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# Finding pathogenic commonalities between Niemann-Pick type C and other lysosomal storage disorders: Opportunities for shared therapeutic interventions

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ABSTRACT

Lysosomal storage disorders (LSDs) are diseases characterized by the accumulation of macromolecules in the late endocytic system and are caused by inherited defects in genes that encode mainly lysosomal enzymes or transmembrane lysosomal proteins. Niemann-Pick type C disease (NPCD), a LSD characterized by liver damage and progressive neurodegeneration that leads to early death, is caused by mutations in the genes encoding the NPC1 or NPC2 proteins. Both proteins are involved in the transport of cholesterol from the late endosomal compartment to the rest of the cell. Loss of function of these proteins causes primary cholesterol accumulation, and secondary accumulation of other lipids, such as sphingolipids, in lysosomes. Despite years of studying the genetic and molecular bases of NPCD and related-lysosomal disorders, the pathogenic mechanisms involved in these diseases are not fully understood. In this review we will summarize the pathogenic mechanisms described for NPCD and we will discuss their relevance for other LSDs with neurological components such as Niemann-Pick type A and Gaucher diseases. We will particularly focus on the activation of signaling pathways that may be common to these three pathologies with emphasis on how the intra-lysosomal accumulation of lipids leads to pathology, specifically to neurological impairments. We will show that although the primary lipid storage defect is different in these three LSDs, there is a similar secondary accumulation of metabolites and activation of signaling pathways that can lead to common pathogenic mechanisms. This analysis might help to delineate common pathological mechanisms and therapeutic targets for lysosomal storage diseases.

## 1. Introduction

Since their discovery by De Duve and colleagues, lysosomes described as a 'group of particles with lytic properties' [1] have aroused great interest because of their role in disease, particularly those resulting from the failure of lysosomal enzymes function.

Today, we know that lysosomes are dynamic organelles involved in fundamental cellular processes such as secretion, plasma membrane repair, degradation and metabolism of a variety of substrates, sensing of nutrient availability, and activation and regulation of energy metabolism [2]. In addition, lysosomes are essential for the autophagy pathway [3]. Therefore, lysosomes function has significant implications in health and disease [4]. Indeed, the impairment of lysosomal enzymes activity, membrane-bound proteins and transporters leads to progressive accumulation of un-metabolized substrates including glycosaminoglycans, sphingolipids and glycerolipids, cholesterol, glycogen and proteins, which results in disorders known as lysosomal storage disorders (LSDs) [5].

LSDs are inborn errors of metabolism characterized by the accumulation of macromolecules in the late endocytic system. Most LDSs are inherited in an autosomal recessive manner, occur at a collective frequency of 1 in 5000 live births and are caused by inherited defects in genes that mainly encode lysosomal proteins, most commonly lysosomal enzymes or transmembrane lysosomal proteins [6,7]. LSDs are normally monogenic (that is, they involve only a single gene) but for most LSDs numerous mutations have been described in the same gene. These mutations include missense, nonsense and splice-site mutations, partial deletions and insertions. Some mutations lead to the complete

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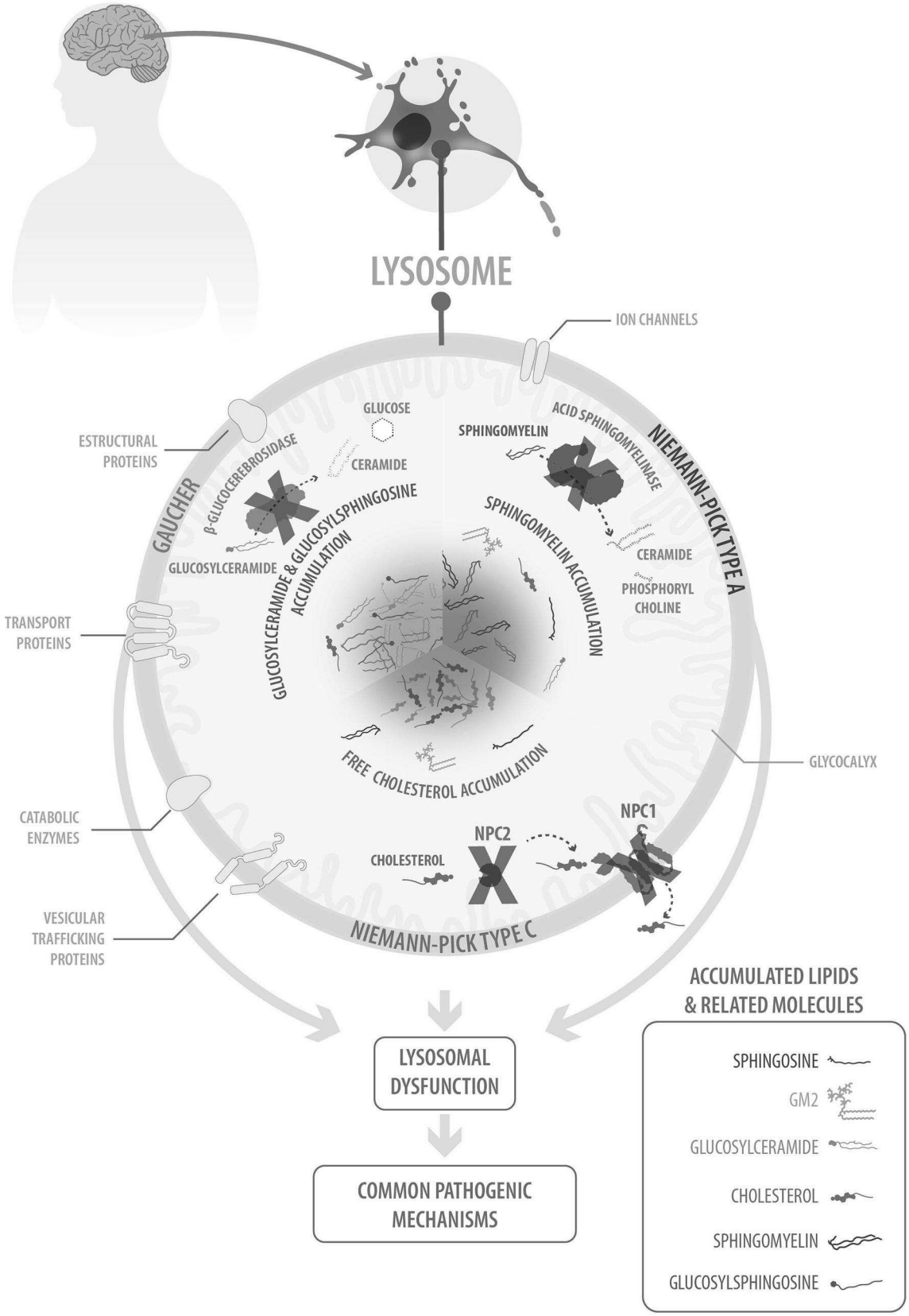


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loss of enzyme activity, whereas others lead to reduced activity [8]. Although the particular mutations in the genes responsible for these diseases have been known for many years, much remains to be understood about the pathogenic alterations produced in cell signaling. The progressive accumulation of undegraded substrates in the lysosomes and the endosomal-lysosomal system leads to cellular

**Fig. 1.** Common features of lysosomal neurodegenerative diseases: Niemann-Pick A, Niemann-Pick C and Gaucher.
Niemann-Pick A, Niemann-Pick C and Gaucher disease 2 and 3 show damage and neuronal death in the CNS. Acid sphingomyelinase (ASM) deficiency causes Niemann Pick disease type A disease (NPAD) resulting in sphingomyelin accumulation in lysosomes. Niemann-Pick C disease (NPCD) is caused by mutations in the *NPC1* or *NPC2* genes that encode lysosomal cholesterol transport proteins, which mediate free cholesterol efflux from this compartment. As consequence, NPC cells accumulate cholesterol in lysosomes. Gaucher disease (GD) is caused by mutations of the gene encoding the β-glucocerebroside 1 (*GBA1*) enzyme, which is responsible for the breakdown of the cellular glycolipids; glucosylceramide (GlcCer) and glucosylsphingosine (GlcSph). The deficiency of this enzyme leads to the accumulation of GSLs in lysosomes. Interestingly, in the three diseases there are common secondary lipids that accumulate for example cholesterol in NPA and GD, and sphingomyelin in NPC, among other. As a consequence, lipid accumulation in lysosomes leads to lysosomal dysfunction and common pathological mechanisms.

dysfunction and eventually cell death.

Cell death occurs in many cell types as a consequence of LSDs, however, neurons are particularly vulnerable to these disorders, an aspect of special interest in this review. A few examples of LSDs that are associated with neurological impairment are Niemann-Pick type C (NPCD), Niemann-Pick type A (NPAD) and Gaucher diseases (GD) type II and III (Fig. 1).

Although these LSDs show affected peripheral tissues, severe neuropathology is the typical hallmark, which leads to death at an early age [9]. Other clinical manifestations such as organomegaly, ocular abnormalities, skeletal deformities, and vasculopathy accompany the neurological symptoms [10].

More than 60 LSDs have been identified so far [11]. Typically, their classification is based on the accumulation of undegraded substrates such as sphingolipidoses, mucopolysaccharidoses, and oligosaccharidosis. Approximately 95% of LSDs are caused by deficiency of lysosomal hydrolases [12]. At present, classification based on the molecular mechanisms of common LSDs is widely used in clinical practice. Therefore, the main open question in the biology of LSDs is the delineation of the biochemical and cellular pathways that cause disease pathology. All LSDs are characterized by the intra-lysosomal accumulation of unmetabolized substrates, which is the primary cause of disease, but the extensive range of disease symptoms indicates that many secondary biochemical and cellular pathways must also be involved. Indeed, the primary accumulated metabolite affects a secondary biochemical or cellular pathway, which then subsequently causes tissue pathology, altered gene expression, and the activation of tertiary biochemical pathways [13]. Any of these events could be the main cause of tissue damage and death but surprisingly little is known about the identity of these pathways or their regulation in LSDs.

The pathogenesis may be due to the deficiency and non-availability of substrates to fulfill their biological function in the cell, which would explain the difference between LSDs given the different substrates that are not available in each disease. However, LSDs pathogenesis could also be attributed to lysosomal dysfunction as a result of the accumulation of substrates within the lysosome, which would explain that many LSDs share symptoms. In general, it is still unknown whether tissue dysfunction and symptoms are due to the lack of one or more lipid species, and/or accumulation of a precursor molecule, or the presence of a potentially toxic metabolite.

Among all LSDs we will focus on NPCD, which is characterized by defects in cholesterol efflux from the lysosome and its consequent accumulation in this organelle. Secondarily, other lipids are also accumulated. Among them we found sphingomyelin (SM) and glycosphingolipids (GSLs) such as GM2 and GM3 [10,14]. There has been a special interest in the scientific community to understand NPCD and the efforts of many researchers and research foundations that support them have allowed significant advances in understanding the disease including the identification of the mutations in the *NPC1* and *NPC2* genes responsible for the disease, the improvement of patient support and even the current development of clinical trials for 2-hydroxypropyl-β-cyclodextrin (HPβCD) as a therapeutic strategy. Nevertheless, the pathogenic mechanisms involved in this disease are not fully understood. Particularly, it is still unknown how this intra-lysosomal accumulation of cholesterol and other lipids leads to the pathology and progression of the disease.

In this review we will summarize the pathogenic mechanisms that have been described for NPCD and we will discuss those that are also relevant in other LSDs that accumulate lipids and show a neurological component, such as NPAD and GD. We will particularly focus on the activation of signaling pathways that may be common among these three pathologies.

We will discuss that in spite of the differences in the primary lipid storage, there is secondary accumulation of lipids and metabolites and activation of signaling pathways that can lead to common pathogenic mechanisms in these three LSDs. This analysis might help to delineate common pathogenic mechanisms to evaluate new therapeutic targets, considering that none of these diseases has a cure.

Therefore, this review is organized as follows: (I) NPCD, NPAD and GD, with particular emphasis on their pathological and biochemical characteristics including the type of lipids and metabolites that they accumulate; (II) Common pathogenic mechanisms for NPCD, NPAD and GD; including: lysosomal calcium homeostasis alterations, mitochondrial dysfunction, oxidative stress, endoplasmic reticulum (ER) stress, alterations in autophagy, neuroinflammation, neuronal death and c-Abl activation as a new cell death signaling pathway; (III) Relevance of understanding pathogenic mechanisms in LSDs for other diseases and (IV) Finally, we will discuss the current knowledge about therapies for NPCD, NPAD and GD.

### *1.1. Niemann Pick type C disease (NPCD, OMIM # 257220; ORPHA646)*

NPCD is caused by mutations in the *NPC1* or *NPC2* genes that encode lysosomal cholesterol transport proteins, which mediate free cholesterol efflux from this compartment (Fig. 1) [15–17]. As consequence, NPC1 or NPC2 deficient cells accumulate cholesterol in lysosomes (Fig. 2).

There is genetic evidence obtained from *NPC1* and *NPC2* single mutants as well as from the *NPC1-NPC2* double mutant mice indicating that NPC1 and NPC2 proteins participate in the same cholesterol processing pathway. For instance, mutations in either the *NPC1* or the *NPC2* genes lead to the same pattern of lipid accumulation and same clinical phenotypes [18]. Recently, the molecular mechanism by which the NPC1 and NPC2 proteins mediate the transport of cholesterol through the glycocalyx, which covers the luminal side of the lysosomal membrane, and through the lysosomal lipid bilayer was proposed based on results obtained in the yeast NPC vacuolar system (composed by NCR1 and NPC2). Winklet et al. proposed a cholesterol transport model in which sterols are transferred between hydrophobic pockets of vacuolar NPC2 and the membrane protein NCR1, which has its N-terminal domain (NTD) positioned to deliver a sterol to a tunnel connecting NTD to the luminal membrane. The sterol is caught inside this tunnel during transport, and a proton-relay network of charged residues in the transmembrane region is linked to this tunnel supporting a proton-driven transport mechanism. Cholesterol would ultimately exit at the sterol sensing domain (SSD) and dissociate into the lysosomal lipid bilayer [19].

The estimated frequency of this disease is 1:90,000 live births [20] and the central nervous system (CNS) and liver are the most affected tissues in NPC patients (reviewed in [21]). In the most common form of NPCD, patients exhibit progressive neurological defects. In the early period of childhood there is a delay in motor development, while in the

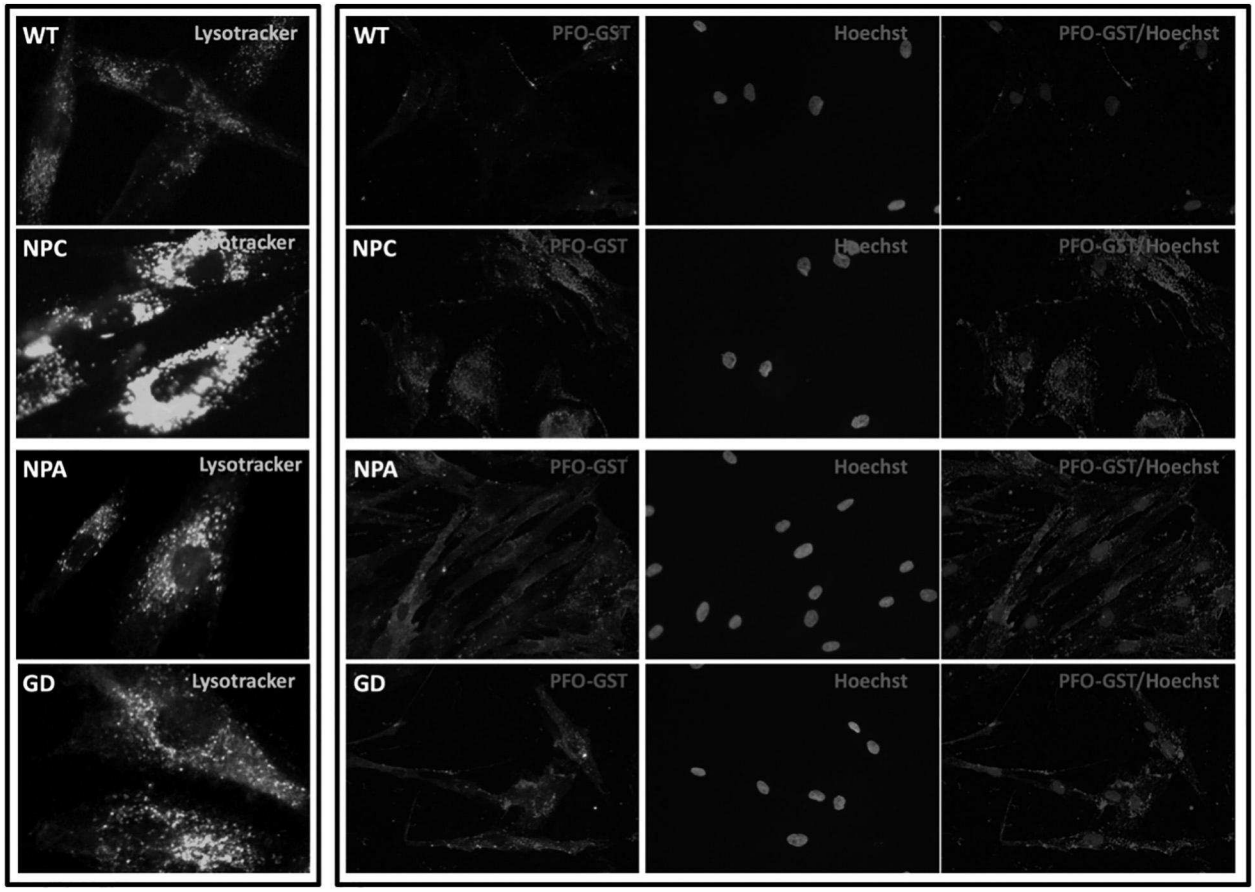


**Fig. 2.** Cholesterol and lysotracker levels are increased in fibroblasts from NPA, NPC and Gaucher patients.
WT (GM05659), NPC (V1165M), NPA (GM13205) and GD (GM00877) fibroblasts were obtained from Coriell repository. In WT, NPC, NPA and Gaucher patient firboblasts, cholesterol accumulation was evaluated by PFO inmmunofluorescence (red) and lysosomes and other acidic vesicles were stained using lysotracker (green). Hoechst was used to stain the nuclei.
Cellular cholesterol was stained with recombinant GST–PFO as follows: cells were fixed with 4% PFA for 15 min, permeabilized with 0.1% Triton X-100 for 5 min and blocked with 3% fat free BSA-PBS for 30 min at RT. Cells were incubated with 10 μg/ml of purified recombinant GST–PFO in blocking buffer for 1 h at RT. Then, cells were incubated with a primary GST-antibody (1:250; Abcam) in BSA-PBS for 1 h at RT, washed and then incubated with a secondary antibody labeled with Alexa Fluor-555 (1:2000; Invitrogen Detection Technologies) for 1 h at RT. After staining, coverslips were mounted in fluoromount G (Electron Microscopy Sciences) and visualized with an Olympus BX51 microscope (Olympus). Lysotracker, 75 nM for 30 min at 37 °C (LysoTracker Green DND-26, Thermo Fisher Scientific) and Hoechst 1:10000 (Thermo Fisher Scientific) detection was performed according to the manufacturer's instructions. As can be observed NPC, NPA and Gaucher fibroblasts accumulate cholesterol compared to wild type fibroblasts. NPC fibroblasts accumulate more cholesterol than NPA and GD, and lysosomes are more abundant in NPC, NPA and Gaucher fibroblasts than in WT fibroblasts. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

later childhood and juvenile periods the symptoms manifest as gait falls, clumsiness, cataplexy, and school problems. In some cases, there are also psychiatric disorders such as progressive dementia [22,23].

The historical gold standard method to confirm the diagnosis of NPCD after a complete physical exam, is the “filipin test”. This test is performed on cultured fibroblasts, which allows the visualization of unesterified cholesterol accumulated in the LE/L compartment [24]. Since the filipin test is very invasive and in some cases inconclusive [24], there have been substantial progress in the screening and diagnosis of NPCD in recent times. These diagnosis methods include the detection of plasma biomarkers. Among these biomarkers, oxyesterols have yielded the best results and are the most frequently used [25]. Oxyesterols are cholesterol oxidation products produced as result of the nonenzymatic oxidation of cholesterol by reactive oxygen species (ROS). Increased levels of 7-ketocholesterol (7-KC) and cholestane-3β,5α,6β-triol (3β,5α,6β-triol) were first reported in peripheral tissues from the NPC mice [26] and there is current evidence of increased oxysterols in plasma from NPC patients [27], supporting their use as biomarkers.

In recent years, the understanding of the disease and how it occurs at the cellular and molecular levels has grown exponentially, including discoveries on alterations in lysosomal calcium homeostasis, mitochondrial dysfunction, increased inflammation, oxidative stress and apoptosis, and decreased autophagy flux [28–30]. The relevance of these alterations in the pathogenesis of the disease will be discussed in detail later.

### *1.1.1. Lipid accumulation in NPCD*

The primary lipid that accumulates into lysosomes in NPCD is cholesterol. At late stages of disease progression the analysis of the liver lipidome revealed alterations in both storage and membrane lipids including cardiolipins, fatty acids, phosphatidylcholamines, phosphatidylglycerols, phosphatidylethanolamines, sphingomyelins (SMs), and triacylglycerols [31,32].

It is worth noting that subsets of NPC patients present low levels of cholesterol buildup and in contrast they accumulate sphingolipids and complex gangliosides in the CNS (Table 1) [33]. In the brain, neurons store significant amounts of glycolipids, particularly GM2 and GM3 gangliosides but no quantitative increase of cholesterol has been observed [34]. In NPCD, the accumulation of cholesterol is not a good

**Table 1**
Summary of the parameters and pathogenic mechanisms analyzed in NPCD, NPAD and GD in this review.

| Parameter | NPC | NPA | Gaucher |
|---|---|---|---|
| Mutated genes | *NPC1* (95%), *NPC2* (5%) | *SMPD1* | *GBA1* |
| Incidence | 1/90,000 [17] | 0.5–1/100,000 [38] | 1/75.000 [65] |
| Most susceptible brain area | Cerebellum (Purkinje neurons) | Cerebellum (Purkinje Neurons) | Cortex (cortical layer V) [86] |
| Stored lipids | Cholesterol, SM, sphingosine GM2 and gangliosides | SM, cholesterol, ceramide, GlcCer, GM2, GM3 gangliosides and sphingosine | GlcCer, GlcSph and cholesterol |
| Cause of death | Neurological symptoms [269] | Respiratory and bleeding complications [39] | CNS/and multi-organ failure [270] |
| $Ca^{+2}$ homeostasis | Increased SERCA in NPC fibroblast<br>Increased resting cytoplasmic $Ca^{2+}$<br>Decreased ER $Ca^{2+}$ [97] | Decreased levels SERCA and IP3R in cerebellum from NPA mice and<br>Reduced $Ca^{2+}$ uptake [95]<br>Increased $[Ca^{2+}]_I$ and PMCA activity in ASMKO-cultured neurons [94] | Increased $[Ca^{2+}]_I$ release in CBE treated-hippocampal neurons by RyRs [92] |
| Mitochondrial dysfunction | Decreased mitochondrial biogenesis in NPC mouse liver [103]<br>Increased mitochondrial cholesterol [112] | Decreased mitochondrial biogenesis and function in NPA patients cells and mouse liver [103] | Mitochondrial dysfunction in patient fibroblast [121].<br>Altered mitochondrial morphology and decreased ATP production in mouse cortical neurons [123] |
| Oxidative stress | Increased ROS in NPC cells models [127].<br>Decreased antioxidant defense in patients plasma [124] | Increased ROS in brain of patient and mice brain [94] | Increased ROS in human fibroblast and plasma [125,126] |
| ER-Stress | Activated ERAD in human fibroblast [131] | Undetermined | Undetermined |
| UPR in patient cells | Probably [30,132] | Not studied yet | Yes [30] |
| Autophagy defects | Block in autophagic flux in NPC1 mouse [142] | Block in autophagic flux in human fibroblast and cerebellum from NPA mouse [144] | Block in autophagic flux in neurons from GD mouse model [148,149] |
| Neuro-inflammation | Increased microglial activation in mouse cerebellum [163] | Astrogliosis in cortex and cerebellum from NPA patients and mice [165] | Astrocytosis and microglial proliferation in GBA KO mouse [167] |
| Apoptosis | Increased in cerebellum and cells [128,214] | Increased caspase signaling in mice cerebellum [144] | Undetermined |
| Necroptosis | Inhibition of necroptosis prevent cell loss in mouse [188] | Not studied yet | Increased RIP3 in mice brain [176] |
| c-Abl activation | Activated in neurons from NPC mice [214] (Figs. 3 and 4) | Activated in human fibroblast (Fig. 3 and 4) | Activated in human fibroblast (Figs. 3 and 4) |

predictor or does not show a good correlation with the severity and neurological compromise of patients; however, there is a correlation between the accumulation of GM and the severity of the disease [34]. Nevertheless, therapies aimed at lowering accumulated cholesterol levels such as HPβCD have shown great benefits, suggesting that the main offending metabolite is cholesterol [35].

### *1.2. Acid sphingomyelinase deficiency (ASMD, OMIM # 257200; ORPHA77292)*

Acid sphingomyelinase deficiency (ASMD) is a rare lysosomal storage disorder that involves the dysfunctional metabolism of sphingolipids. The phenotypic variability of ASMD has led to the categorization of subtypes based on severity and on the degree of neurological involvement [36]:

- Infantile neurovisceral ASMD, also known as Niemann Pick type A disease (NPAD), is the most severe form of ASMD and is characterized by early neurodegeneration, an aspect of special interest in this review. For this reason, in this review we will mainly refer to this ASMD as NPAD, so that it can be more easily identified.
- Chronic neurovisceral ASMD, also known as the intermediate form, NPD A/B or NPD B variant. It is characterized by slower progression of neurological symptoms. Progressive multisystem disease manifestations are similar or more severe than those observed in chronic visceral ASMD.
- Chronic visceral ASMD, also known as NPBD, is characterized by slow but progressive manifestations of multisystem disease without neurodegeneration.

About 97% of the mutations in the *SMPD1* gene, which encodes the acid sphingomyelinase (ASM) enzyme, correspond to the most common mutations fsP330 (frameshift mutation), L302P, and R496L [36,37]. ASMD is an inherited autosomal recessive disorder with an incidence of 0.5 to 1 per 100,000 births [38]. However, ASMD is more frequent among individuals of Ashkenazi Jewish ancestry than in the general population, presenting a carrier frequency of approximately 1 in 90.

NPA patients present developmental delay, hepatosplenomegaly and progressive neurodegeneration (Table 1); while NPB patients exhibit hepatosplenomegaly without neurological defects. NPA patients have normal neonatal development with hepatosplenomegaly as one of the first symptoms. Developmental age does not progress beyond 10 months for adaptive behavior and motor skills and 12 months for expressive language. Respiratory failure and bleeding complications are the most important causes of death [39]. As consequence, NPAD leads to death typically between the ages of 2 and 3, while NPB patients usually live into adulthood.

The standard confirmatory diagnostic procedure for NPAD and NPBD is the ASM enzyme activity assay in cells such as circulating leukocytes or cultured skin fibroblasts [40]. To confirm diagnosis the *SMPD1* gene can be sequenced or the presence of vacuolated cells in peripheral blood or bone marrow can be evaluated. Because there are several diseases that share signs and symptoms, such as NPAD, NPBD, NPCD and Gaucher disease, chemical and/or genetic testing is necessary for differential diagnosis. However, in despite of diagnosis, ASM activity assays are not adequate to precisely predict the onset and degree of brain involvement in NPA patients.

#### *1.2.1. Lipid accumulation in NPAD*

ASM hydrolyzes SM to ceramide and phosphocholine, therefore low or null ASM activity causes abnormal accumulation of SM in lysosomes [41] (Fig. 1). In a very interesting parallel, NPA cells do not only accumulate the primary storage lipid SM, but also cholesterol (Fig. 2) and other lipids, such as glucocerebroside, GM2 and GM3 gangliosides and sphingosine as secondary storage lipids [22,42,43]. SM is the most abundant sphingolipid in the cell and together with cholesterol are

essential elements of the plasma membrane (PM). SM has a ubiquitous distribution within mammalian tissues and is present at particularly high levels in the CNS [44]. It has been described that SM and cholesterol interact in rich-membrane rafts domains, which are relevant for sorting and signaling [45,46]. Because of this, membrane rafts are reorganized into larger “platforms” [47,48] which has deep effects on the biophysical properties of membrane bilayers, such as fluidity and stiffness, as well as on cellular signaling [49,50]. The activity and levels of enzymes related to SM metabolism affect not only the PM but also the lysosomal membrane, and they may directly influence the coalescence of microdomains required for lysosomal signaling [51]. In addition, under stress conditions, including irradiation, conjugation of cell surface receptors, heat shock, exposure of cells to bacterial pathogens and others [52,53] ASM translocates rapidly from lysosomes to the outer leaflet of the PM where it can also hydrolyze sphingomyelin into ceramide [54]. In most cases ASM translocation and ceramide generation signal lead to apoptosis or cell senescence.

Given their importance in cell function SM and cholesterol levels are tightly regulated. It has been described that SM accumulation also generates cholesterol accumulation [55]. Furthermore, cholesterol depletion reduces SM accumulation in NPA/B cells [56]. Interestingly, NPC cells, which accumulate cholesterol within lysosomes, show a dramatic decrease in ASM activity, although these cells contain a normal *ASM* gene [57,58]. These data strongly suggest connections between ASM activity, SM and cholesterol accumulation in NPA/B and in NPC cells indicating that both diseases might be related and could share pathogenic signaling pathways.

Ceramide is a sphingolipid that has been implicated in neuronal death [59]. SM is a major source of ceramide, both in lysosomes and at the PM. While it might be hypothesized that defective ASM activity in ASMD results in depleted ceramide, surprisingly, *ASM* knockout (ASMKO) mice have elevated levels of ceramide in their tissues [60]. This is likely due to the breakdown of accumulated sphingomyelin by other sphingomyelinases present in nonlysosomal compartments. Moreover, abnormalities in the downstream products of ceramide hydrolysis, sphingosine and sphingosine-1-phosphate, are also elevated in ASMKO mouse tissues [60]. These potent signaling lipids may be contributing to the disease pathogenesis as well.

### 1.3. Gaucher disease (GD, OMIM #230800, ORPHA355)

Gaucher disease is the second most prevalent LSD in world's population and is caused by an autosomal recessive defect in the gene encoding β-glucocerebroside 1 (*GBA1*), an enzyme responsible for the breakdown of the cellular glycolipids: glucosylceramide (GlcCer) and glucosylsphingosine (GlcSph) [61], or, more rarely, its activator, saposin C [62]. The deficiency of this enzyme leads to the accumulation of GSLs in lysosomes and a wide spectrum of phenotypic manifestations in Gaucher patients (Table 1) [63].

Deficiency of the enzyme leads to the accumulation of GlcCer and GlcSph in the lysosomes of macrophages and other cell types, primarily in the spleen, liver, bone marrow and osteoclasts; less often in lungs, skin, kidney, conjunctivae, heart; and in the brain, in some forms of the disease (Table 1).

The risk for developing GD and other LDSs increases with consanguinity in the family. Its frequency differs in different populations, being most prevalent in individuals of Ashkenazi Jewish descent (1:450 live births) [64] and an approximate incidence of 1:75,000 live births worldwide [65].

Although the genetic cause of the disease and its consequences leading to GlcCer accumulation in cells has been well described, little is known about the downstream biochemical changes that occur resulting in cell and tissue dysfunction. These changes are even less known in the forms of the disease that affect the CNS and particularly in neurons.

GD is characterized by various degrees of nervous system involvement depending on the severity of the particular *GBA1* mutation and other unknown factors [66]. Three major forms of GD have been clinically described. The most prevalent is the so-called non-neuronopathic form (type 1), characterized by anemia, thrombocytopenia, enlargement of the spleen, skeletal abnormalities [67], and in a small number of patients, by lung involvement with interstitial lung disease [67] and pulmonary hypertension [68]. Type 1 is essentially a macrophage disorder, lacking of primary central nervous system involvement. Type 2 GD is an acute neuronopathic form with severe prognosis and survival limited to the first two to three years of life; it is characterized by neurological impairment in addition to visceral symptoms. The neurological symptoms start with oculomotor abnormalities followed by brainstem involvement. Type 3 GD is also characterized by neurological involvement but the neurological symptoms generally appear later in life than in type 2 disease, and include abnormal eye movements, ataxia, seizures, and dementia, with patients surviving until their third or fourth decade [69].

Interestingly, *GBA1* mutations are also the most frequent genetic risk factor for Parkinson's disease (PD) [70,71] and decreased GBA enzyme activity is linked to α-synuclein accumulation and PD pathogenesis [72,73]. In this review we will give particular attention to the pathogenic mechanisms involved in neuronal death in GD type 2, as we describe below. We will refer to GD type 2 as GD.

#### 1.3.1. Lipid accumulation in GD

It is unknown what determines the severity of GD and the development of the different forms, 1, 2 or 3. More than 200 different mutations have been identified in the *GBA1* gene with no major correlation between genotype and phenotype [74]. Prediction of the clinical course of the disease cannot usually be made on the basis of mutational analysis, with some patients sharing the same mutation being severely affected while others are asymptomatic [75]. It has been suggested that modifier genes play a major role in disease severity [76]. Although many years have passed since GD was first described, little is known about the molecular mechanisms leading from GlcCer accumulation to neurodegeneration and/or neuronal cell death.

GlcCer and its deacylated form, psychosine (d-glucosyl-β1-1′-d-erythro-sphingosine; glucosylsphingosine), accumulate in the brain of Gaucher patients in both neuronal forms [77] and in neuronopathic Gaucher disease (nGD) mice [78]. It has been suggested that psychosine accumulation is the primary event leading to brain pathology in nGD [77,79] but a systematic evaluation of the contribution of psychosine and GlcCer to the initiation of pathological changes in neuronopathic Gaucher brain has not been performed. GlcCer storage in the brain was reported to occur mainly in perivascular macrophages, and GlcCer storage within neurons has been considered rare [80]. While the pathology encountered in GD has been attributed to GlcCer storage, GlcSph, a cytotoxic compound, also accumulates in the tissues. Elevations of brain GlcSph have been reported in patients with types 2 and 3 GD [81]. These findings suggest that the accumulation of GlcSph may also be responsible for the rapid demise of mice with nGD and the devastating clinical course seen in patients with nGD. GM3 ganglioside is also typically increased in liver and spleen in type 1 GD [82]. Gaucher patients show total and free cholesterol levels between 65 and 70% higher than normal. Interestingly, this increase in intracellular cholesterol correlates with increased GBA processing through endoplasmic reticulum-associated degradation (ERAD) in proteasomes, an activity associated with disease severity [83]. Here, we show that fibroblasts from Gaucher patients accumulate cholesterol (Fig. 2).

Recently, the progression of the neuropathology was described in a neuronopathic Gaucher mouse model (the $Gba^{flox/flox}$; nestin-Cre mouse) [84]. The most consistent neuropathological finding in nGD is the periadventitial accumulation of Gaucher cells (enlarged macrophages containing undigested glucocerebroside) along with neuronal loss and astrogliosis [85]. The areas most consistently affected are cerebral cortical layers 3 and 5 and hippocampal CA2–4. Interestingly, adjacent regions, including hippocampal CA1, do not show pathological

changes, highlighting the specificity in the vulnerability of neurons [86].

Consistent with the pathology in the human neuronopathic Gaucher brain, cortical layer V is severely affected in neuronopathic Gaucher mice, with the motor and somatosensory cortex being more affected than caudal cortical regions, such as the visual cortex. Gaucher patients show selective loss of pyramidal neurons in CA2–CA4, but not in the CA1 regions of the hippocampus [86]. A similar pattern was observed in neuronopathic Gaucher mice with respect to microglial activation, although this event occurred late in disease progression and was not as pronounced as in other brain areas. Substantia nigra and red nucleus pathology were observed in both human and in mouse neuronopathic Gaucher brains [86].

## 2. Common pathogenic mechanisms for Niemann-Pick type C and A and Gaucher diseases

Several pieces of evidence suggest that NPCD, NPAD and GD may share pathogenic mechanisms, including: i) as previously shown, cells accumulate similar lipids in the lysosomes. In NPAD and GD, there is accumulation of secondary lipids, such as the GSLs GM2 and GM3 and cholesterol [10,16,29,30,32–35,87,88], which are unrelated to the primary genetic defect. Cholesterol storage in these diseases is probably related to strong interaction among these lipids in cholesterol rich-membrane domains [37,38,89]. Moreover, in NPCD, there is also secondary GM2, GM3 and SM accumulation [10,18,35,36,39]. In actuality, these diseases can be classified as sphingolipidosis. Although NPCD is not caused by a degradative enzyme deficiency and therefore is not strictly a sphingolipidosis, it can be classified within this group because it accumulates, secondarily to cholesterol, large amounts of SM; ii) The three diseases show alterations in lysosomal calcium homeostasis, mitochondrial dysfunction, increased inflammation and oxidative stress and decreased autophagy flux [10,41–43] (Table 1). These antecedents suggest that lysosomal accumulation of lipids leads to lysosomal dysfunction and similar cellular responses to this insult (Fig. 2).

Compounds that accumulate in lysosomal storage diseases can affect signal transduction pathways at different levels. Storage compounds can function as receptor ligands, modify receptor response (NPCD), alter subcellular localization of receptors (NPCD) and the activity of enzymes involved in signal transduction cascades (NPA and GD). Since it may be difficult for the non-specialist reader to distinguish between the various diseases, which we address repeatedly in different sections of this review, we have summarized their main features in Table 1. It is important to mention that although there are several common pathogenic mechanisms, there are also processes that are triggered differentially such as necroptosis in GD, as we will describe below.

### 2.1. Calcium homeostasis alterations

Calcium homeostasis is important hallmarks of LSDs. The lysosome is an important calcium reservoir [90], which can modulate normal trafficking, recycling and vesicular fusion events [91]. Alterations in calcium homeostasis have been described in GD [92], NPCD [93] and NPAD [94,95] and could be a common pathological mechanism in LSDs that may cause neurodegeneration [96].

In cerebellum from NPA mice, reduced expression of the sarco/endoplasmic reticulum $Ca^{+2}$ ATPase (SERCA), which captures calcium from the cytosol, and of the inositol 1,4,5-triphosphate receptor (IP3R), decreases rates of calcium uptake [95]. On the contrary, increased SERCA expression, elevated resting cytoplasmic $Ca^{2+}$ levels and decreased ER $Ca^{2+}$ were reported in NPC fibroblasts [97]. In both publications, the alterations in calcium homeostasis are mainly attributed to changes in the expression of key proteins involved in calcium management, such as SERCA. In NPCD, a direct effect of lipid accumulation on the expression of these proteins has not been addressed. In contrast, data published by Pérez-Cañamás et al., show that excessive SM accumulation at the neuronal plasma membrane decreases the activity of the plasma membrane calcium ATPase (PMCA) leading to increased intracellular calcium levels in NPA cells [94]. Similarly, in cellular models of GD, defective $Ca^{2+}$ homeostasis (large increase in $[Ca^{2+}]i$ release) was associated with the interaction of glucosylceramide, the primary storage lipid, with proteins involved in regulating $Ca^{2+}$ homeostasis [92]. In hippocampal neurons treated with Conduritol B Epoxide (CBE), a chemical inhibitor of GlcCerase that induces the GD phenotype and therefore the accumulation of glucosylceramide (GlcCer), $Ca^{2+}$ release from ryanodine-sensitive intracellular stores was stimulated. As a result the treated neurons are more sensitive to the neurotoxic effects of high concentrations of glutamate [92]. Moreover, enhanced $Ca^{+2}$ release was later reported in microsomes isolated from Gaucher type 1, type 2 and type 3 patient's brains, and enhanced $Ca^{+2}$ release correlates with the increased levels of GlcCer in brain tissue [98].

Different alterations of calcium homeostasis have been demonstrated in the three different lysosomal disease models. Moreover, in all of them, the rescue or prevention of alterations in calcium homeostasis decreases cell death. For example, restoring calcium homeostasis prevented oxidative stress and neurodegeneration in a NPA mouse model [94]. Furthermore, treatment with thapsigargin, a non-competitive inhibitor of SERCA, elevated cytosolic calcium and corrected the NPC cellular phenotype, including GSLs and cholesterol accumulation in NPC1 CHO cells and increased survival of the NPC1 mice [99]. In GD neurons glutamate-induced toxicity was blocked by pre-incubation with ryanodine, suggesting that $Ca^{+2}$ release from ryanodine-sensitive intracellular stores can induce neuronal cell death [92].

The evidence described above show that alterations in intracellular calcium concentrations are relevant in the etiology of NPAD, NPCD and GD. In this regard, it is important to consider that impaired calcium homeostasis leads to ER stress, oxidative stress, and cell death.

### 2.2. Mitochondrial dysfunction

Mitochondrial function is particularly important in tissues with high energy demand, such as the brain [100], and more specifically in neurons, because of their dependency on oxidative phosphorylation for energy supply [101]. Given their central role in cellular homeostasis, mitochondrial dysfunction has been linked to many neurodegenerative diseases [102], including many LSDs, such as NPAD, NPCD [103] and GD [104].

Although membrane contact sites (MCS) between ER and mitochondria have been well studied and characterized in different contexts, emerging evidence indicates that lysosomes also exhibit close proximity with mitochondria [105]. While some findings suggest that the *endo*-lysosome compartment (LE/Lys) can regulate mitochondrial function [106,107], there is also evidence that mitochondrial respiration regulates the biogenesis and function of the LE/Lys compartment [108]. Therefore, alterations in lysosomal function are expected to have an impact on mitochondrial function and vice versa.

A study that evaluated the expression of more than 1000 mitochondrial homeostasis related genes found that a subgroup of mitochondrial biogenesis and respiratory chain subunit genes are downregulated in brain and liver of symptomatic NPC1 KO mice [103]. Similar to these findings, there is a decrease in the expression of mitochondrial biogenesis and function-associated genes in NPA patient fibroblasts and NPA mouse liver [103]. Moreover, cells from NPA and NPC patients and from NPA and NPC mouse models show accumulation of dysfunctional mitochondria in the cytoplasm, decreased mitochondrial respiratory activity and increased superoxide levels. Moreover, there is activation of the transcription Krüppel-like Factor 2 (KLF2) and ETS translocation variant 1 (ETV1), both identified as transcriptional repressors of mitochondrial biogenesis. Interestingly, the defects in mitochondrial biogenesis and function in these cells were rescued by silencing KLF2 or ETV1 [103], suggesting that both transcription

factors are relevant in the mitochondria–lysosome crosstalk.

In NPC cells, alterations in mitochondrial function have been associated with increased cholesterol in the mitochondrial membrane [28,109,110]. However, NPA cells do not seem to have increased mitochondrial cholesterol [28]. Therefore, even though cholesterol is the cause of mitochondrial dysfunction in NPC cells, the cause of mitochondrial disorders in NPA cells has not been well established and seems to be a consequence of lipid accumulation and lysosomal dysfunction.

Increased mitochondrial cholesterol can lead to mitochondrial dysfunction, including reduced fluidity of mitochondrial membranes [111], reduced ATP generation [112,113], and decreased mitochondrial glutathione (mGSH) import [114,115]. A candidate for mediating mitochondrial cholesterol trafficking in NPC cells is StARD3, also known as MLN64. Interestingly, there is increased StARD3 expression in NPC1 cells and its overexpression in hepatocytes increases mitochondrial cholesterol and impairs mitochondrial function [109]. Along with StARD3, NPC2 has been shown to contribute to transport of endosomal cholesterol to the mitochondria [116]. In this regard, it is conceivable that the increased mitochondrial cholesterol observed in NPC1 deficient cells could result from the action of StARD3 and NPC2, since their expression are induced in these cells [109,117]. In agreement with this model, the presence of StARD3 dependent lysosome-mitochondria membrane contact sites (MCSs) was recently shown in cells depleted of NPC1 [118], indicating that the deleterious effects mediated by StARD3 are probably specific for NPC cells.

Whether cholesterol levels, other lipids or MCSs have a significant impact on others LSDs remains to be established. Therefore, dissecting the intricate communication between mitochondria and lysosomes may be critical not only for understanding essential physiological processes but also for uncovering the impact of mitochondrial dysfunction in the development of LSDs.

On the other hand, no alterations have been shown in the cholesterol content in the mitochondria in GD. However, alterations in mitophagy have been reported [29], as in NPA and NPC cells [103,119,120]. Similarly to NPC neurons, which show mitochondrial dysfunction, loss of GBA activity in a dopaminergic cell line results in loss of mitochondrial function [121]. Mitochondrial dysfunction has also been reported to occur in fibroblasts from Gaucher patients and in Gaucher mouse models [122]. The analysis of mitochondrial morphology in cortical neural cells from the Gaucher mouse model revealed disruption of mitochondrial cristae and the presence of numerous larger-sized mitochondria with significant reductions of ATP production and oxygen consumption [123]. Whether these findings are the result of alterations in mitophagy or/and mitochondrial dynamics remains to be determined.

Therefore, all the mitochondrial alterations that have been reported in NPCD, NPAD and GD may contribute, together with the lysosomal dysfunction, to the pathogenesis of these diseases. Understanding these mechanisms may provide us with an opportunity to search for new treatments. It remains to be elucidated whether strategies aimed at improving mitochondrial function could have a significant impact on the pathology of LSDs. More studies are required to understand the communication between mitochondria and lysosomes to unravel the impact of mitochondrial dysfunction on the development of human pathologies, including neurodegenerative diseases and other LSDs.

### *2.3. LSD-mediated oxidative stress and endoplasmic reticulum stress*

There are several studies that show the involvement of oxidative stress in the pathophysiology of LSDs, including NPCD, NPAD and GD. Moreover, the presence of oxidative stress markers has been found in samples from patients. For example, there are increased levels of cholesterol oxidation products in the plasma of NPC patients [27]. They present reduced Coenzyme Q10 and decreased Trolox equivalents, which indicate a decline in antioxidant defenses [124]. Deposits of autofluorescent material indicative of lipofuscin-like aggregates that form due to oxidation of proteins and ROS accumulation, have been described in brains of a NPA patient [94]. Several studies suggest that redox impairment may play a role in the pathogenesis of GD [121,125,126]. The deficiency of the GBA enzyme in cultured human fibroblasts increases the amount of ROS [126]. Its deficiency in the plasma of patients alters the activity of the antioxidant enzymes catalase and superoxide dismutase in erythrocytes [125].

There is increasing evidence indicating the presence of oxidative damage in NPC neurons. Moreover, data connecting oxidative damage with fibrosis and apoptosis in the liver of NPC mice support the possibility that oxidative damage may induce these pathways in NPCD (reviewed in detail in [127]). Furthermore, there are abundant autofluorescent lipofuscin aggregates in the hippocampus of 4-months-old ASMKO mice. In these mice, there is also a two-fold increase in dihydrorhodamine (DHR) staining levels (which measures ROS levels), compared with WT mice [94].

In previous work from our laboratory we reported that oxidative stress activates apoptosis in NPC cells [128] and that an α-tocopherol (α-TOH) rich diet delayed weight loss, improved coordination and locomotor function and increased the survival of NPC mice. Moreover, we found preserved Purkinje neurons and reduced levels of astrogliosis, nitrotyrosine and apoptotic signaling mediated by the c-Abl/p73 pathway in the cerebelum [129]. This observation is particularly relevant because oxidative stress is a potent activator of the c-Abl/p73 proapoptotic pathway [130]. Because oxidative damage is common among cellular models, animal models and patients of several LSDs, it may have a relevant role in the pathogenesis and progression of these diseases. Considering that antioxidant therapies have mild side effects and are easy to administrate, they could be a good strategy to complement other LSDs therapies.

However, the source of oxidative stress remains unclear. The evidence suggests that lipid accumulation [94] and/or mitochondrial dysfunction could play an important role in ROS generation [127]. Studying the mechanisms that promote oxidative stress will provide important information for understanding the pathophysiology of these lysosomal disorders.

In the case of ER stress, it has not always been observed in LSDs. ER stress has not been described in NPAD but has been studied in NPCD and GD. ER-associated degradation (ERAD) is activated in NPC patient cells [131]. However, in different NPC mouse models there is lack of activation of the unfolded protein response (UPR) [132]. In addition, fibroblasts from NPC1-I1061T patients that do not induce the expression of heat shock proteins after a misfolding condition [133], show ER-stress. In GD, the Gba-Nestin Cre mouse model also lacks ER stress [133]. Therefore, it seems that the accumulation of cholesterol and GlcCer per se are not sufficient for triggering ER-stress. However, this condition sensitizes GD and NPC patient cells to induction upon suffering from other stresses. There are other studies suggesting that GBA-mediated ER stress contributes to the development of Parkinsonism. Normally, GBA is produced in the rough ER, processed in the Golgi apparatus and then transported to the lysosome, where it fulfills its function. Mutant GBA, like other misfolded proteins, is subjected to refolding by the ER repair machinery. When the amount of mutant forms of GBA exceeds the ER capacity, the UPR is activated triggering the fragmentation of these misfolded proteins in the Golgi [134]. Upon UPR activation GBA expression is upregulated worsening ER stress [135]. Similar effects are observed with the protein NPC1 in NPCD [136].

As previously mentioned, MCS between ER and mitochondria have been well studied and characterized in different contexts. However, emerging evidence indicate [119,120] that lysosomes also exhibit close proximity with the ER, which translates into mutual functional regulation. This interaction is mediated by an important class of cholesterol carriers called oxysterol binding protein (OSBP) and its anchor at the endoplasmic reticulum (ER). Two of these proteins, VAPA and

VAPB, which are in the membrane of both organelles, allow the regulation of key processes such as autophagy [137]. OSBP was recently proposed to function at contact sites between the ER and endolysosomes [138,139]. Quality control pathways involving the lysosome and ER in NPAD and NPCD remain to be studied. The mechanisms that degrade misfolded transmembrane proteins in the ER and how the manipulation of these quality control pathways may lead to the identification of novel targets for disease-modifying therapies need further research.

### 2.4. Dysfunction of the autophagy-lysosomal pathway

A considerable body of evidence suggests that lysosomal storage in several LSDs impairs autophagy, which is critical for neuronal survival [140]. This impairment results in accumulation of undegraded proteins and dysfunctional organelles causing autophagic stress and triggering autophagic cell death [13,141]. Actually, autophagosomes accumulation has been described in the three sphingolipidoses of our interest. In NPC1 mutant cells the accumulation of autophagosomes seems to be due to a block in autophagic flux and impaired maturation or degradation, associated with defective amphisome formation caused by failure in the SNARE machinery [142]. Furthermore, sphingosine has been suggested as the primary metabolite that triggers autophagy alterations in NPCD [93]. On the other hand, deficiency of ASM impairs autophagosome-lysosome fusion and autophagy progress in NPAD [143]. However, it has also been shown that autophagosomes accumulation in this pathology could be due to inefficient autophago–lysosomal clearance and lysosomal membrane permeabilization leading to cytosolic release of Cathepsin B [144], without affecting autophagosome-lysosome fusion events [145]. In fact, stabilization of the lysosomal membrane has been tested with promising results in both NPCD [146] and NPAD [147]. Also, neurons from Gaucher mouse models that present neuropathology and iPSc from Gaucher patients, show defective autophagic clearance and accumulation of undegraded proteins [148,149]. Accordingly, in CBE treated mice, a pharmacologic Gaucher mouse model that shows neuropathology, there is accumulation of the autophagosome marker p62/SQSTM1 in neurons and astrocytes, along with other ubiquitinated proteins and insoluble alpha-synuclein [150].

Transcriptional regulation of autophagy occurs via TFEB, which drives the expression of genes related to autophagy and lysosomal biogenesis. This transcription factor is susceptible of regulation upstream of the autophagy machinery by both mammalian target of rapamycin (mTOR)-dependent and mTOR-independent signaling pathways [151]. A recent study showed that lysosomal ASM is an important functional determinant of the lysosomal nutrient-sensing complex (LYNUS), a lysosomal membrane-anchored multiprotein complex that includes mTOR and TFEB, which suggests that ASM is an important regulator of autophagy in NPAD [51]. Interestingly, as mentioned before NPC cells show a dramatic decrease in ASM activity, although these cells contain a normal *ASM* gene [57,58]. This could also contribute to the autophagy alterations in NPCD.

Additionally, Gaucher neurons exhibit reduced TFEB levels and stability that results in lysosomal depletion, and a block of autophagic flux due to defective lysosomal clearance of autophagosomes [152]. Furthermore, Gaucher neurons show increased levels of phospho-mTOR and phosphorylated mTORC1 downstream targets, the ribosomal protein S6 (RPS6) and the eukaryotic initiation factor 4E-binding protein 1 (4EBP1), both indicative of mTOR hyperactivation [153]. However, the mechanisms by which GBA loss of function mediates TFEB dysfunction remain unknown. Other publications have documented impaired mitophagy and/or autophagy in iPSCs derived from fibroblasts of Gaucher patients [154]. Furthermore, the GBA L444P/WT knock-in mice, a PD associated GBA mutation, results in disruption of mitophagy, through impaired autophagy and mitochondrial priming [155].

As mentioned, autophagy is a very important process in cell homeostasis and is altered in NPCD, NPAD and GD but also in neurodegenerative diseases, such as Alzheimer's disease (AD), PD and Huntington's disease (HD), emerging as an interesting therapeutic target. Indeed, because TFEB is a central node in defining the autophagy activation status, understanding the basis of TFEB dysfunction provide an exciting opportunity for the development of treatments with broad applications in neurodegeneration. However, the results obtained so far are controversial. The induction of autophagy with rapamycin increases cholesterol buildup in human skin NPC cells, while its inhibition decreased cholesterol accumulation, indicating that autophagy is an important source of stored cholesterol in NPC lysosomes [119]. In addition, the autophagy inhibitor 3-methyladenine can rescue NPC-induced mitochondrial fragmentation in human NPC neurons [156], suggesting that inhibition of autophagy could be a therapeutic option for NPCD. However, Calderon et al. demonstrated that rapamycin has opposite effects on the survival of NPC mice depending on the genetic background [157]. In favor of a beneficial effect, rapamycin was able to rescue autophagic flux and improve cell viability in several NPC cells, including mutant *Npc1* MEFs, *Npc1* $^{-/-}$ mouse neurons and NPC1 patient iPSC-derived neuronal and hepatic cells [158]. There is more evidence supporting that the induction of autophagy is a good therapeutic target in NPC cells. Indeed, the activation of TFEB by AKT inhibition using trehalose rescues autophagic flux and improves cell viability in NPC1 patient-specific iPSC-derived neurons. Moreover, activation of TFEB by Carbamazepine, Lithium or BRD2716 was also able to rescue autophagic flux and improve cell viability in different NPC cells [159]. Finally, lysosomal alterations affect not only autophagy but also other lysosomal related processes such as exocytosis. It has been described that lysosomal exocytosis is defective in multiple LSDs [160]. Most intriguingly, induction of lysosomal exocytosis was found to facilitate the clearance of stored materials regardless of the nature and cause of the storage [2,161]. Because lipid storage is the primary cause of lysosomal dysfunction, pharmacological and genetic manipulations that could clear the accumulated materials can potentially serve as novel therapeutic approaches for LSDs. Furthermore, since TFEB overexpression increases lysosomal exocytosis, manipulating the expression and activity of this transcription factor provides an interesting opportunity for the clearance of lysosomal lipid storage [162].

### 2.5. Neuroinflammation

Neuroinflammation could play an important role in the lysosomal diseases discussed in this review, but the initial events that trigger the inflammatory response and the mechanisms driving the sustained chronic neuroinflammation are not completely understood. However, recent findings in pre-symptomatic NPC mice cerebella showed activated interferon downstream signaling that involves both IFN-γ- and IFN-α-responsive genes, increased microglial activation, anti-viral response, T-lymphocyte activation and expression of chemotaxis pathway genes [163]. Microglial activation and astrogliosis begin in 2 and 4-week-old NPC mice respectively, long before the symptoms appear [164]. Interestingly, astrogliosis has also been described in the cortex and cerebellum from NPA patients and ASMKO mice. Moreover, NPA patients and ASMKO mice show amoeboid microglia in neurodegeneration-prone areas [165] while NPC astrocytes exhibit morphological changes and become activated in NPCD [166]. Similarly, astrocytosis and microglial proliferation associated with substrate accumulation and severe early neuronal loss, reminiscent of nGD, has been shown in GBA knockout mouse models. The levels of IL-1β, TNFα, TNFα receptor, MCSF, and TGFβ mRNA increase up to 30-fold with disease progression. The most significant elevation was detected for chemokines CCL2, CCL3 and CCL5. These results suggest a cytotoxic role for activated microglia in neuronopathic GD [167].

Studies from our laboratory show that NPC astrocytes exhibit decreased gap junctional communication (GJC) and augmented hemichannel (HC) activity [168]. Interestingly, increasing evidence

indicates that under pro-inflammatory conditions, astrocytes exhibit decreased GJC-mediated intercellular communication and increased HC activity [169] maintaining the pro-inflammatory state. Interestingly, the rescue of NPC expression in astrocytes delays neuronal loss and prolongs the lifespan of NPC mice [170]. These results suggest a central role for lipid accumulation in astrogliosis.

However, the importance of neuroinflamation is controversial because the reduction of complement system mediated inflammation in NPC mice does not decrease neuronal death [171]. Moreover, treating NPC mutant mice with anti-inflammatory drugs only slightly increases survival rate and reduces microglial activation [172]. In contrast, treatment with non-steroidal anti-inflammatory drugs (NSAIDs), in combination with miglustat and the antioxidant curcumin, reduce microglial activation and Purkinje cell death, effectively extending NPC mice survival [173]. Although the benefits of such treatments can also be attributed to their antioxidant properties, the effects of the anti-inflammatory drugs cannot be ignored. Moreover, a 10-week treatment with HPβCD, also reduced CD68 (microglia/macrophage) and GFAP (astrocyte) expression in the brain and improved the survival of NPC mutant mice [174]. However, in vivo microglia ablation worsens disease progression in the ASMKO mice, suggesting the coexistence of different microglia phenotypes in NPA brains that produce cytokines or counteract neuronal death by clearing myelin debris. Indeed, overloading microglial lysosomes with myelin debris and SM induces lysosomal damage promoting neuronal death [165].

Accordingly, the ablation of interferon receptor type I or TNF-α has no effect on Gaucher mouse viability [175,176], and Ibuprofen treatment of the Nestin-Cre Gaucher mouse model does not exert phenotypic improvements in the mice [167]. Furthermore, the activation of complement C5a and C5a receptor 1 (C5aR1) controls systemic GlcCer accumulation and the inflammatory response in the peripheric organs in GD type 1 [177]. Marked local and systemic complement activation take place in GBA-deficient mice or after pharmacological inhibition of GBA in mice. This complement activation has been associated with GlcCer storage, tissue inflammation and proinflammatory cytokine production [177]. In mice and humans, GBA deficiency has been associated with complement-activating GlcCer-specific IgG autoantibodies, leading to complement activation and C5a generation. The subsequent activation of C5aR1 controls UDP-glucose ceramide glucosyltransferase production, altering the balance between GlcCer formation and degradation [177]. Thus, extensive GlcCer storage in GD peripheric organs generates a vicious cycle that fuels cellular GlcCer accumulation by inducing complement-activating IgG autoantibodies and C5aR1 activation that promotes innate and adaptive immune cell recruitment and activation. It has not been yet established if the same process occurs in the brain.

Altogether, neuroinflammation is a common characteristic of the sphingolipidoses of our interest. Initially, microglial activation can be a protective process against a noxious stimulus, however when the stimulus persists it can become deleterious and promote neuronal death. Understanding this mechanism could be useful for the development of clinical therapies for several lysosomal disorders.

### 2.6. Neuronal death: apoptosis or necroptosis

Very little is known about the cellular death mechanisms leading to neuronal loss in NPCD, thus the potential efficacy of cell death inhibitors remains unexplored. Several lines of evidence suggest that cell death in the NPCD brain occurs mainly through apoptosis, mediated by the TNF receptor superfamily pathway [178,179]. Apoptotic cells have been detected in the brain and cerebellum of NPC human patients and mouse models. Moreover, up-regulation of genes involved in the TNF-alpha cell death pathway correlates with the progression of the disease. TNF-alpha mRNA expression levels increase up to 30–50 fold in the cerebellum of 7- and 9-week old NPC mice compared with WT animals. Elevated expression of TNF-alpha was detected in both neurons and astrocytes, with TNF-alpha-expressing astrocytes distributed in the affected brain regions [179]. These results suggest that cell death in the NPCD brain occurs through apoptosis with an important contribution of the TNF receptor superfamily pathway. Furthermore, the absence of TNF-alpha in the liver reduces inflammation, apoptosis, and fibrosis in NPC mice [180]. However, anti-TNF treatment only slightly curbs the increase in hepatic apoptosis and stellate cell activation seen in liver of NPC1 knockdown mice [181]. Altogether, these results suggest that TNF-alpha is a key mediator of inflammation, apoptosis, and fibrosis in NPCD, but its absence is not enough to reduce the pathology.

Recently, Erickson et al. [178] evaluated the therapeutic potential of inhibiting caspase-dependent cell death using minocycline and transgenic expression of Bcl-2. Neither approach was effective in delaying the onset of neurological signs or increasing lifespan in Npc1$^{-/-}$ mice. Therefore, this group concluded that neuronal loss in NPC1 is not due to apoptosis [178]. The inconclusive findings involving inhibition of apoptosis (Bcl-2 transgenic) and pyroptosis (minocycline), along with the pathological studies suggesting the presence of necrosis, lead to propose the involvement of necroptosis in NPCD.

Although caspase-independent programmed cell death had previously been described [182], necroptosis was initially delineated by Degterev et al. [183]. Necroptosis is mediated by a heterologous protein complex known as the necrosome, which is a multiprotein complex that includes two protein kinases, receptor interacting protein kinase 1 (RIP1) and 3 (RIP3) [183]. These two kinases are integral part to the necrosome and regulate its function [184]. These proteins accumulate both in the cytosol and at the lysosomes and can lead to cellular sensitization to necroptosis [185]. Conversely, increased function of the autophagy-lysosomal pathway in vivo can decrease necroptosis and general cell damage. These data point to a previously unexplored link between inhibition of the autophagy-lysosomal pathway and induction of neuronal necroptosis. RIP3 is a component of the TNF signaling complex, and can induce cell death both by a caspase 8-dependent mechanism and by a separate Bax/Bak- and caspase-independent mechanism [186,187]. Furthermore, treatment of NPC1 mutant mice with necrostatin-1, an allosteric inhibitor of RIP1, significantly delays cerebellar Purkinje cell loss, progression of neurological symptoms, and death. Collectively, the data identified necroptosis as a key component of the molecular network that contributes to neuronal loss in NPCD and suggest that inhibition of necroptosis is a potential therapeutic option for NPCD [188].

NPCD and NPAD show widespread neuronal degeneration that initially affects Purkinje neurons in the cerebellum [189,190]. Indeed, 3-month-old ASMKO mice present significantly higher caspase-cleaved actin (fractin) in the cerebellum [144]. Similarly to NPCD, in NPAD the mechanisms that explain the greater susceptibility of Purkinje cells are unknown, but could be related with their large cytoplasmic volume and extensive dendritic arbors, which implies high metabolic demands and higher susceptibility to insults [191,192].

As mentioned before, little is known about the events that lead to brain pathology in some forms of GD. Recent studies show that while there is neuronal death in the brain of a genetic neuronopathic Gaucher mice model, there is no increase in apoptosis markers. Instead, an increase of the RIP3 was detected [176]. Congruent with these results, an increase in RIP3 in the brain, particularly in neurons and activated microglia, but not in astrocytes [176], was found in a pharmacological neuronopathic Gaucher mouse model induced by treatment with CBE. These findings suggest that neurons die through necroptosis rather than apoptosis in Gaucher disease brain.

Cell death is well documented in parts of the brain and in other cells of LSD patients and animal models, although little is known about mechanisms by which death pathways are activated in these diseases. In fact, cell death is not induced in all cells exhibiting increased storage material. Lysosomes are essential for maturation and completion of autophagy-initiated protein and organelle degradation. Studies focused on aging and autophagosome formation have shown that mitochondria

are involved in signaling pathways that regulate apoptosis and innate immunity. Furthermore, reduced autophagic flux and the subsequent accumulation of dysfunctional, ROS–generating mitochondria render cells more sensitive to apoptotic and inflammatory stimuli [193–196]. Therefore, the aberrant functioning of mitochondria may be responsible for apoptosis and inflammation in the CNS of multiple LSDs. In turn, compromised ER calcium regulation may impact mitochondria through ER–mitochondria contact sites, resulting in mitochondrial calcium excess and an induction of mitochondria-mediated apoptosis, as seen in GM1 gangliosidosis [197].

Although apoptotic cell death is prevalent in many LSDs, especially in those that cause neurodegeneration, the molecular mechanisms of apoptosis in these diseases remain poorly understood. As a result, although the treatment options for LSDs have significantly increased in recent years, the development of rational and effective treatments for many LSDs awaits advances in our understanding of the molecular mechanisms of pathogenesis of these diseases.

### *2.7. c-Abl activation as a new cell death-signaling pathway*

c-Abl kinase is a non receptor tyrosine kinase with diverse biological functions depending on the cell type. c-Abl participates in a variety of cellular functions, including the regulation of the actin cytoskeleton [198], the cell cycle [199] and the apoptotic/cell cycle arrest response to stress [200–202]. Consistent with its cytoplasmic and nuclear localization and its capacity to regulate gene expression, c-Abl has one nuclear export signal (NES) and three nuclear localization signal (NLS) motifs in its C-terminus [203]. Interestingly, the Abl family of kinases has been shown to play a crucial role in the development of the CNS [200]. In neurons c-Abl is mainly in the cytoplasm, a localization associated with a positive effect on cell cycle re-entry. However, in many cell types, including neurons, oxidative stress and DNA damage stimulate c-Abl nuclear localization, which is associated with c-Abl cell cycle inhibitory and apoptotic functions [200,204].

The Abl family of kinases has been shown to play an important role in neuronal development and recent studies showed that c-Abl may be an important player in neurodegenerative diseases, such as AD and PD [130,205–209]. Also, c-Abl is activated in mouse models of these diseases and in neuronal cultures in response to amyloid beta fibrils and oxidative stress [200]. Overexpression of active c-Abl in adult mouse neurons results in neurodegeneration and neuroinflammation [200]. Based on this evidence, a potential role for c-Abl in the pathogenesis of neurodegenerative diseases is discussed in this review.

The c-Abl pathway has been implicated in the induction of apoptosis [210,211]. Interestingly, we have previously reported that oxidative stress triggers apoptosis through activation of the c-Abl proapoptotic pathway [132]. One of the most classic pathway through which c-Abl induces apoptosis is by phosphorylating the transcription factor p73, inducing its stabilization and decreasing its degradation [212]. Consequently, the expression of p73 target genes like NOXA, Scotin and PUMA is induced in response to DNA damage [213]. We have previously reported increased levels of the activated and phosphorylated forms of c-Abl and p73, and increased mRNA levels of p73 target genes in the cerebellum of NPC mice. Furthermore, inhibition of c-Abl with Imatinib preserves Purkinje neurons and reduces general cell apoptosis in the cerebellum, improves neurological symptoms, and increases survival of NPC mice [214].

Interestingly, we have also found increased p-c-Abl levels and nuclear localization of this kinase, which are related with its proapoptotic functions [211,215], in fibroblasts from NPC patients (Figs. 3 and 4), suggesting that this signaling pathway could also be important.

In addition, unpublished data from our group show that c-Abl is phosphorylated and activated in different NPA models. Moreover, our evidence shows increased p-c-Abl levels and nuclear localization in NPA fibroblasts (Figs. 3 and 4), suggesting that c-Abl could be involved in the pathogenesis of NPA disease.

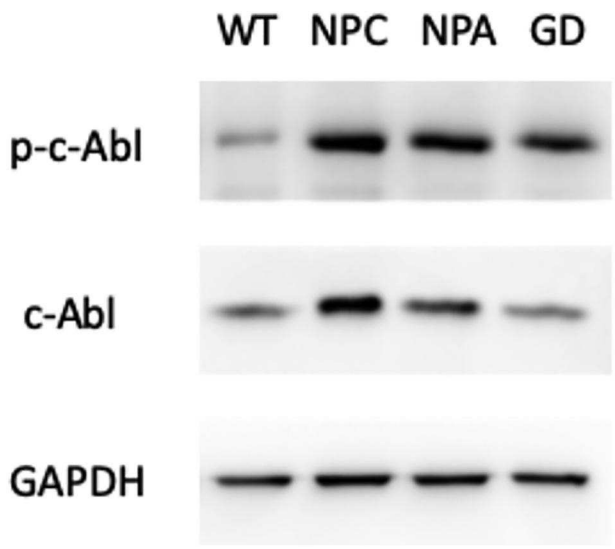


**Fig. 3.** c-Abl activation in fibroblasts from NPA, NPC and Gaucher patients.
c-Abl is activated in fibroblasts from NPC, NPA and GD patients compared with control fibroblasts. WT (GM05659), NPC (V1165M), NPA (GM13205) and GD (GM00877) fibroblasts were obtained from Coriell repository. The cells were lysed in RIPA buffer supplemented with a cocktail of protease inhibitors (Roche). The homogenates were maintained on ice for 30 min and then centrifuged at 10,000*g* for 10 min. The supernatant was recovered, and protein concentration measured with the Pierce BCA protein assay kit (Thermo Fisher Scientific). Proteins were resolved in SDS-PAGE, transferred to Nitrocellulose membranes (Thermo Fisher Scientific), and probed with primary antibodies against p-c-Abl Tyr412 (1:1000), c-Abl (1:1000) and GAPDH (1:5000). The reactions were followed by incubation with HRP labeled secondary antibodies and visualized using the ECL technique (Thermo Fisher Scientific). Total c-Abl and GAPDH levels were used as control.
As can be observed NPC, NPA and Gaucher fibroblasts show increased p-c-Abl levels compared with wild-type (WT) fibroblasts, suggesting that c-Abl is activated in NPA, NPC and Gaucher fibroblasts.

Aberrant c-Abl activation is associated with several deleterious effects in different neurodegenerative diseases including AD [130,206], PD [207,208], Amyotrophic lateral sclerosis (ALS) [216] and NPC [128,217,218]. We have shown that c-Abl phophorylates HDAC2 increasing the expression of this protein and that the inhibition of c-Abl or c-Abl deficiency prevents the increase of HDAC2 protein levels and activity in AD and NPC neuronal models [217,219]. In models of both diseases we have demonstrated that the c-Abl/HDAC2 signaling pathway participates in the epigenetic regulation of gene expression related to the neurological pathology [217,219]. Thus, we propose that inhibition of c-Abl could be a pharmacological approach for preventing the deleterious effects of increased HDAC2 levels in NPCD and AD. Moreover, we have shown that c-Abl inhibition reduces APP amyloidogenic cleavage in NPC cells [218].

As mentioned earlier, several publications have shown that smaller and rounder mitochondria predominate in NPC cells [28]. Recently, the participation of the c-Abl/Drp1 signaling pathway has been implicated in mitochondrial fragmentation [220]. Future research is necessary to clarify if this pathway participates in the presence of smaller mitochondria in NPC cells.

Clearly, the development of RIP3 inhibitors may pave the way for alternative therapeutic approaches for all three subtypes of GD. However, other proapoptotic pathways might be involved in neuronal death. Only caspase-3 activation has been reported in the Nestin-Cre mouse model and at very advanced stages of the disease [167]. Interestingly, our preliminary results show that the c-Abl signaling pathway is activated in neuronopathic Gaucher disease models (unpublished data) and in fibroblasts from Gaucher patients (Figs. 3 and 4). We found an increase in the levels of the activated and phosphorylated form of c-

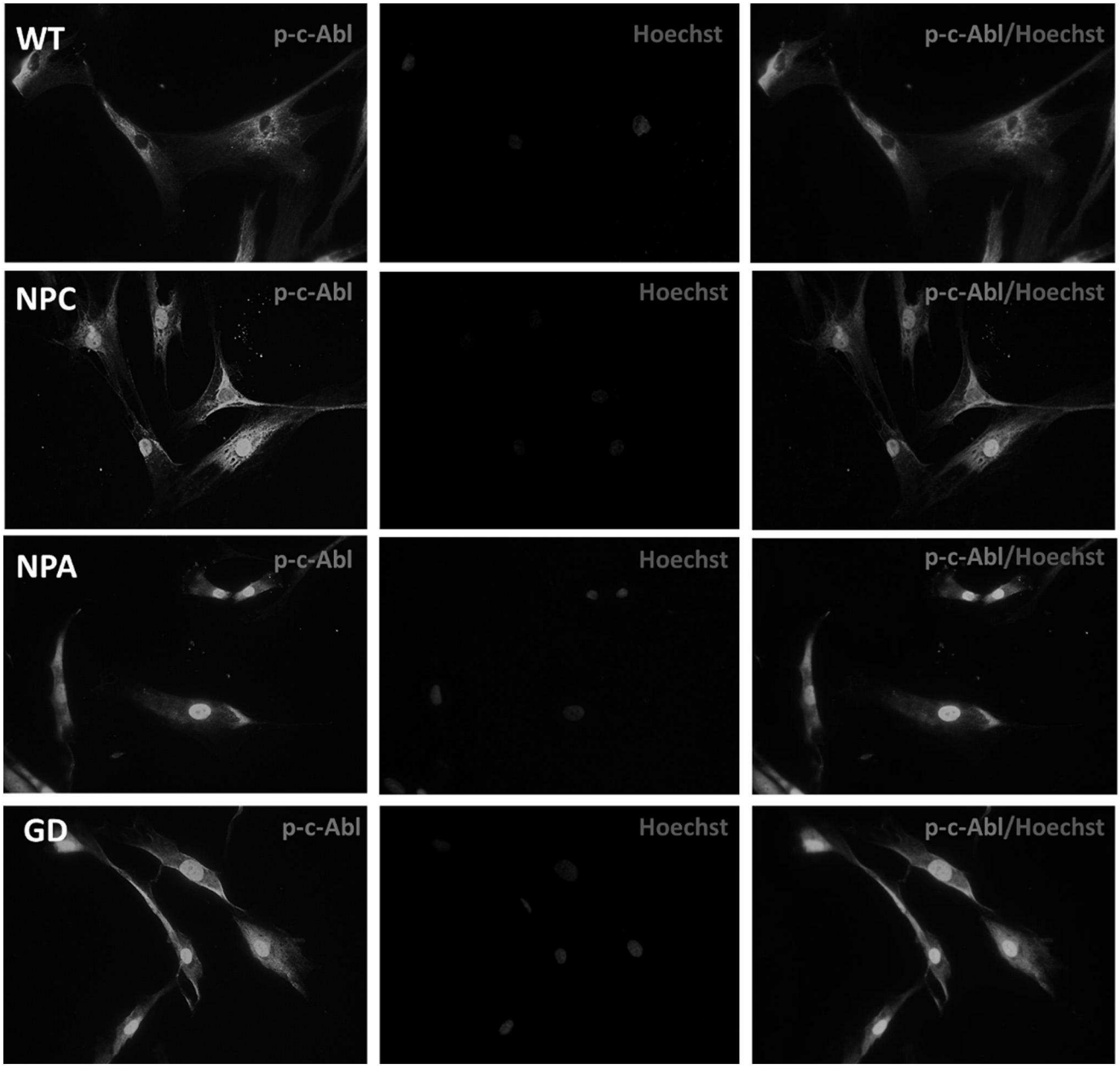


**Fig. 4.** Nuclear p-c-Abl levels are increased in fibroblasts from NPC, NPA and GD patients.
Nuclear p-c-Abl levels are increased in fibroblasts from NPC, NPA and GD patients compared with control fibroblasts. WT (GM05659), NPC (V1165M), NPA (GM13205) and GD (GM00877) fibroblasts were obtained from Coriell repository. Cells were seeded on coverslips (20,000 cells/well) with DMEM 15% BFS. After 24 h, cells were fixed in 4% paraformaldehyde/4% sucrose in PBS and permeabilized with 0.02% Triton X-100. Then, cells were blocked with 3% bovine serum albumin in PBS. Immunostaining was carried out using anti-p-c-Abl Tyr412 (1:500; Sigma Chemical Co) and anti-rabbit-Alexa Fluor-488 (1:1000; Invitrogen Detection Technologies) was used as secondary antibody. Hoechst was used to stain nuclei. Fluorescent images were captured with an Olympus BX51 microscope (Olympus). Objective used was 40×. Merge was performed using Image J software.
p-c-Abl levels (green) and nuclei (blue) were measured by inmmunofluorescence. We found that p-c-Abl levels are increased in fibroblasts of NPA, NPC and Gaucher patients. Moreover, we found that p-c-Abl levels are increased in nuclei in all of them.

Abl and its targets p73 and CRKII in different GD models (unpublished data).

Recent studies revealed that the pharmacological inhibition of c-Abl enhances the autophagy-lysosomal function and provides neuroprotective effects in cells and animal models of PD [221], giving a new relevance to this kinase in lysosomal dysfunction diseases. In addition, considering that c-Abl inhibitors are drugs already approved by the FDA, c-Abl could be a pharmacological target for preventing the deleterious effects of aberrant c-Abl activation in NPCD and other lysosomal storage diseases, as well as in other neurodegenerative diseases. Interestingly, recent reports show that c-Abl inhibitors have been used in clinical trials for PD [222] and dementia with Lewy bodies [223]. Results in Parkinson patients are promising because they show improvement of locomotor function and decrease synuclein accumulation, incentivating a phase 3 clinical trial [222].

## 3. Relevance of understanding the pathogenic mechanisms in LSDs for other diseases

Understanding the molecular mechanisms of LSDs will also help to understand other more frequent diseases such as AD and PD.

Several parallels in the cellular pathology of NPCD and AD have

been described including the formation of neurofibrillary tangles, prominent lysosome dysfunction (enlarged lysosomes and lipid accumulation), and neurodegeneration [224,225]. In addition, mitochondrial cholesterol accumulation and mGSH depletion have been shown in a transgenic AD mouse model [226], and aberrant cholesterol metabolism has been linked to AD [227]. Moreover, a cross-sectional study has shown increased gamma-secretase-dependent amyloid-beta peptide in brains of patients with NPCD [228,229]. In addition, alterations in SM metabolism are present in several pathologies of the CNS, including AD and PD [44]. More recently, Barbero-Camps et al. showed that brain cholesterol homeostasis affects Aβ clearance by impairing autophagy [230]. Interestingly, treatment with HPβCD restores autophagy and reduces lysosomal cholesterol accumulation in NPCD [231]. In addition to NPC1 other lysosomal proteins have been linked to AD pathogenesis. Cell-based experiments have shown that Cathepsins B, D, E, and L are essential in controlling either Aβ peptide generation or degradation [232,233]. Although speculative, it has been suggested that enhancing the activity cathepsins may serve as a strategy for treating AD [234]. Tau pathology is a common feature of LSDs, AD, and other disorders. It was recently shown that targeting the lysosome through inhibition of farnesyltransferase reduces tau pathology in mice [235].

Genetic studies identified many lysosomal gene variants in PD patients [236,237]. Among them, the highest risk factors for developing PD are variants in the GBA gene [238].

Consistent with the genetic results, mechanistic studies have linked lipid species that accumulate in several LSDs, including GlcCer, cholesterol, gangliosides, and others to α-synuclein aggregation [239–242], indicating that PD might be a late-onset LSD [243]. Therefore, strategies aimed at fixing the lysosomes or reducing lysosomal lipids are under investigation for treating PD. Reduction of GlcCer accumulation via inhibition of acid ceramidase reduces oxidized α-synuclein in GBA1-PD patient-derived dopaminergic neurons [244]. Strategies aimed at increasing GBA activity with chaperons such as Ambroxol or other modulators, also decreased α-synuclein accumulation in iPSC-derived dopaminergic neurons from sporadic PD patients and transgenic mice [245,246]. HPβCD treatment, which is used for reducing intracellular cholesterol buildup in NPCD, decreases a-synuclein accumulation in transgenic mice [247]. These studies and others indicate that lysosomal dysfunction plays a central role in PD pathophysiology and therapeutics [243,248–250].

Common putative therapeutic avenues for AD, PD, and LSDs are emerging. We are particularly interested in placing c-Abl as a broad therapeutic target for neurodegenerative lysosomal diseases as well as for AD, since potent inhibitors are already available and others are under development. As described above, we found that c-Abl kinase is activated in NPCD and AD models and that its inhibition is beneficial in these models [205,214,251,252].

## 4. Therapies

For the three lysosomal storage disorders that we have discussed previously, new therapies are available or under development. These therapies include enzyme replacement therapy (ERT) and synthetic molecules. The new therapies cannot cure patients, but can stabilize organ function or slow the progression of the disease.

Studies have shown that HPβCD appears to reduce cholesterol and lipid accumulation in the CNS and prolongs survival times in NPC animal models [253,254]. A phase 1/2 trial with intrathecal administration HPβCD is being completed [255], and a phase 2b/3 is starting (NCT02534844). Another clinical trial with oral administration of arimoclomol, a heat shock protein (hsp70 and hsp40) enhancer, is also underway (NCT02612129).

Current evidence shows that another hallmark of NPCD is the accumulation of sphingolipids in lysosomes. Therefore, researchers studying this disease should take this evidence into account for the development of an integral therapy for NPC patients. NPCD therapy design needs to consider the defects of sphingolipid catabolism in the endolysosomal compartment.

In fact, the only therapy approved for the treatment of NPCD is miglustat (NB-DNJ) a drug that inhibits the synthesis of GSLs [25]. Initial data show that patients are stabilized for one year or more and a slower rate of disease progression has been confirmed [256]. In animal models of NPCD, miglustat reduces neuronal GSLs accumulation, delays the onset of neurological dysfunction, and prolongs survival [257]. Moreover, miglustat has been shown to improve Purkinje cell survival in a NPC feline model [258]. The data obtained from therapies that lower cholesterol and sphingolipids highlight the idea that there is not just one “offending” metabolite in NPC and other sphingolipidosis but rather that the correct lipid balance is lost in these diseases.

Promising therapeutic strategies in NPCD involve LXR agonists, which promote cholesterol efflux from the brain, slow neurodegeneration and prolong life of NPC mice [259].

In summary, in NPCD accumulation of sphingolipids has been strongly implicated in the pathology of this disease and the proper balance of sphingolipids is essential for normal neuronal function. The mechanism by which NPC1 mobilizes cholesterol outside the lysosome was recently described [19]. However, the mechanism by which NPC1 deficiency leads to the accumulation of sphincolipids has not yet been determined.

NPAD has no cure or treatment. It is a fatal disease and NPA patients die between 2–3 years of age. For these reasons, all efforts to understand the pathology and elaborate an effective therapy are important. Neurodegeneration in NPAD is very aggressive and early onset, a hallmark that is difficult to revert or avoid.

To address this challenge ERT has been evaluated in a NPA animal model. Intravenous administration of recombinant human ASM (hASM) into ASMKO mice leads to visceral, but not neurological, correction of the pathophysiology. It is likely that this result is due to the inability of the enzyme to cross the blood brain barrier [260]. Nevertheless, intracerebral injection of gene, cell and protein based therapies administered to the ASMKO mouse can reduce the lysosomal accumulation in the CNS [261,262]. This approach is effective but very invasive. For these reasons, it is important to evaluate other targets, in order to create more suitable therapies.

Treatments and drugs for GD type 1, the most common form of the disease, may vary depending on the severity of the symptoms and the course of treatment.

ERT is administered for the non-neurological manifestations of types 1 and 3 GD. Remarkably, there are no available treatments for type 2, the acute neuronopathic form, which is the most severe and fatal form of the disease. Regrettably, ERT is not suitable for this form of the disease, because the recombinant enzyme is not able to cross the blood brain barrier. Therefore, more studies are required to understand the pathogenic mechanisms involved in neurological damage and neuronal death, which may allow the discovery of new therapeutic targets and the development of new treatments for GD type 2 and the neurological symptoms of GD type 3. Substrate reduction therapy is an alternative approach to treat patients with GD. Miglustat is one of the N-alkylated iminosugars extracted from plants and microorganisms, and inhibits the glycosylceramide synthase, which catalyzes the transfer of glucose from UDP-glucose to ceramide to form GlcCer. The aim is to decrease the biosynthesis of GlcCer so that patients with significant residual enzyme activity can break down GlcCer more efficiently and thus allow clearance of GlcCer from lysosomes [263].

Imino sugars such as miglustat can also target the protein folding and trafficking pathways of glycosidases to assist in the correction of lysosomal enzyme activity (chaperone mediated therapy) [264]. A partial increase in enzyme activity may be sufficient to initiate the metabolic breakdown of GSL and a decrease in lysosomal storage. The efficacy of miglustat in GD type I probably results from both a decrease in the biosynthesis of GlcCer and an increase in the activity of glucocerebrosidase.

Considering that c-Abl activation is involved in a signaling pathway that is shared by three pathologies of interest in this review, we propose that c-Abl inhibitors could be a good therapeutic strategy for all three. Several of the available c-Abl inhibitors are approved by the FDA for the treatment of chronic myeloid leukemia (CML), which expresses the fusion oncoprotein BCR-ABL1 resulting in permanent c-Abl activation. These drugs are safe and present mild secondary effects. Interestingly, the c-Abl signaling pathway has been linked to different lysosomal and neurodegenerative disorders. Imatinib, a classical c-Abl inhibitor, has been tested in NPC and Alzheimer animal models with favorable results [214,218,265–267]. Moreover, Nilotinib, another classic c-Abl inhibitor, was tested in a phase 2 clinical trial in PD with good results [268]. Altogether, we speculate that c-Abl inhibition is a promising therapeutic target for a wide range of pathologies.

## 5. Conclusion

LSDs are complex monogenic disorders whose main hallmark is the intra-lysosomal accumulation of un-degraded metabolites. There are more 60 LSDs, but in this review, we focused on NPAD, NPCD and GD in order to analyze common characteristics that are shared by these similar pathologies.

We described the phenotypic manifestations of these diseases, including neurological and peripheral tissues abnormalities, which are thought to be due to lysosomal storage of un-degraded lipids and lipid metabolites. Nevertheless, despite differences in the primary storage, part of the secondary accumulation and downstream signaling pathways are shared and can lead to common pathogenic mechanisms (Table 1).

Our analysis is consistent with the data presented in the literature and places alterations in autophagy as one of the most relevant common pathogenic mechanism of these three diseases. However, it is necessary to mention that the alterations do not appear to be in exactly the same disease stages.

The correct functioning of the lysosome impacts directly in the autophagy process, so it is expected that this process is altered in all LSDs. Therapies aimed at correcting alterations in autophagy could be useful in the treatment of NPAD, NPCD and GD, as long as they are able to reach the CNS, which is the most affected system in these three pathologies. However, autophagy is not the only process that is altered in these diseases. As can be seen in Table 1, there are other process that are relevant is these pathologies. It is probable that the origin of these alterations is related to the lysosomal dysfunction. We propose that restoration of the lysosomal function would be an interesting approach to improve cellular viability.

While gene therapy is not a really feasible alternative for the treatment of these diseases, a combination treatment that improves several of the aspects mentioned in this review would be effective in LSDs patients.

Considering all the antecedents, our aim was to analyze mechanisms that are shared by these sphingolipidoses and to find common therapeutic targets that could promote the development of novel therapeutic approaches for these diseases.

## Declaration of competing interest

The authors declare no conflicts of interest.

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