). We begin by outlining the complex steps required to complete autophagy, then address the neurodegeneration that has been described in multiple LSDs, and finally examine several LSDs individually and in more detail.

Autophagy is a pathway required for the degradation of cellular macromolecules.[2,3] During autophagy, double membrane-bound vesicles (autophagosomes) isolate cytosolic material destined for degradation. Subsequently, autophagosomes fuse with late endosomes to form amphisomes.[4,5] Amphisomes then coalesce with lysosomes, leading to the formation of autolysosomes (Fig. 1). Because lysosomes contain degradatory enzymes, the contents of amphisomes are broken down following autolysosome formation, with the produced metabolites partly feeding into pathways to satisfy the cell's energy demands.[4,5] Downregulation of autophagy leads to accumulation of misfolded proteins and is speculated to be involved in chronic or late-onset diseases, such as neurodegenerative diseases, including Alzheimer's disease (AD; characterized by two abnormal structures: amyloid plaques consisting of largely insoluble toxic β-amyloid peptides and intraneuronal fibrillary tangles/aggregates composed of highly phosphorylated forms of the microtubule-associated protein tau), Parkinson's disease (PD; well characterized by the accumulation of α-synuclein and ubiquitin into intracytoplasmic inclusions known as Lewy bodies), and Huntington's disease (HD; toxic oligomers and aggregates of mutant huntingtin protein that are not properly cleared accumulate).[6–8] These aforementioned diseases have been extensively covered in the literature, and several excellent reviews focusing on them as neurodegenerative diseases caused by aberrant autophagy exist.[8,9] Therefore, we focus on rarer diseases involving aberrant autophagy, the LSDs.

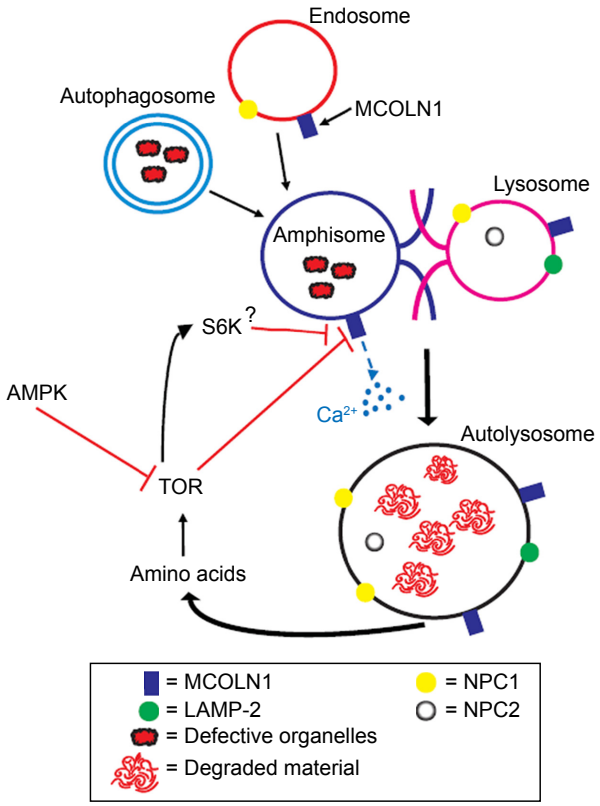

Figure 1. General organization and function of some integral membrane and soluble proteins important for lysosomal function, vesicle fusion, pH regulation, and calcium homeostasis (eg, MCOLN1); cholesterol homeostasis (eg, NPC1 and NPC2); and lysosomal function, vesicle fusion, and cholesterol homeostasis (eg, LAMP2). For MCOLN1, the model also illustrates how mTOR, AMPK, and MCOLN1 possibly interact. When active, AMPK inhibits mTOR (or its downstream effector molecule S6 kinase 1) activity, which in turn modulates MCOLN1 activity in a feedback loop (ie, inactive/less active mTOR leads to increased MCOLN1 activity; however, activating MCOLN1 increases autophagy, leading to increased amino acid production and activating mTOR—a feedback loop that regulates/modulates mTOR, AMPK, and MCOLN1 activities).[14,173]

Since the discovery of the lysosome by De Duve,[10,11] more than 60 distinct LSDs have been described, with the collective incidence of their occurrence estimated to be ~1:5000 worldwide.[12,13] In general, LSDs can be described as a subgroup of inborn errors of metabolism and primarily result from a deficiency/defect of one or more lysosomal enzymes involved in macromolecule degradation (several excellent reviews, which will be cited herein, exist[14–18]). However, in some LSDs, the exact function of the mutated protein(s) has yet to be determined.[18,19] Roughly two-thirds to three-quarters of LSDs have some neurological component, affecting multiple brain regions but dependent on the specific disease type. A few examples of LSDs that are associated with central nervous system (CNS) and peripheral nervous system (PNS) pathology include Gaucher's disease, Krabbe disease, Sandhoff disease (SD), Niemann–Pick type C (NPC), mucolipidoses, and the group of neuronal ceroid lipofuscinoses (NCLs; commonly referred to as Batten disease).[20] This review highlights select LSDs that affect the CNS and PNS, briefly addresses the neuropathology associated with these disorders, and provides some mechanistic detail on the presumptive causes leading to the disorders, focusing on therapeutic strategies and/or targets. The various enzymes/proteins that are mutated in the LSDs discussed in this review will be dissected since they play a critical role in lysosomal homeostasis/function. However, an intriguing finding is that not all LSDs have a dramatic CNS pathology, which brings into question the functional importance of mutated genes in the brain (and in neurons in general) compared to other organs.[18]

Neurodegeneration in LSDs

While the mechanistic details behind the neural degeneration observed in many LSDs are not completely understood, the abnormal accumulation of lysosomal storage material due to defective degradation processes was originally thought to contribute to neuronal loss in LSDs[21–23] and other neurodegenerative disorders typified by protein aggregation, such as AD and PD.[24,25] However, this reasoning has more recently been called into question based on the finding that lysosomal storage material accumulation is typically widespread in neurons throughout the brain, even though only select neuronal populations are affected.[18] Nevertheless, most neurons are postmitotic and unable to eliminate unwanted/damaged organelles and macromolecules by dividing. Therefore, neurons must heavily rely upon functional lysosomes/autophagy to efficiently clear these molecules. Autophagic defects have been reported in several LSDs, including Pompe disease, multiple sulfatase deficiency (MSD), NPC, Gaucher's disease, and NCLs,[23] and are suggested to contribute to neurodegeneration.[18]

Data from electron microscopy (and other imaging) studies and biochemical analyses of cell lines and tissues from LSD mouse models also support the idea that mitochondrial dysfunction in neurons is responsible for various LSDs, including Gaucher's disease, MSD, NPC, and mucopolysaccharidoses.[26–28] In addition, perturbed mitochondrial Ca^{2+} homeostasis and/or release has also been observed in the aforementioned LSDs, including decreased Ca^{2+} buffering capacity, reduced ATP production, and mitochondrial fragmentation.[21,29–31] In fact, a reduction in mitochondrial membrane potential and a concomitant decrease in ATP yield have already been shown in a NPC1 mouse model.[26] Decreased oxygen consumption and mitochondrial electron transport chain enzymes have also been reported in neurons from a mouse model of juvenile NCL (JNCL).[32] Similarly, enlarged mitochondria have been observed in a neuronal cell line derived from JNCL mice;[33] however, it should be noted that this particular neuronal cell type is not lost during the progression of the disease. Therefore, mitochondrial abnormalities such as these may represent a common feature of LSDs, indicating that an energy deficit

could be one of the contributing mechanisms responsible for neurodegeneration.[18]

In terms of the potential molecular mechanisms whereby LSDs alter and affect the function and survival of neurons, other neurodegenerative diseases can serve as examples. For example, various signaling pathways are known to contribute to reactive astrocytosis (astrocyte activation) in acute and chronic neurological conditions.[34,35] These include Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) signaling and ERK1/2 phosphorylation.[36] Notably, JAK/STAT3 activation has been observed in the mouse model of SD, which is mediated by tumor necrosis factor (TNF) α production. Inhibition of TNFα in this double knockout mouse significantly inhibits astrocyte activation and reduces neuronal death. In these mouse models, such changes coincide with a significantly increased lifespan, enhanced coordination, and improved neurological function. Interestingly, these improvements in the mouse model of SD are not accompanied by alterations in ganglioside accumulation in neurons.[37] Similarly, increased ERK phosphorylation has also been shown in a model of infantile NCL (INCL) where reactive astrocytes are a prominent feature and associated with aggressive neurodegeneration.[18,38]

Demyelination (either in the CNS or in the PNS), which also ultimately impacts neuronal survival and function, is another hallmark of LSDs.[39] Specialized neuroglia, nonneuronal cells (oligodendrocytes and Schwann cells) coat axons in the CNS and PNS, respectively, with their cell membrane, forming a membrane known as myelin, producing the myelin sheath.[39,40] This sheath then provides insulation to the axon so that electrical signals can propagate more efficiently.[39,40] In a number of LSDs, eg, Krabbe disease, MSD, and NPC, myelination is aberrant (either delayed or abnormal), resulting in demyelination and subsequently severe neurological impairments (as will be further discussed later).[18,40]

LSDs Associated with Nonmembrane-bound Lysosomal Hydrolases

Gaucher's disease (a sphingolipidosis). Gaucher's disease is a prototypical LSD (prevalence of ~1:50,000 in the general population) caused by mutations in the glucocerebrosidase (*GBA1*) gene, a lysosomal enzyme responsible for the degradation of glucocerebroside, which is an intermediate in glycolipid metabolism.[41–43] Hundreds (nearly 300) of GBA mutations have been identified and include missense, nonsense, and frameshift mutations. Collectively, these mutations have been linked to three forms of Gaucher's disease, types 1–3.[44,45]

Type 1, typically referred to as adult or visceral Gaucher's disease, is generally late onset and represents the most common form, with an increased ethnic incidence among Ashkenazi Jews, a prevalence as high as 1:850 has been previously reported.[46] Type 2 has the earliest onset (approximately three to six months of age), with death usually occurring by two years. Type 3 is a juvenile disease with an onset in early childhood. As a result of GBA deficiency, lysosomes accumulate several glycolipids, including glucocerebroside and glucosylsphingosine.[47,48] The major cell type affected in Gaucher's disease is the macrophage, and resident macrophage populations within the spleen and liver have perturbed homeostatic functions.[47] As a result, there is marked spleen enlargement (splenomegaly), which destroys hematopoietic cells leading to anemia.[49] The neuronopathic forms of Gaucher's disease (types 2 and 3, which are acute and chronic, respectively) are also characterized by microglial proliferation, astrocytosis, and a robust neuroinflammatory response and have no available treatment.[50,51] Currently, it is not well understood why only particular brain regions are selectively targeted given the ubiquitous expression of GBA; however, it is clear that storage material accumulation is not the primary deciding factor, ie, a series of secondary events, including neuroinflammation and neurodegeneration, are apparently triggered by a certain threshold of accumulation, resulting in neuronal death but only in specific brain areas where the neurons are intrinsically more sensitive to the inflammatory response.[48,50,52]

A mouse model of Gaucher's disease, where GBA is selectively deleted in neurons and glia, results in increased expression of the lysosomal enzyme cathepsin D;[53] this may represent a compensatory mechanism to offset GBA deficiency. Compared to wild-type mice, the expression of brain-derived neurotrophic factor and nerve growth factor is reduced in the cerebral cortex, brainstem, and cerebellum of Gaucher mice, and ERK1/2 expression is downregulated in neurons from Gaucher mice, which correlates with a decreased number of neurons.[54] Because brain-derived neurotrophic factor and nerve growth factor protect neurons and activate the MAPK pathway,[55–57] these results suggest that a reduction in neurotrophic factors could be involved in neuronal loss in Gaucher's disease.[18,54]

Fabry's disease and GM1 gangliosidosis (sphingolipidoses). GM1 gangliosidosis is an autosomal recessive lysosomal lipid storage disorder caused by mutations of the lysosomal β-galactosidase and results in the accumulation of GM1 ganglioside. The disease phenotype is characterized by severe CNS (primarily neurons but astrocytes may also be vacuolated) dysfunction and skeletal dysplasia.[58] Increased basal expression of the autophagosome marker microtubule-associated protein light chain 3 (LC3-II) is observed in several sphingolipidosis models, including GM1 gangliosidosis[58] and Fabry's disease,[59] while an increased number of autophagosomes (detected by the LC3 marker), elevated Beclin 1 levels, and dysfunctional (both morphologically abnormal and with a decreased membrane potential) mitochondria are specifically observed in brains from GM1 gangliosidosis mice.[58] The Akt–mTOR and Erk signaling pathways are also activated in the GM1 mouse model,[58] thereby inducing autophagy; however, detailed mechanistic information is still unavailable.[60]

In Fabry's disease, deficiency of the lysosomal enzyme α-galactosidase A results in an accumulation of its substrate, globotriaosylceramide (Gb3), throughout the body, leading to neurological manifestations of disease in both the PNS and CNS, including Schwann cells and dorsal root ganglia together with deposits in CNS neurons.[61] Measurement of LC3-II in cultured cells from patients with Fabry's disease reveals increased basal levels when compared with wild-type cells and, as might be expected, a larger increase in response to starvation. Treatment of starved Fabry's disease cells with lysosomal protease inhibitors reveals a block/impairment in autophagic flux, demonstrating a more severe disruption of degradation through macroautophagy than that observed in other sphingolipidoses. In addition, increased p62/SQSTM1 and ubiquitin staining in renal tissues and in cultured fibroblasts from patients with Fabry's disease further supports impaired autophagic flux.[59] For Fabry's disease and other sphingolipid storage diseases, defining where and how this impairment in autophagic flux occurs and establishing the extent to which alterations in macroautophagy contribute to the disease phenotype remain important research goals.[18]

SD, a GM2 gangliosidosis (a sphingolipidosis). SD is a rare autosomal LSD caused by a deficiency in β-hexosaminidases A and B and results in the excessive lysosomal accumulation of GM2 gangliosides and oligosaccharides.[62] There are three clinical subtypes of SD, namely infantile, juvenile, and adult onset. The infantile form is the most aggressive—typically presenting between two and nine months of age—with death occurring before three years. The juvenile form of SD is less common than the infantile variant, with clinical symptoms evident between the ages of 3 and 10 years, which include organomegaly, bone deformations, and CNS (ballooned neuronal cells, astrocytes, and histiocytes) manifestations, such as speech disabilities, cerebral ataxia, and severe psychomotor disturbances.[63] Neuropathological abnormalities associated with SD include prominent brain atrophy and dilatation. Histologically, neurons harbor membranous cytoplasmic bodies formed by the accumulation of GM gangliosides and other lipopigments in the lysosome.[62] An earlier report examining primary astrocytes isolated from a mouse model of SD demonstrated an increased proliferation that was associated with elevated ERK phosphorylation and sphingosine-1-phosphate (S1P) synthesis.[64] These changes were dependent on GM2 ganglioside accumulation within the lysosome. In addition, a direct relationship between S1P metabolism and reactive astrocytosis is indicated by the mouse model of SD, where the deletion of sphingosine kinase (which synthesizes S1P) or S1P receptor reduces astrocyte proliferation and, therefore, reactive astrocytosis.[65] Interestingly, S1P has recently emerged as a key neuroinflammatory mediator in multiple sclerosis and is being explored as a potential therapeutic target to attenuate disease severity.[18,66–68]

SD shares many features with other neurodegenerative disorders, such as increased reactive astrocyte pathology,[69] and activating the JAK2/STAT3 pathway using the inflammatory factor TNFα may be a mechanism for astrocyte activation in the disease.[37] Bone marrow transplantation experiments have revealed that both CNS-derived and bone marrow-derived TNFα have a pathological effect in SD mouse models, with CNS-derived TNFα playing a larger role. Therefore, TNFα can presumably function as a neurodegenerative cytokine, mediating astrocytic pathology and neuronal cell death in SD, and as a potential therapeutic target to attenuate the observed neuropathology.[37]

Krabbe disease (a sphingolipidosis). Krabbe disease, also known as globoid cell leukodystrophy, results from β-galactocerebrosidase deficiency, the enzyme catalyzing the hydrolysis of galactose from several sphingolipids to generate ceramide and sphingosine.[70,71] β-Galactocerebrosidase loss leads to the accumulation of the glycosphingolipid psychosine, which is toxic—in particular to oligodendrocytes.[72] Krabbe disease is an early onset LSD—symptoms typically present at approximately six months of age—and mortality occurs by two years.[73] Krabbe disease primarily affects the CNS, resulting in extensive demyelination of the myelin sheath, leading to ataxia, blindness, seizures, and severe dementia.[74,75] The neuropathology associated with Krabbe disease has been attributed, in large part, to the abnormal accumulation of psychosine in the brain, which will be discussed further below.[76–78] Metabolic alterations in astrocytes have been reported in the mouse model of Krabbe disease, the twitcher mouse, and include increased glutamine levels and upregulation of lactate-specific transporters.[79] Microglial activation has also been reported in patients with Krabbe disease, which is consistent with a prominent neuroinflammatory response.[80] This inflammatory response likely results from cell loss and the release of danger-associated molecular patterns from damaged/dying neurons, which can trigger inflammatory pathways and further exacerbate neuronal damage. Indeed, psychosine has also been reported to exert inflammatory and apoptotic effects in glia,[81] which correlates well with the increased concentration of psychosine in the brains of patients with Krabbe disease and in the respective animal model, the twitcher mouse.[18,82–84] Several mechanisms of action have been proposed for psychosine in Krabbe disease:

I. Lysosphingolipids, such as psychosine, are potent reversible inhibitors of protein kinase C (PKC).[85] It is well-known that PKC is activated by the lipid diacylglycerol, which is generated from phosphatidylinositol bisphosphate in signal transduction pathways mediated by phospholipase C. As mentioned earlier, psychosine accumulates in Krabbe disease, leading to the apoptosis of neurons and astrocytes.[86–88] It is, therefore, of interest that Schwann cells from twitcher mice are 10-fold more sensitive to staurosporine—a PKC inhibitor—than normal cells, indicating a preexisting inhibition of PKC—possibly by psychosine. Interference with PKC-mediated

growth factor signaling could therefore partially account for the loss of myelin-producing cells in Krabbe disease.

II. In oligodendrocytes, insulin-like growth factor 1 (IGF-1) acts through the activation of the antiapoptotic PI3K-Akt/Protein kinase B (PKB) or the MAPK/Erk1/2 signal transduction pathways, and in murine oligodendrocyte precursor cells, psychosine leads to a dose-dependent decrease in both Akt and ERK1/2 phosphorylation accompanied by an activation of caspase-3, resulting in apoptosis. When psychosine-treated cells are exposed to high doses of IGF-1, Akt phosphorylation, and to a lesser extent Erk1/2 phosphorylation, is restored. This leads to a reduced cleavage of caspase-3, resulting in a reduced apoptotic rate in oligodendrocyte precursor cells.[89] Thus, the inhibition of IGF-1 mediated antiapoptotic signaling pathways by psychosine may be one reason for the death of oligodendrocytes in Krabbe disease.

III. Another major target of psychosine is phospholipase A2, which cleaves the membrane lipid phosphatidylcholine into lysophosphatidylcholine and arachidonic acid. Both products are biologically highly active lipids involved in numerous physiological and pathophysiological reactions, with the injection of lysophosphatidylcholine into the brain inducing demyelination in vivo.[90]

IV. Psychosine also reduces AMPK activity. AMPK, which is considered as an important enzyme in the regulation of glucose and lipid metabolism, senses cellular energy levels and maintains the balance between ATP production and consumption.[91,92] In a status of low energy, it is activated, switching off anabolic pathways and activating catabolic pathways and vice versa.[93,94] Exposing cells to psychosine downregulates AMPK activity, leading to a preponderance of biosynthetic pathways in treated cells, eg, oligodendrocytes treated with psychosine display an enhanced synthesis of fatty acids and cholesterol, while β-oxidation as a catabolic pathway is inhibited. Thus, psychosine may also influence the energetic status of a cell by modulating the master switch AMPK, affecting the energy balance.[95] The inhibition of this kinase by psychosine favors energy-consuming pathways over energy-generating pathways, and the resulting lower energy load could also contribute to oligodendrocyte loss.

Glycogen storage disease type II (also known as Pompe disease) (a glycogenosis). Though first discovered more than 80 years ago,[96] Pompe disease would only later (~30 years later) be the first recognized LSD.[97] The disease is caused by a deficiency in acid maltase, also known as acid α-glucosidase, leading to the accumulation of glycogen in the lysosome, lysosomal enlargement, a dramatic expansion of all vesicles of the endocytic/autophagic pathways, and a slowdown in the vesicular trafficking in the overcrowded cells, ultimately leading to profound muscle and nerve cell damage.[98–100] Clinical heterogeneity of the disease is a well-established phenomenon.[101,102] In the most serious infantile form, the disease leads to profound weakness and heart failure and, if left untreated, causes death within one year.[23,103–105] However, even in the milder late onset form, the illness is extremely debilitating, with patients eventually becoming confined to a wheelchair or bedridden, and many die prematurely from respiratory failure.[23,103–105]

Only recently has enzyme replacement therapy using recombinant human α-glucosidase designed to supplement the defective enzyme been approved for all forms of the disease. This therapy stemmed from a straightforward approach to explain the pathogenesis of the disease that the progressive enlargement of glycogen-filled lysosomes would lead to lysosomal rupture and to release of glycogen and other toxic substances into the cytosol.[23] The assumption was that early treatment, initiated before lysosomal integrity was compromised, would reverse this pathogenic cascade. However, this assumption is apparently only partially correct—cardiac muscle responds very well to therapy, but skeletal muscle does not. In particular, this poor muscle response to the therapy has led to a revisiting of the pathogenesis of the disease, and more recently modulating transcription factor EB has been proposed as a new approach to circumvent the problem of inefficient enzyme delivery by exploiting the ability of lysosomes to expel their contents into the extracellular space, providing clearance of the stored material.[106,107] Indeed, transcription factor EB overexpression in Pompe disease muscle has been demonstrated to alleviate autophagic pathology—it promotes the formation and removal of excessive autophagic vacuoles. Thus, a promising new drug target for treating Pompe disease does exist.[107]

Multiple sulfatase deficiency (a mucopolysaccharidosis/sulfatidosis). Mucopolysaccharidoses represent a substantial proportion (~25%) of all LSDs.[22] MSD is caused by a mutation in sulfatase-modifying factor 1 (*sumf*1), resulting in posttranslational defects in lysosomal sulfatases and the pathological accumulation of mucopolysaccharides and sulfatide.[108,109] Therefore, MSD can be more accurately defined as both a mucopolysaccharidosis and a sulfatidosis, or a mucosulfatidosis.[110,111] There are three types of MSD, neonatal, late infantile, and juvenile.[112] The infantile form of MSD is the most aggressive, with symptoms beginning soon after birth. Clinical manifestations include coarsened facial features, deafness, splenomegaly, and hepatomegaly.[113–115] Children with MSD develop a specific neurodegenerative pathology (leukodystrophy), leading to movement disorders and developmental delay with occasional seizures.[116,117] The late infantile form is the most common type of MSD. These children have normal cognitive development in early childhood but experience a rapid decline in motor and cognitive abilities that are attributed to progressive leukodystrophy.[75] Neuroimaging studies have revealed lesions extending into the brain stem.[116] MSD is also typified by extensive demyelination, with the accumulation of cholesterol and galactolipid pigments in the CNS.[118] A recent study utilizing a mouse model demonstrated that the targeted deletion of *sumf*1 in astrocytes results in

severe lysosomal storage material deposition and neuronal loss in vivo.[119] A defective autophagic flux has also been demonstrated by the accumulation of autophagy substrates, such as polyubiquitinated proteins and dysfunctional mitochondria, both of which are significantly increased in tissues from MSD and mucopolysaccharidosis type IIIA mice.[18,22]

Both of these mouse models, MSD and mucopolysaccharidosis type IIIA, present an observed accumulation of autophagosomes resulting from defective/impaired autophagosome–lysosome fusion. This impairment of the autophagic pathway is demonstrated by the inefficient degradation of exogenous aggregate-prone proteins (ie, expanded huntingtin and mutated α-synuclein) in cells from these mice; thus, these LSD models can be defined as *autophagy disorders* resembling more common neurodegenerative diseases, such as AD, PD, and HD. While there are major differences in the initial steps involved in all these diseases (ie, impaired degradation of polyubiquitinated proteins in LSDs versus expression of aggregate-prone proteins in AD, PD, and HD), they may share common mechanisms, eg, blocked autophagy due to defective fusion between autophagosomes and lysosomes, suggesting the possibility of overlapping therapeutic strategies.[22,120]

Mucolipidosis type II and mucolipidosis type III. Mucolipidosis type II (MLII) and mucolipidosis type III (MLIII) are autosomal recessive diseases caused by deficiency of the enzyme *N*-acetylglucosamine 1-phosphotransferase.[121–123] This enzyme modifies newly synthesized lysosomal hydrolases by attaching a molecule of mannose-6-phosphate, which functions as a tag for delivery to lysosomes.[124] Mutations in GlcNAc-phosphotransferase result in the missorting and cellular loss of lysosomal enzymes and the lysosomal accumulation of storage material.[125] MLII is characterized by skeletal abnormalities, short stature, cardiomegaly, and developmental delays, while MLIII is a later onset, milder form of MLII.[126] Alterations in autophagy have recently been reported in MLII and MLIII fibroblasts, including the accumulation of autophagosomes, p62/SQSTM1, ubiquitin, and fragmented mitochondria. Additionally, the lysosomal pH of MLII cells has been shown to be higher than that of normal cells.[127] In contrast, no variations in the levels of Beclin 1 are observed, suggesting that the formation of autophagosomes is not increased in these disorders.[128] Accumulation of LC3-positive structures and ubiquitin aggregates has also been reported in neuronal cells from a patient with MLIII.[129] Importantly, inhibition of autophagy restores mitochondrial alterations in MLII and MLIII cells, suggesting that increased autophagy might be detrimental for proper mitochondrial function.[128]

LSDs Associated with Integral Lysosomal Membrane Proteins

Niemann–Pick type C (a sphingolipidosis). NPC is caused by mutations in one of the two genes, *NPC1* (95% of cases) and *NPC2* (5% of cases), which manifest as severe abnormalities in lipid trafficking, eg, NPC1-positive vesicles are believed to be transiently targeted to lysosomes and once there to facilitate clearing of unesterified cholesterol from this organelle, with *NPC1* loss of function and the subsequent accumulation of unesterified cholesterol commonly viewed as the principal lesion in NPC.[130,131] Both *NPC1* and *NPC2* are predicted to encode for proteins involved in cholesterol homeostasis, which accounts for the cholesterol accumulation within the lysosome.[131–138] NPC affects both peripheral organs and the nervous system, and symptoms include neurological abnormalities, ie, psychomotor disturbances, ataxia, and seizures.[130,137] Neuroimaging studies have characteristically revealed diffuse cerebral atrophy and changes within the white matter of the CNS.[132] In chronic progressive cases, neurofibrillary tangles similar to the aggregates of hyperphosphorylated tau protein found in AD have also been observed.[139] Astrocyte activation is also associated with NPC,[140–142] with these cells exhibiting mitochondrial dysfunction.[143] Increased levels of IL-1β and increased ApoE, a genetic risk factor for AD, have been reported in animal models of NPC.[144] Consistent with this study, increased expression of amyloid precursor protein as well as β- and γ-secretases has been found in reactive astrocytes in mice suffering from NPC disease,[145] suggesting an association between NPC and AD.[18]

Danon disease (a glycogenosis). Danon disease, which is also known as *lysosomal glycogen storage disease with normal acid maltase activity* or *glycogen storage disease due to lysosomal-associated membrane protein 2 (LAMP2) deficiency*, is a lysosomal glycogen storage disease due to LAMP2 deficiency.[146,147] The disease is inherited as an X-linked trait and is extremely rare. The disease phenotype is characterized by severe cardiomyopathy and variable skeletal muscle weakness and is often associated with mental retardation.[23] Interestingly, Danon disease was the first LSD described in 1981 involving a mutation in a lysosomal structural protein rather than an enzymatic protein,[146,147] with the accumulation of autophagic vacuoles in several tissues, particularly in muscle.[148] In fact, a patient with Danon disease was initially believed to suffer from another rare LSD, Pompe disease, based on a tissue biopsy. However, the tests for Pompe disease were normal for acid maltase activity.[146]

Mucolipidosis type IV. Mucolipidosis type IV (MLIV) is an autosomal recessive disorder characterized by acute psychomotor delays, achlorydria, and visual abnormalities, including retinal degeneration and corneal clouding.[19,149] Lysosomal inclusions are found in most tissues in patients with MLIV, with the composition of the storage material being heterogeneous and including lipids and mucopolysaccharides forming characteristic multiconcentric lamellae, as well as soluble, granulated proteins.[150–155] MLIV is thought to be solely due to mutations in *MCOLN1* (mucolipin 1; also known as *TRPML1*, transient receptor potential MCOLN1), an endolysosomal cation channel belonging to the transient receptor potential superfamily of ion channels.[154,156–158]

Whole cell patch clamping and native endolysosomal recordings have led to the conclusion that MCOLN1 functions as an inwardly (from lumen to cytoplasm) rectifying channel permeable to Ca^{2+}, Na^{+}, K^{+}, and Fe^{2+}/Mn^{2+}, whose activity is potentiated by low pH.[159–163] Although the cellular role of MCOLN1 is still under investigation, the current model suggests that this protein mediates Ca^{2+} efflux from late endosomes and lysosomes.[164,165] Localized Ca^{2+} release from such acidic stores is required for fusion between endocytic vesicles and to maintain organelle homeostasis, thus suggesting that MCOLN1 is a key regulator of membrane trafficking along the endosomal pathway.

In MCOLN1-deficient fibroblasts, both the degradation of the autophagosome content and the fusion of autophagosomes with late endosomes/lysosomes are delayed compared to control cells.[166] This leads to a dramatic accumulation of autophagosomes in the cytosol of MLIV cells as demonstrated by indirect immunofluorescence, LC3-II/LC3-I immunoblot, and electron microscopy.[166] This impairment of the autophagic pathway has detrimental consequences for the cell leading to inefficient degradation of protein aggregates and damaged organelles. In particular, accumulation of p62/SQSTM1 inclusions and abnormal mitochondria has been described in MLIV fibroblasts and epithelial cells.[28,166,167]

A mouse model for MLIV supports late endosomal defects as an important site of dysfunction, and autophagy has also been shown to be defective in primary neurons cultured from these mice.[168–170] The *MCOLN1*$^{-/-}$ mice provide an excellent phenotypic model of the human disease, and all of the hallmarks of MLIV are present in the mice with the exception of corneal clouding.[168] Analysis of the brain at eight months shows lysosomal inclusions in multiple cell types, including neurons, astrocytes, oligodendrocytes, microglia, and endothelial cells, with larger inclusions present in neurons, and electron microscopy of primary cerebellar neurons from MCOLN1-deficient mouse embryos demonstrates significant membranous intracytoplasmic storage bodies, despite the lack of gross phenotype at birth.[170] Evaluation of macroautophagy in neurons by LC3-II/LC3-I immunoblot also shows increased levels of LC3-II, similar to that observed in human MLIV fibroblasts. LC3-II clearance is also defective, as treatment of the *MCOLN1*$^{-/-}$ neuronal cultures with protease inhibitors to stimulate autophagy does not result in increased LC3-II levels.[170] Demonstration of defective autophagy in MCOLN1-deficient neurons suggests a possible mechanism underlying neurodegeneration, whereby increased protein aggregation and organelle damage lead to autophagic stress and eventual neuronal death.[166] The MLIV mouse model provides an important tool for evaluating the complicated interplay between chaperone-mediated autophagy and macroautophagy and their role in neurodegenerative disease.

As mentioned earlier, MCOLN1 is an inwardly rectifying channel permeable to Ca^{2+}, Na^{+}, K^{+}, and Fe^{2+}/Mn^{2+}. Ca^{2+}, in particular, is believed to be significant with regard to the physiological function and regulation of MCOLN1, with the channel releasing luminal Ca^{2+} to facilitate the Ca^{2+}-dependent fusion of amphisomes with lysosomes. The amino acids generated by the degradation of proteins in the autolysosomes promote TORC1 activation. In addition to inhibiting the initiation of autophagy, activated TORC1 (target of rapamycin complex) also diminishes the endocytosis of MCOLN1.[171] In the absence of MCOLN1, fusion of amphisomes and lysosomes is impaired. This leads to a decrease in autophagic flux of amino acids, causing a reduction in TORC1 and upregulation of autophagy. Biochemical (mass spectrometry [MS] and in vitro phosphorylation) and Ca imaging data indicate that the MCOLN1 channel may be directly phosphorylated (at Ser^{572} and Ser^{576}) and negatively regulated by the TOR kinase, but that AMPK could be involved indirectly through activity on the TOR pathway.[172,173] This particular finding validates and expands upon previous studies that have strongly suggested links between TOR and the endocytic system, eg, TOR has been localized to endocytic membranes in yeast, fly, and mammalian cell culture.[174–176]

However, another study suggests that MCOLN1 activity is negatively regulated by protein kinase A phosphorylation at two different sites (Ser^{557} and Ser^{559}).[172]

The Neuronal Ceroid Lipofuscinoses

Though not deemed *classic* LSDs,[17] the NCLs are the most common cause of neurodegeneration among children.[177] These disorders typically manifest with blindness, seizures, progressive cognitive defects, and motor failure.[178] NCL, commonly referred to as Batten disease, encompasses a family of disorders caused by mutations in the ceroid lipofuscinosis (CLN) genes.[177,179,180] Currently, mutations in 14 different CLN genes have been identified that are broadly classified into infantile, late infantile, juvenile (the juvenile form is not a typical LSD, ie, not associated with a typical lysosomal enzyme deficiency[16,23,181]), and adult onset forms.[180,182,183] The childhood forms of Batten disease are characterized by the typical symptoms listed earlier and often result in premature death.[183,184] A histopathological hallmark of all NCLs is the lysosomal accumulation of autofluorescent lipopigments and proteins; however, the structural appearance of inclusion material varies according to each disease type.[185] Biochemical characterization of storage material has also identified lipophilic proteins, including subunit C of mitochondrial ATP synthase (primarily in JNCL) and sphingolipid pigments (in other forms of NCL).[33,186,187] The INCL is the most aggressive, with a life expectancy of two to six years.[188,189] INCL is due to a mutation in *CLN1*, which encodes for palmitoyl protein thioesterase, an enzyme responsible for the cleavage of long-chain fatty acids on several proteins containing cysteine residues.[190,191] Late INCL is caused by mutations in *CLN2*, a lysosomal enzyme (tripeptidyl peptidase I), that cleaves tripeptides from the terminal amine groups of partially unfolded proteins.[192,193] JNCL results from mutations in the CLN3 gene.[183] The precise function of CLN3 remains unknown; however, based on

several functional analyses, CLN3 is predicted to regulate lysosomal acidification, endocytic and vesicle trafficking, and proper maintenance of mitochondrial function.[194–196] JNCL is similar to INCL and late INCL and also presents with visual impairment, seizures, and progressive cognitive and motor decline, however, with an advanced onset, typically between 5 and 10 years of age.[18,183] In addition, the accumulation of dysfunctional mitochondria, increased expression of LC3-II, and the downregulation of the mammalian target of rapamycin (mTOR) pathway, indicating the activation of autophagosome formation, are detected in JNCL due to mutations of the CLN3 gene, with autophagy likely disrupted at the level of autophagic vacuolar maturation.[197,198]

Conclusion

LSDs are particularly debilitating metabolic disorders; however, the past several decades have witnessed our ever evolving understanding of their complex biology. At the very least, the study of LSDs has helped highlight vital cellular processes, including calcium homeostasis, pH regulation, apoptosis, autophagy, molecular trafficking, endocytosis, and exocytosis, as well as some of the intra- and intercellular signaling events involved in these processes. This deeper understanding of the biology has broadened the range of therapeutic targets for LSDs and other neurodegenerative disorders, as well as for cancer, eg, targeting LAMP2 (a deficiency of which is the underlying cause of Danon disease) may be a viable treatment option for both AD and HD in the future.[199,200] Currently, we have no cure for these diseases, but approved therapies for a handful of LSDs, and many ideas for the development of new treatment options, do exist. Genetic screening programs for at-risk populations, screening of newborns for treatable disorders, provisions for genetic counseling, prenatal diagnosis for at-risk pregnancies, and more recently, preimplantation diagnoses remain the best remedies to decrease, or to at least be better prepared for, the complexities that LSDs present to society.[17] The current aim for these disorders is still timely diagnoses to enable the early implementation of available and emerging therapies when available.

Abbreviations

AD, Alzheimer's disease; AMPK, AMP-activated protein kinase; BECN1, Beclin 1; ERK, Extracellular signal-regulated kinases; HD, Huntington's disease; JAK/STAT3, Janus Kinase/Signal transducer and activator of transcription 3; LSDs, lysosomal storage diseases; MAPK, Microtubule-associated protein kinase; MSD, multiple sulfatase deficiency; NPC, Niemann–Pick type C; PD, Parkinson's disease; TOR, target of rapamycin.

Author Contributions

Conceived and designed the topic and structure of the review: RUO. Prepared first draft of the manuscript: RUO. Contributed to the writing of the manuscript: RUO and JEB. Made critical revisions and prepared final version: RUO. All authors reviewed and approved of the final manuscript.

REFERENCES

1. Shintani T, Klionsky DJ. Autophagy in health and disease: a double-edged sword. *Science*. 2004;306(5698):990–995.
2. Klionsky DJ. Autophagy: from phenomenology to molecular understanding in less than a decade. *Nat Rev Mol Cell Biol*. 2007;8(11):931–937.
3. Rubinsztein DC. The roles of intracellular protein-degradation pathways in neurodegeneration. *Nature*. 2006;443(7113):780–786.
4. Fader CM, Colombo MI. Autophagy and multivesicular bodies: two closely related partners. *Cell Death Differ*. 2009;16(1):70–78.
5. Metcalf D, Isaacs AM. The role of ESCRT proteins in fusion events involving lysosomes, endosomes and autophagosomes. *Biochem Soc Trans*. 2010;38(6):1469–1473.
6. Komatsu M, Waguri S, Chiba T, et al. Loss of autophagy in the central nervous system causes neurodegeneration in mice. *Nature*. 2006;441(7095):880–884.
7. Williams A, Jahreiss L, Sarkar S, et al. Aggregate-prone proteins are cleared from the cytosol by autophagy: therapeutic implications. *Curr Top Dev Biol*. 2006;76:89–101.
8. Nah J, Yuan J, Jung YK. Autophagy in neurodegenerative diseases: from mechanism to therapeutic approach. *Mol Cells*. 2015;38(5):381–389.
9. Ciechanover A, Kwon YT. Degradation of misfolded proteins in neurodegenerative diseases: therapeutic targets and strategies. *Exp Mol Med*. 2015;47:e147.
10. De Duve C. The lysosome. *Sci Am*. 1963;208:64–72.
11. De Duve C, Wattiaux R. Functions of lysosomes. *Annu Rev Physiol*. 1966;28:435–492.
12. Fuller M, Meikle PJ, Hopwood JJ. Epidemiology of lysosomal storage diseases: an overview. In: Mehta A, Beck M, Sunder-Plassmann G, eds. *Fabry Disease: Perspectives from 5 Years of FOS*. Oxford: Oxford PharmaGenesis, 2006.
13. Raben N, Shea L, Hill V, Plotz P. Monitoring autophagy in lysosomal storage disorders. *Methods Enzymol*. 2009;453:417–449.
14. Schultz ML, Tecedor L, Chang M, Davidson BL. Clarifying lysosomal storage diseases. *Trends Neurosci*. 2011;34(8):401–410.
15. Cox TM, Cachon-Gonzalez MB. The cellular pathology of lysosomal diseases. *J Pathol*. 2012;226(2):241–254.
16. Platt FM, Boland B, van der Spoel AC. The cell biology of disease: lysosomal storage disorders: the cellular impact of lysosomal dysfunction. *J Cell Biol*. 2012;199(5):723–734.
17. Boustany RM. Lysosomal storage diseases—the horizon expands. *Nat Rev Neurol*. 2013;9(10):583–598.
18. Rama Rao KV, Kielian T. Astrocytes and lysosomal storage diseases. *Neuroscience*. 2015:pii.
19. Wakabayashi K, Gustafson AM, Sidransky E, Goldin E. Mucolipidosis type IV: an update. *Mol Genet Metab*. 2011;104(3):206–213.
20. Prada CE, Grabowski GA. Neuronopathic lysosomal storage diseases: clinical and pathologic findings. *Dev Disabil Res Rev*. 2013;17(3):226–246.
21. Kiselyov K, Jennigs JJ Jr, Rbaibi Y, Chu CT. Autophagy, mitochondria and cell death in lysosomal storage diseases. *Autophagy*. 2007;3(3):259–262.
22. Settembre C, Fraldi A, Jahreiss L, et al. A block of autophagy in lysosomal storage disorders. *Hum Mol Genet*. 2008;17(1):119–129.
23. Lieberman AP, Puertollano R, Raben N, Slaugenhaupt S, Walkley SU, Ballabio A. Autophagy in lysosomal storage disorders. *Autophagy*. 2012;8(5):719–730.
24. Matsuda N, Tanaka K. Does impairment of the ubiquitin-proteasome system or the autophagy-lysosome pathway predispose individuals to neurodegenerative disorders such as Parkinson's disease? *J Alzheimers Dis*. 2010;19(1):1–9.
25. Tan CC, Yu JT, Tan MS, Jiang T, Zhu XC, Tan L. Autophagy in aging and neurodegenerative diseases: implications for pathogenesis and therapy. *Neurobiol Aging*. 2014;35(5):941–957.
26. Yu W, Gong JS, Ko M, Garver WS, Yanagisawa K, Michikawa M. Altered cholesterol metabolism in Niemann–Pick type C1 mouse brains affects mitochondrial function. *J Biol Chem*. 2005;280(12):11731–11739.
27. Osellame LD, Duchen MR. Quality control gone wrong: mitochondria, lysosomal storage disorders and neurodegeneration. *Br J Pharmacol*. 2014;171(8):1958–1972.
28. Coblentz J, St Croix C, Kiselyov K. Loss of TRPML1 promotes production of reactive oxygen species: is oxidative damage a factor in mucolipidosis type IV? *Biochem J*. 2014;457(2):361–368.
29. Kiselyov K, Yamaguchi S, Lyons CW, Muallem S. Aberrant Ca2+ handling in lysosomal storage disorders. *Cell Calcium*. 2010;47(2):103–111.
30. de Pablo-Latorre R, Saide A, Polishhuck EV, Nusco E, Fraldi A, Ballabio A. Impaired parkin-mediated mitochondrial targeting to autophagosomes differentially contributes to tissue pathology in lysosomal storage diseases. *Hum Mol Genet*. 2012;21(8):1770–1781.

31. Chandrachud U, Walker MW, Simas AM, et al. Unbiased cell-based screening in a neuronal cell model of Batten disease highlights an interaction between Ca2+ homeostasis, autophagy, and CLN3 protein function. *J Biol Chem*. 2015;290(23): 14361–14380.
32. Luiro K, Kopra O, Blom T, et al. Batten disease (JNCL) is linked to disturbances in mitochondrial, cytoskeletal, and synaptic compartments. *J Neurosci Res*. 2006; 84(5):1124–1138.
33. Fossale E, Wolf P, Espinola JA, et al. Membrane trafficking and mitochondrial abnormalities precede subunit c deposition in a cerebellar cell model of juvenile neuronal ceroid lipofuscinosis. *BMC Neurosci*. 2004;5:57.
34. Pekny M, Nilsson M. Astrocyte activation and reactive gliosis. *Glia*. 2005;50(4): 427–434.
35. Burda JE, Sofroniew MV. Reactive gliosis and the multicellular response to CNS damage and disease. *Neuron*. 2014;81(2):229–248.
36. Sriram K, Benkovic SA, Hebert MA, Miller DB, O'Callaghan JP. Induction of gp130-related cytokines and activation of JAK2/STAT3 pathway in astrocytes precedes up-regulation of glial fibrillary acidic protein in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of neurodegeneration: key signaling pathway for astrogliosis in vivo? *J Biol Chem*. 2004;279(19): 19936–19947.
37. Abo-Ouf H, Hooper AW, White EJ, van Rensburg HJ, Trigatti BL, Igdoura SA. Deletion of tumor necrosis factor-alpha ameliorates neurodegeneration in Sandhoff disease mice. *Hum Mol Genet*. 2013;22(19):3960–3975.
38. Kanninen KM, Grubman A, Caragounis A, et al. Altered biometal homeostasis is associated with CLN6 mRNA loss in mouse neuronal ceroid lipofuscinosis. *Biol Open*. 2013;2(6):635–646.
39. Folkerth RD. Abnormalities of developing white matter in lysosomal storage diseases. *J Neuropathol Exp Neurol*. 1999;58(9):887–902.
40. Saher G, Stumpf SK. Cholesterol in myelin biogenesis and hypomyelinating disorders. *Biochim Biophys Acta*. 2015;1851(8):1083–1094.
41. Kampine JP, Brady RO, Kanfer JN, Feld M, Shapiro D. Diagnosis of Gaucher's disease and Niemann–Pick disease with small samples of venous blood. *Science*. 1967;155(3758):86–88.
42. Jmoudiak M, Futerman AH. Gaucher disease: pathological mechanisms and modern management. *Br J Haematol*. 2005;129(2):178–188.
43. Vitner EB, Futerman AH, Platt N. Innate immune responses in the brain of sphingolipid lysosomal storage diseases. *Biol Chem*. 2015;396(6–7):659–667.
44. Grabowski GA, Dinur T, Osiecki KM, Kruse JR, Legler G, Gatt S. Gaucher disease types 1, 2, and 3: differential mutations of the acid beta-glucosidase active site identified with conduritol B epoxide derivatives and sphingosine. *Am J Hum Genet*. 1985;37(3):499–510.
45. Grabowski GA, Goldblatt J, Dinur T, et al. Genetic heterogeneity in Gaucher disease: physicokinetic and immunologic studies of the residual enzyme in cultured fibroblasts from non-neuronopathic and neuronopathic patients. *Am J Med Genet*. 1985;21(3):529–549.
46. Gan-Or Z, Giladi N, Rozovski U, et al. Genotype-phenotype correlations between GBA mutations and Parkinson disease risk and onset. *Neurology*. 2008; 70(24):2277–2283.
47. Conradi NG, Kalimo H, Sourander P. Reactions of vessel walls and brain parenchyma to the accumulation of Gaucher cells in the Norrbottnian type (type III) of Gaucher disease. *Acta Neuropathol*. 1988;75(4):385–390.
48. Farfel-Becker T, Vitner EB, Kelly SL, et al. Neuronal accumulation of glucosylceramide in a mouse model of neuronopathic Gaucher disease leads to neurodegeneration. *Hum Mol Genet*. 2014;23(4):843–854.
49. Appel MF, Markowitz AM. Massive splenomegaly in Gaucher's disease. *JAMA*. 1971;217(3):343–344.
50. Vitner EB, Farfel-Becker T, Eilam R, Biton I, Futerman AH. Contribution of brain inflammation to neuronal cell death in neuronopathic forms of Gaucher's disease. *Brain*. 2012;135(pt 6):1724–1735.
51. Vitner EB, Futerman AH. Neuronal forms of Gaucher disease. *Handb Exp Pharmacol*. 2013;216:405–419.
52. Vitner EB, Salomon R, Farfel-Becker T, et al. RIPK3 as a potential therapeutic target for Gaucher's disease. *Nat Med*. 2014;20(2):204–208.
53. Vitner EB, Dekel H, Zigdon H, et al. Altered expression and distribution of cathepsins in neuronopathic forms of Gaucher disease and in other sphingolipidoses. *Hum Mol Genet*. 2010;19(18):3583–3590.
54. Kim EY, Hong YB, Go SH, Lee B, Jung SC. Downregulation of neurotrophic factors in the brain of a mouse model of Gaucher disease; implications for neuronal loss in Gaucher disease. *Exp Mol Med*. 2006;38(4):348–356.
55. Crowley C, Spencer SD, Nishimura MC, et al. Mice lacking nerve growth factor display perinatal loss of sensory and sympathetic neurons yet develop basal forebrain cholinergic neurons. *Cell*. 1994;76(6):1001–1011.
56. Nonomura T, Kubo T, Oka T, et al. Signaling pathways and survival effects of BDNF and NT-3 on cultured cerebellar granule cells. *Brain Res Dev Brain Res*. 1996;97(1):42–50.
57. Dudek H, Datta SR, Franke TF, et al. Regulation of neuronal survival by the serine-threonine protein kinase Akt. *Science*. 1997;275(5300):661–665.
58. Takamura A, Higaki K, Kajimaki K, et al. Enhanced autophagy and mitochondrial aberrations in murine G(M1)-gangliosidosis. *Biochem Biophys Res Commun*. 2008;367(3):616–622.
59. Chevrier M, Brakch N, Celine L, et al. Autophagosome maturation is impaired in Fabry disease. *Autophagy*. 2010;6(5):589–599.
60. Corcelle E, Nebout M, Bekri S, et al. Disruption of autophagy at the maturation step by the carcinogen lindane is associated with the sustained mitogen-activated protein kinase/extracellular signal-regulated kinase activity. *Cancer Res*. 2006;66(13):6861–6870.
61. Schiffmann R. Neuropathy and Fabry disease: pathogenesis and enzyme replacement therapy. *Acta Neurol Belg*. 2006;106(2):61–65.
62. Itoh H, Tanaka J, Morihana Y, Tamaki T. The fine structure of cytoplasmic inclusions in brain and other visceral organs in Sandhoff disease. *Brain Dev*. 1984; 6(5):467–474.
63. O'Dowd BF, Klavins MH, Willard HF, Gravel R, Lowden JA, Mahuran DJ. Molecular heterogeneity in the infantile and juvenile forms of Sandhoff disease (O-variant GM2 gangliosidosis). *J Biol Chem*. 1986;261(27):12680–12685.
64. Kawashima N, Tsuji D, Okuda T, Itoh K, Nakayama K. Mechanism of abnormal growth in astrocytes derived from a mouse model of GM2 gangliosidosis. *J Neurochem*. 2009;111(4):1031–1041.
65. Wu YP, Mizugishi K, Bektas M, Sandhoff R, Proia RL. Sphingosine kinase 1/S1P receptor signaling axis controls glial proliferation in mice with Sandhoff disease. *Hum Mol Genet*. 2008;17(15):2257–2264.
66. Brinkmann V. FTY720 (fingolimod) in Multiple Sclerosis: therapeutic effects in the immune and the central nervous system. *Br J Pharmacol*. 2009;158(5): 1173–1182.
67. Graler MH. Targeting sphingosine 1-phosphate (S1P) levels and S1P receptor functions for therapeutic immune interventions. *Cell Physiol Biochem*. 2010; 26(1):79–86.
68. Chun J, Brinkmann V. A mechanistically novel, first oral therapy for multiple sclerosis: the development of fingolimod (FTY720, Gilenya). *Discov Med*. 2011; 12(64):213–228.
69. Igdoura SA, Mertineit C, Trasler JM, Gravel RA. Sialidase-mediated depletion of GM2 ganglioside in Tay-Sachs neuroglia cells. *Hum Mol Genet*. 1999;8(6): 1111–1116.
70. Andrews JM, Cancilla PA. Cytoplasmic inclusions in human globoid cell leukodystrophy. Krabbe's Disease. *Arch Pathol*. 1970;89(1):53–55.
71. Andrews JM, Cancilla PA, Grippo J, Menkes JH. Globoid cell leukodystrophy (Krabbe's disease): morphological and biochemical studies. *Neurology*. 1971; 21(4):337–352.
72. Suzuki K, Suzuki K. Genetic galactosylceramidase deficiency (globoid cell leukodystrophy, Krabbe disease) in different mammalian species. *Neurochem Pathol*. 1985;3(1):53–68.
73. Wenger DA, Rafi MA, Luzi P. Molecular genetics of Krabbe disease (globoid cell leukodystrophy): diagnostic and clinical implications. *Hum Mutat*. 1997; 10(4):268–279.
74. Husain AM, Altuwaijri M, Aldosari M. Krabbe disease: neurophysiologic studies and MRI correlations. *Neurology*. 2004;63(4):617–620.
75. Kohlschutter A. Lysosomal leukodystrophies: Krabbe disease and metachromatic leukodystrophy. *Handbook Clin Neurol*. 2013;113:1611–1618.
76. Igisu H, Suzuki K. Analysis of galactosylsphingosine (psychosine) in the brain. *J Lipid Res*. 1984;25(9):1000–1006.
77. Igisu H, Suzuki K. Progressive accumulation of toxic metabolite in a genetic leukodystrophy. *Science*. 1984;224(4650):753–755.
78. Cantuti Castelvetri L, Givogri MI, Hebert A, et al. The sphingolipid psychosine inhibits fast axonal transport in Krabbe disease by activation of GSK3beta and deregulation of molecular motors. *J Neurosci*. 2013;33(24):10048–10056.
79. Meisingset TW, Ricca A, Neri M, Sonnewald U, Gritti A. Region- and age-dependent alterations of glial-neuronal metabolic interactions correlate with CNS pathology in a mouse model of globoid cell leukodystrophy. *J Cereb Blood Flow Metab*. 2013;33(7):1127–1137.
80. Smith BR, Santos MB, Marshall MS, et al. Neuronal inclusions of alpha-synuclein contribute to the pathogenesis of Krabbe disease. *J Pathol*. 2014;232(5): 509–521.
81. Giri S, Jatana M, Rattan R, Won JS, Singh I, Singh AK. Galactosylsphingosine (psychosine)-induced expression of cytokine-mediated inducible nitric oxide synthases via AP-1 and C/EBP: implications for Krabbe disease. *FASEB J*. 2002; 16(7):661–672.
82. Svennerholm L, Vanier MT, Mansson JE. Krabbe disease: a galactosylsphingosine (psychosine) lipidosis. *J Lipid Res*. 1980;21(1):53–64.
83. Esch SW, Williams TD, Biswas S, Chakrabarty A, LeVine SM. Sphingolipid profile in the CNS of the twitcher (globoid cell leukodystrophy) mouse: a lipidomics approach. *Cell Mol Biol*. 2003;49(5):779–787.
84. Kobayashi T, Shinoda H, Goto I, Yamanaka T, Suzuki Y. Globoid cell leukodystrophy is a generalized galactosylsphingosine (psychosine) storage disease. *Biochem Biophys Res Commun*. 1987;144(1):41–46.
85. Hannun YA, Bell RM. Functions of sphingolipids and sphingolipid breakdown products in cellular regulation. *Science*. 1989;243(4890):500–507.

86. Jatana M, Giri S, Singh AK. Apoptotic positive cells in Krabbe brain and induction of apoptosis in rat C6 glial cells by psychosine. *Neurosci Lett*. 2002;330(2):183–187.
87. Zaka M, Wenger DA. Psychosine-induced apoptosis in a mouse oligodendrocyte progenitor cell line is mediated by caspase activation. *Neurosci Lett*. 2004;358(3):205–209.
88. Tanaka K, Webster HD. Effects of psychosine (galactosylsphingosine) on the survival and the fine structure of cultured Schwann cells. *J Neuropathol Exp Neurol*. 1993;52(5):490–498.
89. Zaka M, Rafi MA, Rao HZ, Luzi P, Wenger DA. Insulin-like growth factor-1 provides protection against psychosine-induced apoptosis in cultured mouse oligodendrocyte progenitor cells using primarily the PI3K/Akt pathway. *Mol Cell Neurosci*. 2005;30(3):398–407.
90. Fressinaud C. Repeated injuries dramatically affect cells of the oligodendrocyte lineage: effects of PDGF and NT-3 in vitro. *Glia*. 2005;49(4):555–566.
91. Hardie DG, Hawley SA, Scott JW. AMP-activated protein kinase—development of the energy sensor concept. *J Physiol*. 2006;574(pt 1):7–15.
92. Hardie DG. AMP-activated/SNF1 protein kinases: conserved guardians of cellular energy. *Nat Rev Mol Cell Biol*. 2007;8(10):774–785.
93. Williams T, Forsberg LJ, Viollet B, Brenman JE. Basal autophagy induction without AMP-activated protein kinase under low glucose conditions. *Autophagy*. 2009;5(8):1155–1165.
94. Onyenwoke RU, Forsberg LJ, Liu L, Williams T, Alzate O, Brenman JE. AMPK directly inhibits NDPK through a phosphoserine switch to maintain cellular homeostasis. *Mol Biol Cell*. 2012;23(2):381–389.
95. Giri S, Khan M, Nath N, Singh I, Singh AK. The role of AMPK in psychosine mediated effects on oligodendrocytes and astrocytes: implication for Krabbe disease. *J Neurochem*. 2008;105(5):1820–1833.
96. Pompe JC. Concerning idiopathic hypertrophy of the heart [in Dutch]. *Ned Tijdschr Geneeskd*. 1932;76:304–311.
97. Hers HG. alpha-Glucosidase deficiency in generalized glycogen storage disease (Pompe's disease). *Biochem J*. 1963;86:11–16.
98. Thurberg BL, Lynch Maloney C, Vaccaro C, et al. Characterization of pre- and post-treatment pathology after enzyme replacement therapy for Pompe disease. *Lab Invest*. 2006;86(12):1208–1220.
99. Fukuda T, Ahearn M, Roberts A, et al. Autophagy and mistargeting of therapeutic enzyme in skeletal muscle in Pompe disease. *Mol Ther*. 2006;14(6):831–839.
100. Lim JA, Li L, Raben N. Pompe disease: from pathophysiology to therapy and back again. *Front Aging Neurosci*. 2014;6:177.
101. van Capelle CI, Winkel LP, Hagemans ML, et al. Eight years experience with enzyme replacement therapy in two children and one adult with Pompe disease. *Neuromuscul Disord*. 2008;18(6):447–452.
102. van der Ploeg AT, Reuser AJ. Pompe's disease. *Lancet*. 2008;372(9646):1342–1353.
103. Chien YH, Lee NC, Thurberg BL, et al. Pompe disease in infants: improving the prognosis by newborn screening and early treatment. *Pediatrics*. 2009;124(6):e1116–e1125.
104. Kishnani PS, Hwu WL, Mandel H, et al. A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. *J Pediatr*. 2006;148(5):671–676.
105. van den Hout HM, Hop W, van Diggelen OP, et al. The natural course of infantile Pompe's disease: 20 original cases compared with 133 cases from the literature. *Pediatrics*. 2003;112(2):332–340.
106. Medina DL, Fraldi A, Bouche V, et al. Transcriptional activation of lysosomal exocytosis promotes cellular clearance. *Dev Cell*. 2011;21(3):421–430.
107. Spampanato C, Feeney E, Li L, et al. Transcription factor EB (TFEB) is a new therapeutic target for Pompe disease. *EMBO Mol Med*. 2013;5(5):691–706.
108. Austin JH. Studies in metachromatic leukodystrophy. XII. Multiple sulfatase deficiency. *Arch Neurol*. 1973;28(4):258–264.
109. Eto Y, Numaguchi S, Tahara T, Rennert OM. Multiple sulfatase deficiency (mucosulfatidosis): impaired degradation of labeled sulfated compounds in cultured skin fibroblasts in vivo. *Eur J Pediatr*. 1980;135(1):85–89.
110. Basner R, von Figura K, Glossl J, Klein U, Kresse H, Mlekusch W. Multiple deficiency of mucopolysaccharide sulfatases in mucosulfatidosis. *Pediatr Res*. 1979;13(12):1316–1318.
111. Sabourdy F, Mourey L, Le Trionnaire E, et al. Natural disease history and characterisation of SUMF1 molecular defects in ten unrelated patients with multiple sulfatase deficiency. *Orphanet J Rare Dis*. 2015;10:31.
112. Busche A, Hennermann JB, Burger F, et al. Neonatal manifestation of multiple sulfatase deficiency. *Eur J Pediatr*. 2009;168(8):969–973.
113. Burk RD, Valle D, Thomas GH, et al. Early manifestations of multiple sulfatase deficiency. *J Pediatr*. 1984;104(4):574–578.
114. Macaulay RJ, Lowry NJ, Casey RE. Pathologic findings of multiple sulfatase deficiency reflect the pattern of enzyme deficiencies. *Pediatr Neurol*. 1998;19(5):372–376.
115. Diaz-Font A, Santamaria R, Cozar M, et al. Clinical and mutational characterization of three patients with multiple sulfatase deficiency: report of a new splicing mutation. *Mol Genet Metab*. 2005;86(1–2):206–211.
116. Guerra WF, Verity MA, Fluharty AL, Nguyen HT, Philippart M. Multiple sulfatase deficiency: clinical, neuropathological, ultrastructural and biochemical studies. *J Neuropathol Exp Neurol*. 1990;49(4):406–423.
117. Incecik F, Ozbek MN, Gungor S, et al. Multiple sulfatase deficiency: a case series of four children. *Ann Indian Acad Neurol*. 2013;16(4):720–722.
118. Annunziata I, Bouche V, Lombardi A, Settembre C, Ballabio A. Multiple sulfatase deficiency is due to hypomorphic mutations of the SUMF1 gene. *Hum Mutat*. 2007;28(9):928.
119. Di Malta C, Fryer JD, Settembre C, Ballabio A. Autophagy in astrocytes: a novel culprit in lysosomal storage disorders. *Autophagy*. 2012;8(12):1871–1872.
120. Settembre C, Fraldi A, Rubinsztein DC, Ballabio A. Lysosomal storage diseases as disorders of autophagy. *Autophagy*. 2008;4(1):113–114.
121. Shapiro LJ, Hickman S, Hall CW, Neufeld EF. Biochemical studies in mucolipidoses II and III. *Birth Defects Orig Artic Ser*. 1975;11(6):301–305.
122. Tiede S, Storch S, Lubke T, et al. Mucolipidosis II is caused by mutations in GNPTA encoding the alpha/beta GlcNAc-1-phosphotransferase. *Nat Med*. 2005;11(10):1109–1112.
123. Kudo M, Brem MS, Canfield WM. Mucolipidosis II (I-cell disease) and mucolipidosis IIIA (classical pseudo-hurler polydystrophy) are caused by mutations in the GlcNAc-phosphotransferase alpha/beta-subunits precursor gene. *Am J Hum Genet*. 2006;78(3):451–463.
124. Hickman S, Neufeld EF. A hypothesis for I-cell disease: defective hydrolases that do not enter lysosomes. *Biochem Biophys Res Commun*. 1972;49(4):992–999.
125. Vladutiu GD, Rattazzi MC. Abnormal lysosomal hydrolases excreted by cultured fibroblasts in I-cell disease (mucolipidosis II). *Biochem Biophys Res Commun*. 1975;67(3):956–964.
126. Paik KH, Song SM, Ki CS, et al. Identification of mutations in the GNPTA (MGC4170) gene coding for GlcNAc-phosphotransferase alpha/beta subunits in Korean patients with mucolipidosis type II or type IIIA. *Hum Mutat*. 2005;26(4):308–314.
127. Otomo T, Higaki K, Nanba E, Ozono K, Sakai N. Lysosomal storage causes cellular dysfunction in mucolipidosis II skin fibroblasts. *J Biol Chem*. 2011;286(40):35283–35290.
128. Otomo T, Higaki K, Nanba E, Ozono K, Sakai N. Inhibition of autophagosome formation restores mitochondrial function in mucolipidosis II and III skin fibroblasts. *Mol Genet Metab*. 2009;98(4):393–399.
129. Kobayashi H, Takahashi-Fujigasaki J, Fukuda T, et al. Pathology of the first autopsy case diagnosed as mucolipidosis type III alpha/beta suggesting autophagic dysfunction. *Mol Genet Metab*. 2011;102(2):170–175.
130. Lloyd-Evans E, Platt FM. Lipids on trial: the search for the offending metabolite in Niemann–Pick type C disease. *Traffic*. 2010;11(4):419–428.
131. Zervas M, Dobrenis K, Walkley SU. Neurons in Niemann–Pick disease type C accumulate gangliosides as well as unesterified cholesterol and undergo dendritic and axonal alterations. *J Neuropathol Exp Neurol*. 2001;60(1):49–64.
132. Palmer DN, Husbands DR, Jolly RD. Phospholipid fatty acids in brains of normal sheep and sheep with ceroid-lipofuscinosis. *Biochim Biophys Acta*. 1985;834(2):159–163.
133. Blanchette-Mackie EJ, Dwyer NK, Amende LM, et al. Type-C Niemann–Pick disease: low density lipoprotein uptake is associated with premature cholesterol accumulation in the Golgi complex and excessive cholesterol storage in lysosomes. *Proc Natl Acad Sci U S A*. 1988;85(21):8022–8026.
134. Sokol J, Blanchette-Mackie J, Kruth HS, et al. Type C Niemann–Pick disease. Lysosomal accumulation and defective intracellular mobilization of low density lipoprotein cholesterol. *J Biol Chem*. 1988;263(7):3411–3417.
135. Zervas M, Somers KL, Thrall MA, Walkley SU. Critical role for glycosphingolipids in Niemann–Pick disease type C. *Curr Biol*. 2001;11(16):1283–1287.
136. Zhou SY, Xu SJ, Yan YG, Yu HM, Ling SC, Luo JH. Decreased purinergic inhibition of synaptic activity in a mouse model of Niemann–Pick disease type C. *Hippocampus*. 2011;21(2):212–219.
137. Mengel E, Klunemann HH, Lourenco CM, et al. Niemann–Pick disease type C symptomatology: an expert-based clinical description. *Orphanet J Rare Dis*. 2013;8:166.
138. Platt FM, Wassif C, Colaco A, et al. Disorders of cholesterol metabolism and their unanticipated convergent mechanisms of disease. *Annu Rev Genomics Hum Genet*. 2014;15:173–194.
139. Ohm TG, Treiber-Held S, Distl R, et al. Cholesterol and tau protein—findings in Alzheimer's and Niemann Pick C's disease. *Pharmacopsychiatry*. 2003;36(suppl 2):S120–S126.
140. Patel SC, Suresh S, Kumar U, et al. Localization of Niemann–Pick C1 protein in astrocytes: implications for neuronal degeneration in Niemann–Pick type C disease. *Proc Natl Acad Sci U S A*. 1999;96(4):1657–1662.
141. German DC, Liang CL, Song T, Yazdani U, Xie C, Dietschy JM. Neurodegeneration in the Niemann–Pick C mouse: glial involvement. *Neuroscience*. 2002;109(3):437–450.
142. Suzuki H, Sakiyama T, Harada N, Abe M, Tadokoro M. Pathologic changes of glial cells in murine model of Niemann–Pick disease type C: immunohistochemical, lectin-histochemical and ultrastructural observations. *Pediatr Int*. 2003;45(1):1–4.

143. Saez PJ, Orellana JA, Vega-Riveros N, et al. Disruption in connexin-based communication is associated with intracellular Ca(2)(+) signal alterations in astrocytes from Niemann–Pick type C mice. *PLoS One*. 2013;8(8):e71361.
144. Yan X, Yang F, Lukas J, et al. Hyperactive glial cells contribute to axonal pathologies in the spinal cord of Npc1 mutant mice. *Glia*. 2014;62(7):1024–1040.
145. Kodam A, Maulik M, Peake K, et al. Altered levels and distribution of amyloid precursor protein and its processing enzymes in Niemann–Pick type C1-deficient mouse brains. *Glia*. 2010;58(11):1267–1281.
146. Danon MJ, Oh SJ, DiMauro S, et al. Lysosomal glycogen storage disease with normal acid maltase. *Neurology*. 1981;31(1):51–57.
147. Nishino I, Fu J, Tanji K, et al. Primary LAMP-2 deficiency causes X-linked vacuolar cardiomyopathy and myopathy (Danon disease). *Nature*. 2000;406(6798):906–910.
148. Tanaka Y, Guhde G, Suter A, et al. Accumulation of autophagic vacuoles and cardiomyopathy in LAMP-2-deficient mice. *Nature*. 2000;406(6798):902–906.
149. Altarescu G, Sun M, Moore DF, et al. The neurogenetics of mucolipidosis type IV. *Neurology*. 2002;59(3):306–313.
150. Berman ER, Livni N, Shapira E, Merin S, Levij IS. Congenital corneal clouding with abnormal systemic storage bodies: a new variant of mucolipidosis. *J Pediatr*. 1974;84(4):519–526.
151. Riedel KG, Zwaan J, Kenyon KR, Kolodny EH, Hanninen L, Albert DM. Ocular abnormalities in mucolipidosis IV. *Am J Ophthalmol*. 1985;99(2):125–136.
152. Bargal R, Bach G. Phospholipids accumulation in mucolipidosis IV cultured fibroblasts. *J Inherit Metab Dis*. 1988;11(2):144–150.
153. Bargal R, Bach G. Phosphatidylcholine storage in mucolipidosis IV. *Clin Chim Acta*. 1989;181(2):167–174.
154. Slaugenhaupt SA, Acierno JS Jr, Helbling LA, et al. Mapping of the mucolipidosis type IV gene to chromosome 19p and definition of founder haplotypes. *Am J Hum Genet*. 1999;65(3):773–778.
155. Shen D, Wang X, Li X, et al. Lipid storage disorders block lysosomal trafficking by inhibiting a TRP channel and lysosomal calcium release. *Nat Commun*. 2012;3:731.
156. Bargal R, Avidan N, Ben-Asher E, et al. Identification of the gene causing mucolipidosis type IV. *Nat Genet*. 2000;26(1):118–123.
157. Bassi MT, Manzoni M, Monti E, Pizzo MT, Ballabio A, Borsani G. Cloning of the gene encoding a novel integral membrane protein, mucolipidin-and identification of the two major founder mutations causing mucolipidosis type IV. *Am J Hum Genet*. 2000;67(5):1110–1120.
158. Sun M, Goldin E, Stahl S, et al. Mucolipidosis type IV is caused by mutations in a gene encoding a novel transient receptor potential channel. *Hum Mol Genet*. 2000;9(17):2471–2478.
159. Bach G, Chen CS, Pagano RE. Elevated lysosomal pH in Mucolipidosis type IV cells. *Clin Chim Acta*. 1999;280(1–2):173–179.
160. Soyombo AA, Tjon-Kon-Sang S, Rbaibi Y, et al. TRP-ML1 regulates lysosomal pH and acidic lysosomal lipid hydrolytic activity. *J Biol Chem*. 2006;281(11):7294–7301.
161. Dong XP, Cheng X, Mills E, et al. The type IV mucolipidosis-associated protein TRPML1 is an endolysosomal iron release channel. *Nature*. 2008;455(7215):992–996.
162. Puertollano R, Kiselyov K. TRPMLs: in sickness and in health. *Am J Physiol Renal Physiol*. 2009;296(6):F1245–F1254.
163. Dong XP, Shen D, Wang X, et al. PI(3,5)P(2) controls membrane trafficking by direct activation of mucolipin Ca(2+) release channels in the endolysosome. *Nat Commun*. 2010;1:38.
164. Cheng X, Shen D, Samie M, Xu H. Mucolipins: intracellular TRPML1-3 channels. *FEBS Lett*. 2010;584(10):2013–2021.
165. Abe K, Puertollano R. Role of TRP channels in the regulation of the endosomal pathway. *Physiology*. 2011;26(1):14–22.
166. Vergarajauregui S, Connelly PS, Daniels MP, Puertollano R. Autophagic dysfunction in mucolipidosis type IV patients. *Hum Mol Genet*. 2008;17(17):2723–2737.
167. Jennings JJ Jr, Zhu JH, Rbaibi Y, Luo X, Chu CT, Kiselyov K. Mitochondrial aberrations in mucolipidosis Type IV. *J Biol Chem*. 2006;281(51):39041–39050.
168. Venugopal B, Browning MF, Curcio-Morelli C, et al. Neurologic, gastric, and opthalmologic pathologies in a murine model of mucolipidosis type IV. *Am J Hum Genet*. 2007;81(5):1070–1083.
169. Micsenyi MC, Dobrenis K, Stephney G, et al. Neuropathology of the Mcoln1(-/-) knockout mouse model of mucolipidosis type IV. *J Neuropathol Exp Neurol*. 2009;68(2):125–135.
170. Curcio-Morelli C, Charles FA, Micsenyi MC, et al. Macroautophagy is defective in mucolipin-1-deficient mouse neurons. *Neurobiol Dis*. 2010;40(2):370–377.
171. Wong CO, Li R, Montell C, Venkatachalam K. Drosophila TRPML is required for TORC1 activation. *Curr Biol*. 2012;22(17):1616–1621.
172. Vergarajauregui S, Oberdick R, Kiselyov K, Puertollano R. Mucolipin 1 channel activity is regulated by protein kinase A-mediated phosphorylation. *Biochem J*. 2008;410(2):417–425.
173. Onyenwoke RU, Sexton JZ, Yan F, et al. The Mucolipidosis IV Ca2+ Channel TRPML1 (MCOLN1) is Regulated by the TOR Kinase. *Biochem J*. 2015;470(3):331–342.
174. Sancak Y, Peterson TR, Shaul YD, et al. The Rag GTPases bind raptor and mediate amino acid signaling to mTORC1. *Science*. 2008;320(5882):1496–1501.
175. Kunz J, Schneider U, Howald I, Schmidt A, Hall MN. HEAT repeats mediate plasma membrane localization of Tor2p in yeast. *J Biol Chem*. 2000;275(47):37011–37020.
176. Wedaman KP, Reinke A, Anderson S, Yates J III, McCaffery JM, Powers T. Tor kinases are in distinct membrane-associated protein complexes in *Saccharomyces cerevisiae*. *Mol Biol Cell*. 2003;14(3):1204–1220.
177. Wisniewski KE, Kida E, Golabek AA, Kaczmarski W, Connell F, Zhong N. Neuronal ceroid lipofuscinoses: classification and diagnosis. *Adv Genet*. 2001;45:1–34.
178. Wisniewski KE, Zhong N, Philippart M. Pheno/genotypic correlations of neuronal ceroid lipofuscinoses. *Neurology*. 2001;57(4):576–581.
179. Getty AL, Rothberg PG, Pearce DA. Diagnosis of neuronal ceroid lipofuscinosis: mutation detection strategies. *Expert Opin Med Diagn*. 2007;1(3):351–362.
180. Aberg L, Lauronen L, Hamalainen J, Mole SE, Autti T. A 30-year follow-up of a neuronal ceroid lipofuscinosis patient with mutations in CLN3 and protracted disease course. *Pediatr Neurol*. 2009;40(2):134–137.
181. Kollmann K, Uusi-Rauva K, Scifo E, Tyynela J, Jalanko A, Braulke T. Cell biology and function of neuronal ceroid lipofuscinosis-related proteins. *Biochim Biophys Acta*. 2013;1832(11):1866–1881.
182. Lebrun AH, Moll-Khosrawi P, Pohl S, et al. Analysis of potential biomarkers and modifier genes affecting the clinical course of CLN3 disease. *Mol Med*. 2011;17(11–12):1253–1261.
183. Cotman SL, Karaa A, Staropoli JF, Sims KB. Neuronal ceroid lipofuscinosis: impact of recent genetic advances and expansion of the clinicopathologic spectrum. *Curr Neurol Neurosci Rep*. 2013;13(8):366.
184. Sinha S, Satishchandra P, Santosh V, Gayatri N, Shankar SK. Neuronal ceroid lipofuscinosis: a clinicopathological study. *Seizure*. 2004;13(4):235–240.
185. Palmer DN, Barns G, Husbands DR, Jolly RD. Ceroid lipofuscinosis in sheep. II. The major component of the lipopigment in liver, kidney, pancreas, and brain is low molecular weight protein. *J Biol Chem*. 1986;261(4):1773–1777.
186. Pardo CA, Rabin BA, Palmer DN, Price DL. Accumulation of the adenosine triphosphate synthase subunit C in the mnd mutant mouse. A model for neuronal ceroid lipofuscinosis. *Am J Pathol*. 1994;144(4):829–835.
187. Goebel HH, Schochet SS, Jaynes M, Bruck W, Kohlschutter A, Hentati F. Progress in neuropathology of the neuronal ceroid lipofuscinoses. *Mol Genet Metab*. 1999;66(4):367–372.
188. Hawkins-Salsbury JA, Cooper JD, Sands MS. Pathogenesis and therapies for infantile neuronal ceroid lipofuscinosis (infantile CLN1 disease). *Biochim Biophys Acta*. 2013;1832(11):1906–1909.
189. Verkruyse LA, Natowicz MR, Hofmann SL. Palmitoyl-protein thioesterase deficiency in fibroblasts of individuals with infantile neuronal ceroid lipofuscinosis and I-cell disease. *Biochim Biophys Acta*. 1997;1361(1):1–5.
190. Vesa J, Hellsten E, Verkruyse LA, et al. Mutations in the palmitoyl protein thioesterase gene causing infantile neuronal ceroid lipofuscinosis. *Nature*. 1995;376(6541):584–587.
191. Hofmann SL, Lee LA, Lu JY, Verkruyse LA. Palmitoyl-protein thioesterase and the molecular pathogenesis of infantile neuronal ceroid lipofuscinosis. *Neuropediatrics*. 1997;28(1):27–30.
192. Sleat DE, Donnelly RJ, Lackland H, et al. Association of mutations in a lysosomal protein with classical late-infantile neuronal ceroid lipofuscinosis. *Science*. 1997;277(5333):1802–1805.
193. Sleat DE, Gin RM, Sohar I, et al. Mutational analysis of the defective protease in classic late-infantile neuronal ceroid lipofuscinosis, a neurodegenerative lysosomal storage disorder. *Am J Hum Genet*. 1999;64(6):1511–1523.
194. Pearce DA, Carr CJ, Das B, Sherman F. Phenotypic reversal of the btn1 defects in yeast by chloroquine: a yeast model for Batten disease. *Proc Natl Acad Sci U S A*. 1999;96(20):11341–11345.
195. Kim Y, Ramirez-Montealegre D, Pearce DA. A role in vacuolar arginine transport for yeast Btn1p and for human CLN3, the protein defective in Batten disease. *Proc Natl Acad Sci U S A*. 2003;100(26):15458–15462.
196. Luiro K, Yliannala K, Ahtiainen L, et al. Interconnections of CLN3, Hook1 and Rab proteins link Batten disease to defects in the endocytic pathway. *Hum Mol Genet*. 2004;13(23):3017–3027.
197. Cao Y, Espinola JA, Fossale E, et al. Autophagy is disrupted in a knock-in mouse model of juvenile neuronal ceroid lipofuscinosis. *J Biol Chem*. 2006;281(29):20483–20493.
198. Koike M, Shibata M, Waguri S, et al. Participation of autophagy in storage of lysosomes in neurons from mouse models of neuronal ceroid-lipofuscinoses (Batten disease). *Am J Pathol*. 2005;167(6):1713–1728.
199. Qi L, Zhang XD, Wu JC, et al. The role of chaperone-mediated autophagy in huntingtin degradation. *PLoS One*. 2012;7(10):e46834.
200. Koga H, Cuervo AM. Chaperone-mediated autophagy dysfunction in the pathogenesis of neurodegeneration. *Neurobiol Dis*. 2011;43(1):29–37.