Lysosomal Storage Diseases—Regulating Neurodegeneration

Supplementary Issue: Molecular and Cellular Mechanisms of Neurodegeneration

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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

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. 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, Ca2+ 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. During autophagy, double membrane-bound vesicles (autophagosomes) isolate cytosolic material destined for degradation. Subsequently, autophagosomes fuse with late endosomes to form amphisomes. 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. 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). 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. Therefore, we focus on rarer diseases involving aberrant autophagy, the LSDs.
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LSDs with CNS involvement often present with neurodegeneration, which can be attributed to the accumulation of storage material within neurons. This storage material can lead to decreased autophagy, which is the process by which cells remove and recycle damaged or unnecessary organelles and macromolecules. In LSDs, autophagy may be compromised due to defects in lysosomal function or decreased calcium buffering capacity. 82

Neurodegeneration in LSDs

While the mechanistic details behind the neural degeneration observed in many LSDs are not completely understood, the normal functioning of the nervous system requires energy and stability provided by mitochondria. Mitochondrial dysfunction can be a consequence of storage material accumulation in neurons, leading to decreased ATP production and impaired calcium homeostasis. 6

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 14,173). However, in some LSDs, the exact function of the mutated protein(s) has yet to be determined. 18 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

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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 Ca2+ homeostasis and/or release has also been observed in the aforementioned LSDs, including decreased Ca2+ buffering capacity, reduced ATP production, and mitochondrial fragmentation. 21,29–31 In fact, a reduction in mitochondrial membrane potential and a concomitant decrease in A TP 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.  

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 astrogliosis (astrocyte activation) in acute and chronic neurological conditions. These include Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) signaling and ERK1/2 phosphorylation. 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 astrogliosis 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. 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.  

Demyelination (either in the CNS or in the PNS), which also ultimately impacts neuronal survival and function, is another hallmark of LSDs. 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. This sheath then provides insulation to the axon so that electrical signals can propagate more efficiently. 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).  

**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 glucocerebroside (GBA1) gene, a lysosomal enzyme responsible for the degradation of glucocerebroside, which is an intermediate in glycolipid metabolism. 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.  

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. 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. 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. As a result, there is marked spleen enlargement (splenomegaly), which destroys hematopoietic cells leading to anemia. The neuropathic forms of Gaucher’s disease (types 2 and 3, which are acute and chronic, respectively) are also characterized by microglial proliferation, astrogliosis, and a robust neuroinflammatory response and have no available treatment. 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.  

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, 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. Because brain-derived neurotrophic factor and nerve growth factor protect neurons and activate the MAPK pathway, these results suggest that a reduction in neurotrophic factors could be involved in neuronal loss in Gaucher’s disease.  

**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. Increased basal expression of the autophagosome marker microtubule-associated protein light chain 3 (LC3-II) is observed in several sphingolipidosis models, including GM1 gangliosidosis and Fabry’s disease, 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. The Akt–mTOR and Erk signaling pathways are also activated in the GM1 mouse model, thereby inducing autophagy; however, detailed mechanistic information is still unavailable.
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. 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 organomegal, 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 (SIP) synthesis.64 These changes were dependent on GM2 ganglioside accumulation within the lysosome. In addition, a direct relationship between SIP metabolism and reactive astrocytosis is indicated by the mouse model of SD, where the deletion of sphingosine kinase (which synthesizes SIP) or SIP receptor reduces astrocyte proliferation and, therefore, reactive astrocytosis.65 Interestingly, SIP has recently emerged as a key neuroinflammatory mediator in multiple sclerosis and is being explored as a potential therapeutic target to attenuate disease severity.19,66–68 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.71 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.38,82–84 Several mechanisms of action have been proposed for psychosine in Krabbe disease:

1. 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 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 (sumf1), 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.78 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 sumf1 in astrocytes results in
severe lysosomal storage material deposition and neuronal loss in vivo.\(^\text{119}\) 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 II A mice.\(^\text{18,22}\)

Both of these mouse models, MSD and mucopolysaccharidosis type II A, 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 \(\alpha\)-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.\(^\text{32,120}\)

**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.\(^\text{121–123}\) This enzyme modifies newly synthesized lysosomal hydrolases by attaching a molecule of mannose-6-phosphate, which functions as a tag for delivery to lysosomes.\(^\text{124}\) Mutations in GlcNAc-phosphotransferase result in the missorting and cellular loss of lysosomal enzymes and the lysosomal accumulation of storage material.\(^\text{125}\) MLII is characterized by skeletal abnormalities, short stature, cardiomegaly, and developmental delays, while MLIII is a later onset, milder form of MLII.\(^\text{126}\) 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.\(^\text{127}\) In contrast, no variations in the levels of Beclin 1 are observed, suggesting that the formation of autophagosomes is not increased in these disorders.\(^\text{128}\) Accumulation of LC3-positive structures and ubiquitin aggregates has also been reported in neuronal cells from a patient with MLIII.\(^\text{129}\) Importantly, inhibition of autophagy restores mitochondrial alterations in MLII and MLIII cells, suggesting that increased autophagy might be detrimental for proper mitochondrial function.\(^\text{128}\)

**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.\(^\text{130,131}\) Both NPC1 and NPC2 are predicted to encode for proteins involved in cholesterol homeostasis, which accounts for the cholesterol accumulation within the lysosome.\(^\text{131–138}\) NPC affects both peripheral organs and the nervous system, and symptoms include neurological abnormalities, ie, psychomotor disturbances, ataxia, and seizures.\(^\text{130,137}\) Neuroimaging studies have characteristically revealed diffuse cerebral atrophy and changes within the white matter of the CNS.\(^\text{132}\) In chronic progressive cases, neurofibrillary tangles similar to the aggregates of hyperphosphorylated tau protein found in AD have also been observed.\(^\text{139}\) Astrocyte activation is also associated with NPC,\(^\text{140–142}\) with these cells exhibiting mitochondrial dysfunction.\(^\text{143}\) Increased levels of IL-1\(\beta\) and increased ApoE, a genetic risk factor for AD, have been reported in animal models of NPC.\(^\text{144}\) Consistent with this study, increased expression of amyloid precursor protein as well as \(\beta\)- and \(\gamma\)-secretases has been found in reactive astrocytes in mice suffering from NPC disease,\(^\text{145}\) suggesting an association between NPC and AD.\(^\text{18}\)

**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.\(^\text{146,147}\) 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.\(^\text{23}\) Interestingly, Danon disease was the first LSD described in 1981 involving a mutation in a lysosomal structural protein rather than an enzymatic protein,\(^\text{146,147}\) with the accumulation of autophagic vacuoles in several tissues, particularly in muscle.\(^\text{148}\) 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.\(^\text{146}\)

**Mucolipidosis type IV.** Mucolipidosis type IV (MLIV) is an autosomal recessive disorder characterized by acute psychomotor delays, achlorhydria, and visual abnormalities, including retinal degeneration and corneal clouding.\(^\text{19,149}\) 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.\(^\text{150–155}\) MLIV is thought to be solely due to mutations in \(MCOLN1\) (mucolipin 1; also known as \(\text{TRPML1}\), transient receptor potential MCOLN1), an endolysosomal cation channel belonging to the transient receptor potential superfamily of ion channels.\(^\text{154,156–158}\)
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\(^{2+}/\text{Mn}^{2+}\), 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 endolysosomal inclusions and abnormal mitochondria has been described in MLI V fibroblasts and epithelial cells.\(^{28,166,167}\)

A mouse model for MLI V 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 \textit{MCOLN} \textit{N} \textit{I}\(^{2-}\) mice provide an excellent phenotypic model of the human disease, and all of the hallmarks of MLI V 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 immunoblotting 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 \textit{MCOLN} \textit{N} \textit{I}\(^{2-}\) 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\(^{2+}/\text{Mn}^{2+}\). 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\(^{579}\)) 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\(^{577}\) and Ser\(^{579}\)).\(^{172}\)

### 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).\(^{186,187}\) The INCL is the most aggressive, with a life expectancy of two to six years.\(^{188,189}\) INCL is due to a mutation in \textit{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 \textit{CLN2}, a lysosomal enzyme (tripalmitinyl peptidase I), that cleaves tripeptides from the terminal amine groups of partially unfolded proteins.\(^{192,193}\) JNCL results from mutations in the CLN3 gene.\(^{185}\) 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.\textsuperscript{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.\textsuperscript{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 involved at the level of autophagic vacuolar maturation.\textsuperscript{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.\textsuperscript{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 at least be better prepared for, the complexities that LSDs present to society.\textsuperscript{37} 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.

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