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Deregulation of signalling in genetic conditions affecting the lysosomal metabolism of cholesterol and galactosyl-sphingolipids

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Abstract

The role of lipids in neuroglial function is gaining momentum in part due to a better understanding of how many lipid species contribute to key cellular signalling pathways at the membrane level. The description of lipid rafts as membrane domains composed by defined classes of lipids such as cholesterol and sphingolipids has greatly helped in our understanding of how cellular signalling can be regulated and compartmentalized in neurons and glial cells. Genetic conditions affecting the metabolism of these lipids greatly impact on how some of these signalling pathways work, providing a context to understand the biological function of the lipid. Expectedly, abnormal metabolism of several lipids such as cholesterol and galactosyl-sphingolipids observed in several metabolic conditions involving lysosomal dysfunction are often accompanied by neuronal and myelin dysfunction. This review will discuss the role of lysosomal biology in the context of deficiencies in the metabolism of cholesterol and galactosyl-sphingolipids and their impact on neural function in three genetic disorders: Niemann-Pick type C, Metachromatic leukodystrophy and Krabbe's disease.

Keywords

Cholesterol; Psychosine; Sulfatides; Lipids; Metabolism; Lysosomes; Myelin; Lipid raft; Endosome; Exosome; Signalling; Akt; Niemann-Pick type C disease; Krabbe's disease; Metachromatic leukodystrophy

1. Introduction

Inborn errors of the metabolism of lipids are generally accompanied by lysosomal storage of undegraded material, affecting the physiology of multiple organs and systems (Parenti et al., 2013). Most often, patients develop manifestations early in life, leading to severe neurological and lethal infantile forms. Late onset variants of these diseases may also develop later in life and are often associated with cognitive and behavioural problems (Kolodny and Cable, 1982). Some of adult onset lipidoses have manifestations also present

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in other neurodegenerative diseases like Parkinson's disease (PD), Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS) suggesting that the involvement of common cellular pathogenic mechanisms (Kiriyama and Nochi, 2015; Ramanan and Saykin, 2013). The hallmarks of lysosomal storage diseases (LSD) include lysosomal dysfunction due to storage of specific lipids, dysmyelination and/or demyelination and neurodegeneration (Table 1). Due to their involvement in myelin production and lipid requirements, oligodendrocytes and Schwann cells are chiefly targeted in many lipidoses, which is also accompanied by neuronal and axonal abnormalities. In this review, due to the wide range of human diseases with errors of lipid metabolism, we will focus on some of the altered signalling and pathways that have been descried in three pathologies: Nieman-Pick type C (NPC), Metachromatic leukodystrophy (MLD) and Krabbe's disease (KD).

2. Generalities on lysosomal biology. Understanding possible secondary targets affected in LSD

While this review focuses on dysregulation of lysosomal lipid metabolism in NPC, MLD and KD, several key aspects of lysosome function and regulation including lysosome transport, signalling events at its surface and interaction with other organelles, are affected by lipid homeostasis (Settembre and Ballabio, 2014; Thelen and Zoncu, 2017). For this reason, we provide the readers with an introductory description of lysosome structure, function, its transcriptional regulation, key signalling processes that occur on the lysosomal surface and its interaction with other organelles. In each case, we also emphasize its relevance to lipid metabolism. Lastly, we briefly highlight other neurodegenerative diseases such as Parkinson's disease (PD) that include lysosome dysfunction as part of their pathology, as this may bear relevance to the diseases discussed here as well. Indeed, in many of these neurodegenerative diseases, dysregulation in lysosomal lipid metabolism is a critical part of their pathology.

2.1. Lysosomes structure and function

Lysosomes, meaning "digestive body" in Greek, were discovered by the biochemist Christian De Duve in 1955 (de Duve, 2005; De Duve et al., 1955). Due to their role in terminal degradation, they are often thought of as the cell's "garbage disposal system" and also thought to be relatively stable compartments. Lysosomes participate in numerous cellular processes including gene regulation, metabolic signalling, plasma membrane repair, immunity, cell adhesion and migration (Ballabio and Bonifacino, 2020; Saftig and Klumperman, 2009). They are also highly dynamic organelles whose number, shape, size and position can vary depending on external and internal cues (Ballabio and Bonifacino, 2020).

De Duve and colleagues first isolated the organelle from liver cells by the sucrose gradient centrifugation method. They worked out a five-fraction centrifugation process, refining on the process previously developed by Albert Claude at Rockefeller University, to isolate the "L" fraction enriched for acid phosphatase activity (De Duve et al., 1955). By 1955, they had discovered five acid hydrolases in this fraction, including the acid phosphatase; β-glucuronidase, Cathepsin D, ribonuclease and deoxyribonuclease. The presence of

multiple hydrolases targeting very different substrates within these membrane-enclosed ‘sacs’ strongly implied that these were digestive organelles- hence named ‘Lysosome’ by De Duve and colleagues. Thus, originally identified by biochemists, lysosomes were then characterized morphologically, by electron microscopy studies of purified preparations from liver cells by Novikoff and colleagues (Novikoff et al., 1956). Novikoff subsequently developed a cytochemical staining method for acid phosphatase as a marker of lysosomes (Novikoff et al., 1956).

Historically, lysosome dysfunction has been associated only with rare LSDs that result from genetic impairment in of different lysosomal hydrolases (Ballabio and Gieselmann, 2009; Platt et al., 2018) (see Table 1). However, in recent years, it has become apparent that lysosome dysfunction is associated with numerous neurodegenerative diseases including Alzheimer’s disease (AD), Parkinson’s disease (PD), and Amyotrophic Lateral Sclerosis (ALS) as well as several metabolic disorders (Malik et al., 2019; Nixon, 2020). This has led to lysosome biology becoming a central topic in fields beyond cell biology, such as neuroscience as well as physiology.

2.2. Lysosome composition

Lysosomes are composed of specific luminal, integral membrane proteins as well as peripherally associated proteins (Fig 1). Lysosomes have over 40 different membrane proteins (Callahan et al., 2009; Xu and Ren, 2015). LAMP (Lysosome associated membrane protein) 1 and 2 are two highly glycosylated proteins that are the most abundant lysosomal membrane proteins followed by lysosomal integral membrane protein 2 (LIMP; also called SCARB2) and the tetraspanin, CD63. LAMP1 and 2 form a glycocalyx that protects the lysosomes from its own very acidic environment (pH 4.5–5) and the activity of numerous catabolic enzymes (Eskelinen et al., 2004). These integral membrane proteins participate in many lysosomal functions, including membrane fusion events, motor-based transport of lysosomes and lysosome acidification (Ballabio and Bonifacino, 2020; Saftig and Klumperman, 2009). These membrane proteins also aid in cholesterol, ions and amino acid transport, protein import from cytosol, transport of degradation products to cytosol, and nutrient sensing (through interactions with peripherally associated proteins) (Amick et al., 2020). The soluble lysosomal proteins include more than 60 different enzymes (soluble hydrolases) that target specific substrates for degradation (Lubke et al., 2009). In addition to degrading their substrates, these enzymes are also involved in degradation of extracellular matrix (upon lysosome exocytosis), initiating apoptosis as well as antigen presentation (Conus and Simon, 2008). NPC2 is also a soluble lysosomal protein shuttles free cholesterol to NPC1, the integral membrane protein key for exporting this lipid from lysosomes (Hamer et al., 2012; Li and Pfeffer, 2016). These proteins and their role in cholesterol transport are discussed in detail later in this review.

Soluble and integral lysosomal proteins are delivered to the lysosome via the specific routes of vesicular transport from the Golgi (Pols et al., 2013; Swetha et al., 2011). The detailed mechanisms of transport and delivery of lysosomal proteins is reviewed elsewhere (Ballabio and Bonifacino, 2020; Saftig and Klumperman, 2009). Other proteins and protein complexes, including transcription factors, mTORC1 complex, adaptors for motor-base

transport, small GTPases, etc. dynamically associate with the cytosolic side of the lysosome surface and help execute the relevant roles (Ballabio and Bonifacino, 2020; Saftig and Klumperman, 2009).

Like with proteins, lipids are an integral part of lysosomal membranes and affect the organelle's function (Hamer et al., 2012). Reciprocally, lysosomes play an important role in cellular lipid homeostasis. Both endogenous and exogenous lipids get delivered to lysosomes. Exogenous lipids include lipoproteins and cholesteryl esters derived from LDLs (low density lipoproteins). These are processed by lysosomal acid lipase (Jaishy and Abel, 2016). Endogenous lipids such as from lipid droplets are delivered to lysosomes through the autophagic pathway and also processed by the lysosomal acid lipase that acts at an acidic pH (Settembre and Ballabio, 2014). Deficiency of this enzyme leads to Wolman disease, a lysosomal storage disorder (Table 1).

2.3. Transcriptional regulation of lysosome biogenesis

TFEB or Transcription factor EB is a key regulator of lysosome biogenesis and function and often referred to as the "master-regulator" of lysosome function. Since its discovery, this transcription factor and its modulation to augment lysosome function, have become the focus of therapeutic strategies for different LSDs as well as neurodegenerative diseases (Napolitano and Ballabio, 2016). A little over a decade ago, a study that began with an in-silico approach (e.g. pattern discovery analysis of the promoter regions of 96 lysosomal genes) lead to the identification of "CLEAR" ('coordinated lysosome expression and regulation') elements in promoter regions (Sardiello et al., 2009). This 10 bp palindromic sequence, GTCACGTGAC, was found to be highly enriched in lysosomal genes, as a single copy or in multiple sequences, about 200 bp from their transcription start site. These elements were demonstrated to be binding sites for a basic helix-loop-helix leucine zipper transcription factor, TFEB.

TFEB belongs to the MiTF- TFE family along with MITF, TFE3, TFEC (Napolitano and Ballabio, 2016). At the subcellular level, TFEB localizes to the cytosol, lysosomal surface and the nucleus (Roczniak-Ferguson et al., 2012). TFEB has now been shown to regulate numerous cellular processes relating to lysosome biology including lysosome positioning, lysosome fusion, autophagosome biogenesis, autophagosome–lysosome fusion, (Settembre et al., 2011) as well as lysosomal degradation pathways, including its acidification (Napolitano and Ballabio, 2016). When lysosome function is perturbed, TFEB translocates to the nucleus to promote lysosomal biogenesis. In fact, cells from patients with LSDs such as NPC, show increased nuclear TFEB (Sardiello et al., 2009). Evidence from several laboratories has demonstrated that translocation of TFEB in the nucleus is largely regulated by phosphorylation via nutrient-regulated mTORC1 kinase complex (Roczniak-Ferguson et al., 2012; Settembre et al., 2012). When lysosome function (as well as nutrient levels) are optimal, TFEB translocation to the nucleus is blocked by binding to the lysosomal 14–3-3 protein via mTOR-dependent phosphorylation of Ser 211 (Roczniak-Ferguson et al., 2012). Conversely, nutrient- and mTOR-dependent phosphorylation at S142 and S138 promotes nuclear export of TFEB to the cytosol under conditions of adequate nutrient availability (Napolitano et al., 2018).

TFEB has been implicated in directly controlling lipid catabolism, by regulating expression of lysosomal acid lipase (Palmieri et al., 2011; Settembre and Ballabio, 2014; Thelen and Zoncu, 2017). TFEB also regulates expression of several other genes involved in different steps of lipid degradation, including β-oxidation of fatty acid in mitochondria {Cpt1, carnitine acetyltransferase (Crat), acyl-CoA dehydrogenase} and peroxisomes (CYP4a) (Settembre et al., 2013).

TFEB and other members of this family have also been implicated in various developmental processes including osteoclast differentiation and embryonic stem cell renewal (Napolitano and Ballabio, 2016; Roundy et al., 1999). Thus, the MITF family of transcription factors, by regulating lysosome homeostasis ensure proper functioning of key signalling pathways (including lipid catabolism), and also orchestrate various differentiation and developmental processes.

2.4. Lysosomes as centres for signalling events

Lysosomes are increasingly recognized as a key site of many signalling cascades (Lamming and Bar-Peled, 2019; Perera and Zoncu, 2016). Two of these, nutrient sensing via mTORC1 and calcium homeostasis, are intimately tied with lipid homeostasis (Thelen and Zoncu, 2017).

Lysosomes serve as a platform for the nutrient sensing mTORC1-mediated pathway (Lawrence and Zoncu, 2019). The mTORC1 complex dynamically associates with lysosomes. Under nutrient-rich conditions, mTORC1 promotes growth and anabolic pathways and inhibits catabolic processes such as autophagy through phosphorylation of Unc-51 like autophagy activating kinase (ULK1). mTOR activation requires its recruitment to lysosomes through the hetero-dimeric Rag GTPases. These Rag GTPases are additionally responsible for the recruitment of several other nutrient-responsive molecules such as the Folliculin-FNIP1 complex (Petit et al., 2013) and the transcription factor, TFEB. C9ORF72, a molecule mutated in ALS and frontotemporal dementia (FTD), along with its binding partner SMCR8, is also recruited to lysosomes in a nutrient-dependent manner (Amick et al., 2016).

mTORC1 activation on the surface of lysosomes has important consequences for lipid homeostasis in cells. Its activation promotes de novo synthesis of lipids while also actively suppressing lipid catabolism (Thelen and Zoncu, 2017). It strongly drives expression, trafficking and proteolytic processing of sterol-responsive element-binding proteins (SREBPs), which are master regulators for synthesis of sterols and fatty acids (Düvel et al., 2010). mTOR potently supresses lipid droplet breakdown as well as peripheral β-oxidation. Reciprocally, mTOR activity is also regulated by lipid-derived signals. Phosphoinositides, including PI3P and PI(3,4)P2 have been linked to mTOR regulation (Dong and Czaja, 2011; Thelen and Zoncu, 2017). Recently, cholesterol has been shown to recruit mTOR to the lysosomal surface and this also appears to involve the NPC1 protein (Castellano et al., 2017). This study also suggests impaired mTORC1 activity could contribute to the pathology of NPC (Castellano et al., 2017). Given its effect on lipid metabolism and its reciprocal dependence on lipid homeostasis, the biology of mTORC1 signalling is a critical aspect of lysosomal lipid regulation. Further details of nutrient sensing

and mTORC1 signalling pathways at the surface of lysosome, can be found in recent reviews (Lawrence and Zoncu, 2019; Saxton and Sabatini, 2017).

Lysosomal Ca^{2+} plays an important role in many of the organelle's functions, including fusion with other organelles such as endosomes, autophagosomes and the plasma membrane. Lysosomal Ca^{2+} also plays a key role in formation of'contacts' (discussed in following section) with the ER, which in turn helps fill the lysosome with Ca^{2+} from the ER (Wang et al., 2017). Lysosomal Ca^{2+} signalling is also intimately tied up with lipid homeostasis in the organelle. The best characterized lysosomal Ca^{2+} transporter is mucolipin1 or TRPML1. Activation of TRPML1 by PI(3,5)P2 (Dong et al., 2010) as well as starvation and ROS (Ballabio and Bonifacino, 2020), releases Ca^{2+} from lysosomes to the cytosol. TRPML1 deficiency causes Mucolipidosis type IV, a LSD characterized by neurodegeneration (Bassi et al., 2000). TRPML1-mediated Ca^{2+} release from lysosomes is also impaired in NPC disease cells, potentially as a secondary effect of accumulating lipids in the organelle (Hoglinger et al., 2015; Shen et al., 2012). It remains to be seen if TRPML1 activity is altered in other LSDs. TRPML1 mediated Ca^{2+} release also regulates plasma membrane repair and participates in a feed-back loop with TFEB, mediating TFEB's ability to promote clearance of substrates in LSDs (Medina et al., 2011). Thus, like with mTORC1 signalling, lysosomal Ca^{2+} signalling is intimately interwoven with lipid metabolism.

2.5. Interaction of lysosomes with other organelles

Lysosomes undergo homotypic fusion among themselves as well as heterotypic fusion with endosomes, autophagosomes as well as the plasma membrane (Moreau et al., 2013). SNARE proteins are at the centre of these fusion events with lysosomal Ca^{2+} also playing a key role in the process. Small GTPases ARL8 and Rab7 regulate these SNARE-mediated fusion events between late endosomes and lysosomes as well as homotypic lysosome fusion, through their effector, the hetero hexameric tethering complex, HOPS (Homotypic fusion and vacuolar Protein Sorting) complex (Ballabio and Bonifacino, 2020; Saftig and Klumperman, 2009).

2.6. Lysosome contacts with other organelles

Over the last decade, non-fusogenic interactions of lysosomes with different organelles such as ER, mitochondria, have been characterized (Fig. 2). These contacts appear to have a particularly important role to play in lipid metabolism. These organelle contacts often serve specific functions such as lipid transfer, organelle movement and positioning. While there is no membrane fusion involved, the membranes of the organelles are closely apposed and tethered by specific 'contact site' proteins that populate or enrich at these contact sites (Phillips and Voeltz, 2016). Lysosome contact with the ER and its subsequent reorganization around endosomal tubules helps in severing of tubules from *endo*-lysosomes (Rowland et al., 2014). A major function of ER-lysosome contacts is lipid transfer between these organelles. Cholesterol generated in lysosomal lumen from cholesteryl esters is exported out of lysosomes through concerted action of lysosomal membrane proteins NPC1 and NPC2. They are imported into the ER by the lipid transfer proteins ORP1L and ORP5 and ER resident proteins at contacts, VAPA and VAPB (Dong et al., 2016). The protein STARD3, on lysosomes, interacts with VAP proteins on ER to transfer cholesterol from

ER to *endo*-lysosomes (Wilhelm et al., 2017). Another protein involved in lipid transfer at ER-lysosome contact sites, is VPS13C. The protein is enriched at these organelle contacts and contains a lipid-binding domain and transfers phospholipids (Kumar et al., 2018), although the direction of transfer and its precise function haven't been identified as yet. One more potential route for lipid transport at ER- lysosome contact sites could involve PDZD8. PDZD8, a resident ER protein, contains a lipid transport SMP module, interacts with GTP-RAB7 on lysosomes, and concentrates at ER-lysosome contact sites (Guillen-Samander et al., 2019). Its precise function in lipid transport is yet to be determined. Lysosomes transfer of free cholesterol to peroxisomes through contacts with these organelles involves lysosomal synaptotagmin 7 and peroxisomal PI(4,5)P2 (Chu et al., 2015).

ER-Lysosome contacts also play a role in lysosome movement and positioning. The ER anchored protein, Protrudin, binds RAB7 and PI3P on lysosomal membranes and promotes the interaction of another PI3P-binding protein, FYCO1 with Kinesin 1 and thus drives lysosome movement to cell periphery (Raiborg et al., 2015). Lysosomal contacts with the Golgi complex, on the other hand, seem to be involved in their peri-nuclear clustering (Starling et al., 2016). Lysosomes also contact mitochondria via RAB7 (Wong et al., 2018). This interaction is counteracted by mitochondrial FIS1 protein through the recruitment of RAB7 GTPase activating protein (GAP), TBC1D15. These lysosome-mitochondria contacts regulate lysosomal RAB7 activity and mark the sites of mitochondrial fission (Wong et al., 2018).

In addition to non-fusogenic contacts with membrane-bound organelles, lysosomes have recently been shown to interact with RNA granules, which are membraneless organelles through the tethering protein, Annexin A11. This hitchhiking of RNA granules on lysosomes, in axons, appears to play a role in local translation of certain mitochondrial proteins (Liao et al., 2019).

Thus, organelle contacts with the lysosome appear to be a critical part of the machinery through which lipid homeostasis is maintained in cells; these sites allow for quick exchange as well as consumption of lipids, when compared to vesicle mediated transport. The growing list of lipid transfer proteins being identified at these contact sites, bears further evidence of the importance of lysosome-other organelle-contacts in maintaining cellular lipid homeostasis.

2.7. Lysosome positioning and lysosomal heterogeneity

The dynamic nature of lysosomes has come to be appreciated over the last decade (Bonifacino and Neefjes, 2017). Lysosomes exhibit microtubule-based movement over long distances. They move from the cell periphery to the perinuclear region (retrograde movement) in a dynein-dependent manner. The movement of perinuclear lysosomes towards the periphery is kinesin-dependent. Lysosome positioning in the cell influences many cellular processes including mTORC1 activity: lysosomes being more peripheral (through overexpression of adaptors/ regulators that promote kinesin-based outward movement) enhance mTORC1 activity while perinuclear clustering reduces it. Likewise, lysosome fusion with autophagosome is also influenced by lysosome positioning, with lysosomal movement towards perinuclear region favoring the fusion events (Korolchuk et al., 2011).

Lastly, some heterogeneity in pH and protease content has been observed in lysosomes, based on their position in the cell. Peripheral lysosomes have less acidic pH and lower content of proteases (and thus degradative capacity) (Gowrishankar and Ferguson, 2016; Johnson et al., 2016). This feature was in fact first reported in neurons where axonal and dendritic lysosomes were protease-deficient when compared to lysosomes in soma (Gowrishankar et al., 2015). This lysosome heterogeneity in position and content is a relatively new area of research and the extent of lysosome heterogeneity, in terms of lipid and protein composition, remains to be determined. Experiments that examine the cholesterol and sphingolipid levels of lysosomes in relation to their position (in both non-neuronal and neuronal cells), will shed insight into possible heterogeneity relating to lipid composition of lysosomes. This heterogeneity may also affect how we evaluate the pathology of LSDs. For instance, examination of pH and chloride ion concentrations in lysosomes of NPC-patient fibroblasts revealed that a subset of lysosomes (with high chloride content and low pH) were specifically depleted (Leung et al., 2019). This specific lysosomal population was recovered in the patient fibroblast, after treatment of cells to reduce lipid accumulation. Thus, further elucidation of lysosome heterogeneity could be beneficial to understanding the pathology of various LSDs, as well as designing therapeutic approaches for them.

2.8. Lysosome size: role in physiological function and change in disease states

Lysosomes vary in shape and size depending on cell type (Ballabio and Bonifacino, 2020). Additionally, being highly dynamic, they change their number, size and position in response to various intra and extracellular stimuli. EM-based morphometry analysis has proven to be quite reliable in measuring even moderate changes in organelle ultrastructure. A relatively small change in diameter of lysosomes, results in more drastic effect on surface area and volume these organelles (de Araujo et al., 2020). Organelle size represents a physical constraint determining ratio of membrane surface area to organelle volume: reduction in diameter (and consequently, volume) of endosomal vesicles is shown to reduced intraluminal vesicle budding, which in turn affects cargo sorting and degradation. Lysosome size also affects its dynamics. While the microtubule-based active transport of lysosomes does not seem to be affected by its size, the diffusive component seems to be inversely correlated with organelle size. Increased lysosomal size also appears to negatively impact lysosomal exocytosis. Lysosome size is also altered (often enlarged), due to lipid accumulation in different lysosomal storage disorders (Xu et al., 2014). For instance, NPC and KD deficient cells exhibit enlarged lysosomes (Marshall et al., 2018a; Xu et al., 2012). Lysosomal size is regulated by phospho-inositide composition with lysosomal PI (3,5)P2 being a key regulator (Rutherford et al., 2006). Lysosomal acidification mediated by the vacuolar proton ATPase is another important in regulating vacuole size. In addition to the organelle pH, the V-ATPase has been implicated in lysosomal fission and fusion steps, which will also impact organelle size (Strasser et al., 2011). Loss of acidification and reduced PI (3,5)P2 levels both cause lysosomal enlargement. Thus, a wide variety of conditions including dysregulation of lipid composition, alter lysosomes size.

3. Lysosome dysfunction in neurodegeneration

Neurons, being post-mitotic, are particularly sensitive to build up of damaged organelles and mis-folded proteins arising from lysosome dysfunction. Thus, lysosome dysfunction is an important component of the pathology associated with many neurodegenerative diseases such as AD, PD, ALS and FTD. Abnormal accumulation of protease-deficient lysosomes in swollen axons around amyloid plaques is observed in human AD as well as mouse models of the disease (Gowrishankar et al.,2015). Autophagic dysfunction is also a feature of both early and late stages of AD pathology (Nixon and Yang, 2011). AD patients with mutations in presenilin (PSEN1) exhibit defects in autophagic and lysosome function, which is attributed to defective lysosome acidification and dysregulated Ca2+ homeostasis (Lee et al., 2015). Likewise, the β-CTF studies using mouse models of AD indicate that defects in axonal lysosome transport contribute to AD pathology (Rodrigues et al., 2012). In recent years, many lysosome-autophagy genes have been identified as risk factors associated with PD. For example, heterozygous mutations in the lysosomal enzyme glucosylceramidase (GBA) increase risk for PD while homozygous mutations cause an LSD. GBA mutations leads to reduced lysosome function and contributes to synuclein accumulation, thus linking lysosomes, lipid metabolism and PD pathology (Dodge, 2017). In 2017, met-analysis of genome-wide association studies (GWAS) identified 17 new risk loci (Chang et al., 2017). This included several genes associate with lysosome biology in addition to GBA. These are TMEM175 (recently shown to encode a potassium channel that could regulate lysosome function), CTSB (Cathepsin B, a lysosomal cysteine protease), and GALC (Galatosylceramidase), a gene also signalled as a risk for PD, (Abdelkarim et al., 2018; Marshall et al., 2018b; Smith et al., 2014). A PD risk allele results in reduced levels of CTSB mRNA. CTSB is involved in degrading soluble and membrane-bound α-synuclein in mice. Viral over expression of CTSB also helps clear amyloid plaques in AD mouse models (Sun et al., 2008).

In addition to these links with lysosomes, as described in PD, many of these neurodegenerative diseases also exhibit altered lipid metabolism. In AD, for instance, the most common genetic risk factor, ApoE, is involved in lipid transport and metabolism (Chew et al., 2020). The involvement of lipids in AD pathology has been reviewed extensively, elsewhere (Chew et al., 2020). Likewise, age- and dose-dependent changes in glycolipid cell metabolism can lead to PD (Hallett et al., 2019). Thus, understanding pathologies of other neurodegenerative diseases that relate to lipid metabolism could yield important insight into LSDs.

3.1. Lysosomal storage disorders or LSDs

LSDs are a classical example of disorders cause by lysosome dysfunction. Currently, they include about 40 different monogenic diseases characterized by multi-system phenotypes and often, early-onset neurodegeneration (Ballabio and Gieselmann, 2009). They are caused by mutations or loss of function of lysosomal resident proteins or non-lysosomal proteins that regulate lysosomal degradation leading to accumulation of undigested material (lipofuscin) (Platt, 2018). These can be due to mutations leading to loss of soluble hydrolases, in which case there is accumulation of a specific substrate. In others, such as

loss of function of TRPML1, the Ca2+ transporter, there are broader cellular consequences to the disease (Bassi et al., 2000). Certain cases of LSDs arise from mutations in genes that are involved in sorting, transport or post-translational modification of lysosomal enzymes. In addition to pathology arising from loss of the enzyme function, studies have demonstrated that there can be secondary pathological consequences. For instance, autophagosome-lysosome fusion is affected in many LSDs, often due to aberrant cholesterol accumulation. Another key secondary consequence is altered mTORC1 activity. While in the case of NPC, there is increased mTORC1 activity (Bartolomeo et al., 2017), fly models of Gaucher's disease (GD) show reduced mTORC1 activity (Kinghorn et al., 2016. Table 1 provides a brief description of some of the major LSDs and their symptoms. We further discuss three of these lysosomal storage diseases, NPC, MLD, and KD. Detailed description of other LSDs, their cellular phenotypes have been reviewed elsewhere (Platt, 2014; Platt, 2018; Platt et al., 2012; Platt et al., 2018).

4. Lipidosis affecting the transport of cholesterol: Niemann-Pick type C

4.1. Synthesis and transport

Cholesterol metabolism is a highly regulated process that involves several organelles across different organs. The biosynthesis begins with acetyl-CoA through the mevalonate pathway with squalene synthesis as the critical point to sterol production and ultimately the reduction of 7-dehydrocholesterol to cholesterol as the final product. Post-squalene processes occur in the endoplasmic reticulum (ER) through several enzymatic steps. Cholesterol levels are tightly regulated with contributions from dietary intake as well as de novo synthesis. De novo synthesis is primarily controlled by HMG-CoA regulation in a feedback inhibition manner. However, additional roles of the membrane-bound transcription factor, sterol-regulated element binding protein (SREBP) further contribute to maintaining cholesterol levels. Upon synthesis, cholesterol is esterified by the appropriate enzymes and transport is carried out via lipoprotein particles. Specialized cholesterol transporters can also participate in the movement of cholesterol. In addition to structural and signalling roles, cholesterol also serves as a precursor for bile acids and other steroid hormones. The general concepts of cholesterol biosynthesis have been recently reviewed including considerations for the brain (Alphonse and Jones, 2016; Jin et al., 2019; Zhang and Liu, 2015). Given the diverse roles of cholesterol in cellular compartments, the movement as well as the recycling process of cholesterol must be highly specialized. Important for the topic of this article, we focus on post-lysosomal cholesterol movement and how its defect can alter cell function. Various routes of cholesterol transport have been identified. Lange et al., reported that LDL-derived cholesterol trafficked through lysosomes does not directly traffic to the ER but rather to the plasma membrane first (Lange et al., 1997). However, reports of direct transfer to the ER from the lysosome has been presented by other groups (Neufeld et al., 1996) including one report which utilizes a pharmacological model of impaired lysosomal cholesterol trafficking (Underwood et al., 1996). Regardless, of these divergent findings it is well regarded that cholesterol trafficking through the *endo*-lysosomal system is critical and multiple destinations are feasible which may depend on the source of cholesterol (Storch and Cheruku, 2005). Interestingly, a recent report investigating lysosomal-derived cholesterol indicated that phosphatidylserine is needed for cholesterol

trafficking to the plasma membrane then the ER (Trinh et al., 2020), highlighting the complexity of cholesterol metabolism. The sophistication of cholesterol synthesis, transport and metabolism highlights the potential impact on cellular function and human disease when this important lipid is altered.

4.2. Cholesterol and Niemann-Pick type C disease

Disruption in cholesterol homeostasis has been implicated in a variety of human diseases. For example, impaired cholesterol biosynthesis causes Lathosterolosis (*SC5D* mutations) and Smith-Lemli-Opitz Syndrome (*DHCR7* mutations) (Porter and Herman, 2011). Tangier disease (OMIM: 205400) arises from mutations of the *ATP binding cassette transporter, ABCA1*, which impairs transport and release of cholesterol results in low levels of high-density lipoproteins and therefore accumulation of cholesterol (Fitzgerald et al., 2010). Regarding lysosomes and cholesterol, the most classical example is Niemann-Pick Type C (NPC) disease (Vanier and Millat, 2003). NPC arises from mis-trafficking of cholesterol through the *endo*-lysosomal system and is caused by mutations of either the NPC cholesterol transporters 1 or 2 (*NPC1* or *NPC2*) genes, which work in tandem to transport unesterified cholesterol through the lysosome (Cologna and Rosenhouse-Dantsker, 2019; Kwon et al., 2009; Li et al., 2017; Pfeffer, 2019) (Fig. 3).

As an autosomal recessive LSD, NPC has an estimated incidence of 1:100000 live births (Wassif et al., 2016) (Table 1). Approximately 95% of NPC diagnoses arise from *NPC1* mutations and the clinical phenotype is broad. Impaired cholesterol trafficking leads to accumulation of cholesterol and multi-organ dysfunction. Examples of alterations in NPC laboratory models and patients include oxidative stress (Fu et al., 2010; Klein et al., 2011), mitochondrial defects (Kennedy et al., 2014) impaired autophagy (Guo et al., 2016; Pacheco et al., 2007; Sarkar et al., 2013), and neuroinflammation (Cologna et al., 2014), among others. Several recent review articles have discussed NPC disease both in terms of basic findings and clinical perspectives (Newton et al., 2018; Papandreou and Gissen, 2016; Wheeler and Sillence, 2019).

Over the past five years, the NPC research community has made several important contributions and findings to our understanding of the disease. Many of these reports are built upon previous work to investigate potential drug therapies for NPC patients including the glycosphingolipid inhibitor Miglustat (Zavesca ®) which is not FDA-approved but is approved in other countries (Lachmann, 2003; Lachmann et al., 2004; Patterson et al., 2007). Currently, the most promising therapy is 2-hydroxypropyl-beta-cyclodextrin, which is known to bind cholesterol molecules (De Caprio et al., 1992). However, the direct mechanism of action in NPC is still an active area of research. In small animal studies, 2-hydroxypropyl-beta-cyclodextrin has been shown to ameliorate cholesterol storage, reduce clinical signs and extend lifespan (Davidson et al., 2009). Using a feline model of NPC, Vite and co-workers showed that direct central nervous system administration of 2-hydroxypropyl-beta-cyclodextrin results in improved Purkinje cell survival and lifespan (Vite et al., 2015).

Clinically, reports have indicated that 2-hydroxypropyl-beta-cyclodextrin is safe in single patient (Maarup et al., 2015) and multi-patient trials (Berry-Kravis et al.,

2018; Garcia-Robles et al., 2016; Ory et al.,2017. Several groups are investigating the mechanism of action of 2-hydroxypropyl-beta-cyclodextrin. For example, 2-hydroxypropyl-beta-cyclodextrin has been reported to affect synaptic transmission (Frech et al., 2015), to enhance *endo*-lysosome secretion (Vacca et al., 2019), and upregulates LAMP1 levels which may assist in cholesterol efflux in the absence of functional NPC1 protein (Singhal et al., 2018). Additionally, 2-hydroxypropyl-beta-cyclodextrin reduces microglial activation (Cougnoux et al., 2018), restores APMA receptors function (Feng et al., 2019) and promotes re-distribution of cholesterol (Feltes et al., 2020). Additionally, 2-hydroxypropyl-beta-cyclodextrin has been shown to promote cholesterol secretion which is dependent upon the Mucolipin-1 (MCOLN1) cation channel (Vacca et al., 2019).

Continued efforts have been focused on biomarker discovery in NPC (Bradbury et al., 2016; Giese et al., 2015; Mazzacuva et al., 2016; Rauniyar et al., 2015) and validation in patients (Sidhu et al., 2015; Sidhu et al., 2019; Wos et al., 2016). Examples range from untargeted differential proteomic (Cologna et al., 2012; Pergande et al., 2019a; Pergande et al., 2019c) and lipidomic analysis (Fan et al., 2013; Pergande et al., 2019b). Examples of biomarkers that have been utilized beyond the research laboratory include bile acid monitoring in newborn screening (Jiang et al., 2016), serum cholesterol oxidation products for diagnostics (Jiang et al., 2011) and current monitoring of serum 24(*S*)-hydroxycholesterol as well as cerebrospinal fluid fatty acid binding protein 3 and Calbindin D protein biomarkers in drug trials (Ory et al., 2017). It is expected that these types of studies will continue to further understand the roles of different mutations, experimental treatments, and modulation of known alterations in NPC.

In 2015, the Ory laboratory developed the homozygous I1061T mouse model (Praggastis et al., 2015), which has been critical for the NPC community. This mouse model represents the most common mutation seen in NPC patients and provides an additional resource beyond the other genetic animal models available (as reviewed in (Fog and Kirkegaard, 2019)). Biochemically and phenotypically the I1061T NPC1 mouse model mimics the previously more commonly used null *nih* model; however, the onset of symptoms and lifespan of mutant mice are slightly longer in this model, which is on a different genetic background than the null model. The same group had previously shown that the I1061T mutation produces a functional, yet, rapidly degraded version of the NPC1 protein (Gelsthorpe et al., 2008). Moreover, Schultz et al. (Schultz et al., 2018) have shown that this degradation is carried out by selective ER autophagy and requires the autophagy receptor, FAM134B. Although the I1061T point mutation is the most common, hundreds of clinically relevant mutations have been reported including evidence of mutational differences in protein phenotype and function (Shammas et al., 2019) which further highlights the need for additional studies to understand the consequences of specific mutations.

The NPC research field has many new and exciting findings that are on the horizon for making lasting impacts on the patients and research community. In terms of developing therapies for NPC patients, perhaps the next emerging option is gene therapy (Chandler et al., 2017). Direct brain administration of AAV9-human NPC1 shows overexpression of the protein and lysosomal localization in wild-type mice, and shows improved phenotypic characteristics and biochemical markers in mutant mice (Hughes et al., 2018). Similar

findings show single injections also result in Purkinje cell survival in mutant mice and increase lifespan of these animals (Xie et al., 2017). Membrane contact sites have also been an emerging research theme in the NPC community. Membrane contact sites allow for inter-organelle transport of materials (as reviewed: (Prinz et al., 2020)). In the context of NPC, a recent study provides evidence that NPC1 plays a tethering role in ER-endocytic and ER-lysosome contacts namely with Gramd1b (Hoglinger et al., 2019). However, in the absence of NPC1, membrane contact sites between lysosomes and mitochondria are observed (Lim et al., 2019). Finally, the oxysterol binding protein, ORP1L, has been shown to facilitate cholesterol transfer between ER-lysosome membranes and that this transport is increased in cells lacking NPC1 (Rocha et al., 2009). These findings are further complemented by a recent report of ER-lysosome contact sites facilitating cholesterol transport via the oxysterol binding protein 1, which can enable mTORC1 signalling through cholesterol sensing by the mTORC1 protein (Lim et al., 2019). Together, these new reports of membrane contact sites and their importance in NPC disease provide new insights to understanding the pathophysiology of the disorder and to develop new therapeutic strategies.

Ca^{2+} is a critical secondary messenger and participates in an array of signalling processes within the cell. Suggestions for alterations in Ca^{2+} levels, distributions and signalling were implicated in NPC in the 1980s and 1990s specifically looking at phospholipase c activity (Beaudet et al., 1980) and Ca^{2+} channel function in fibroblasts (Yamamoto et al., 1994). Over the next several decades, implications of Ca^{2+} dysfunction were included in several reports; however in 2008, Lloyd-Evans et al., suggested that NPC includes lysosomal Ca^{2+} defects (Lloyd-Evans et al., 2008). Subsequent findings show Ca^{2+} release mediated by TRPML-1 from lysosomes is impaired in NPC (Shen et al., 2012). Alterations have also been shown in astrocytes (Saez et al., 2013), iPSC derived neurons (Rabenstein et al., 2017) and primary neuron cultures (Tiscione et al., 2019). The critical role of Ca^{2+} homeostasis may indicate that understanding the causes and effects of Ca^{2+} dysfunction is critical for development treatment options for NPC.

While much of the NPC research has focused on the progressive neurodegeneration and specifically loss of Purkinje neurons, it is also important to recognize the presence of demyelination in animal models (Qiao et al., 2018) and patients (Davies-Thompson et al., 2016). Perhaps not surprising, the dysregulation of cholesterol synthesis and trafficking in NPC directly affects oligodendrocyte function and myelin maintenance. Reports of demyelination show myelin damage in the NPC corpus collosum (German et al., 2002; Yang et al., 2019). Interestingly, deletion of neuronal NPC1 results in impaired maturation of oligodendrocytes while loss of NPC1 in oligodendrocytes leads to delayed myelination (Yu and Lieberman, 2013). Importantly studies using a feline model of NPC showed decreased myelin thickness and reduced axon diameter in support of mouse model studies (Bagel et al., 2013). These reports demonstrate the importance of considering neuron-glial cross talk as well as the role of impaired cholesterol trafficking in demyelination. It is likely that the NPC field will see a shift in focus from neuron-centric to a more holistic and glial inclusive disease.

4.3. Deregulation of signalling cellular function by cholesterol

The direct defect of cholesterol trafficking in NPC provides evidence to the critical relationship in cholesterol metabolism and signalling in neurodegenerative disorders (see review (Arenas et al., 2017)). Beyond NPC, impairments in cholesterol metabolism and cholesterol mediated processes have been reported in several neurological diseases (Fig. 4). Just over three decades ago, Ignatius et al., described the connection of upregulated ApoE upon sciatic and optic nerve injury and proposed that this occurs as a repair mechanism (Ignatius et al., 1986). This study was further followed by clarification that upregulation of ApoE was a result of oligodendrocyte synthesis thereby providing lipids for myelin repair (Stoll et al., 1989). The relationship between ApoE and AD has been vastly studied and recently reviewed, perhaps with the most striking link being the APOE4 genotype with pre-disposition to developing AD (Balu et al., 2019; Huang and Mahley, 2014; Tai et al., 2017).

Given the diverse roles of cholesterol in signalling and cellular maintenance it is perhaps not surprising that many similar pathways are altered in neurodegenerative disorders. For example, the PI3K-Akt pathway, which is controlled in cholesterol rich membrane domains is dysregulated in NPC (Bi et al., 2005) and familial AD (Baki et al., 2008). Similarly, a loss of Akt signalling has been reported in familial PD (Yang et al., 2005). Although not performed in a neuronal cell type, Yamauchi et al., demonstrated that PI3K-Akt-mTOR1 played a role in SREBP regulation (Yamauchi et al., 2011). Akt and cholesterol biosynthesis are intimately intertwined with regard to myelin maintenance (Mathews and Appel, 2016).

Another critical cholesterol-involved signalling pathway is the Hedgehog pathway. In terms of NPC research, this area has not been extensively studied. The Scott group showed that Shh is produced by cerebellar Purkinje neurons and that granule cell precursor division can be regulated by Shh (Wechsler-Reya and Scott, 1999). The progressive loss of Purkinje cells in NPC may have an effect on gradual cell populations in animal models and patients; however, a specific link has not been shown to our knowledge. The protein Patched,is a cholesterol binding protein and negative regulator of the Hedgehog signalling pathway. In the absence of Patched, neurodegeneration results and Patched has been shown to be decreased in NPC models (Formichi et al., 2018) as well as impairment of primary cilia (Canterini et al., 2017). Similar to NPC, the role of Shh and AD pathophysiology is also limited however, there is some evidence that altered Shh signalling is present via Patched deregulation in AD implicating a critical role for cholesterol homeostasis (He et al., 2014).

It is also important to add the critical role of cholesterol in canonical Wnt signalling (Sheng et al., 2014), downstream to PI3K/Akt. Related to LSDs, defects in Wnt have been reported in iPSC cells of NPC (Efthymiou et al., 2015), GD (Awad et al., 2017; Zancan et al., 2015) but not in KD or other lipidoses. Significant effort has been put towards linking Wnt signalling in AD. In a study of familial AD, presilin 1 mutations result in trafficking of beta-catenin and downstream Wnt signalling (Nishimura et al., 1999). Increased phospho-beta-catenin is present in AD hippocampal pyramidal neurons and links proteasome defects with Wnt signalling and AD (Ghanevati and Miller, 2005). In fact, multiple groups have led efforts to develop treatments targeting Wnt for AD including investigating fluoxetine (Huang et al., 2018), sodium selenate (Jin et al., 2017) and ethosuximide (Tiwari et al., 2015) among

others. These reports all point to similarities in the alterations among neurodegenerative disorders and highlight the need for additional work to understand cholesterol signalling among the many LSDs with neurodegenerative phenotypes.

5. Lipidoses of galactolipids: metachromatic leukodystrophy and Krabbe's disease

5.1. Metabolism of galactosylceramides and sulfated galactosylceramides

Sphingolipids are synthesized in the endoplasmic reticulum and the Golgi apparatus, through the production of 3-ketodihydrosphingosine by serine palmitoyl-transferase activity on serine and palmitoyl CoA (Pralhada Rao et al., 2013). This precursor leads to the formation of ceramide, a key component of these complex sphingolipids. Ceramide is composed by sphingosine and fatty acyl chains and glycosylation of ceramides by ceramide glycosyltransferases renders galactosylceramides and glucosylceramides, important lipids in myelin and neuronal membranes. An additional pathway for the production of ceramide is mediated by the hydrolysis of membrane-bound sphingomyelin by the activity of neutral and acid sphingomyelinases (Fig. 5). Sulfatides, also known as 3-O-sulfogalactosylceramide, SM4, or sulfated galactocerebrosides, are a heterogenous populations of lipids, characterized by the presence of a negative charged sulfate group. Sulfates are added to galactosylceramides via the activity of 3′-phosphoadenosine-5′-phosphosulfate:cerebroside sulfotransferase (CST) enzyme, utilizing 3'phosphoadenosine-5′-phosphoslfate (PAPS) as a donor. Due to availability of multiple forms of acyl fatty acid chains (e.g. short, long, saturated, unsaturated, hydroxylated), galactosylceramides and sulfatides show multiple isoforms (Marbois et al., 2000; Svennerholm and Stallberg-Stenhagen, 1968). For example, galactosylceramides and sulfatides show more than 30 isoforms or species in the mouse and human brain.

Glycosphingolipids are degraded by specific hydrolases in the lysosome. Glucosylceramides and their lysosphingolipid glucosylsphingosine (glucopsychosine) variant are degraded by GBA while galactosylceramides and their lysosphingolipid variant galactosylsphingosine (psychosine) are degraded by galactosylceramidase (GALC). Sulfatides are largely degraded by arylsulfatase A (ARSA). Mutations in the GBA, GALC and ARSA genes are the genetic cause for GD, KD and MLD, respectively, lysosomal deficiencies with serious neurological complications. Deficiency in sphingomyelinase activity is the cause of Niemann-Pick type A and B diseases.

6. Metachromatic leukodystrophy: a sulfatide lysosomal storage disease

6.1. Genetics and pathophysiology

Metachromatic Leukodystrophy (MLD) is an autosomal recessive inherited metabolic disease caused by mutations in the ARSA gene (Gieselmann et al., 1998). Most MLD patients show early symptoms but late-infantile, juvenile and adult forms are also present. The incidence is ~1:40,000 births, being the infantile form the most frequent (Gustavson and Hagberg, 1971) (Table 1). Infantile MLD patients present with early cognitive and locomotor dysfunction, demyelination and neurodegeneration, with premature death. MLD

is still incurable although hematopoietic stem cell transplantation from healthy donors provides some control of the disease when administered in pre-symptomatic patients (Biffi et al., 2013; Boucher et al., 2015; Cartier and Aubourg, 2008; Groeschel et al., 2016). Additionally, recent advances in gene therapy using lentiviruses and adeno-associated viruses (AAV) are promising (Miyake et al., 2014; Piguet et al., 2012; Rosenberg et al., 2016).

The accepted pathogenic mechanism involves the progressive accumulation of sulfatides in oligodendrocytes, causing cell dysfunction and myelin loss (Gieselmann, 2008). However, the finding of sulfatides in non-myelin membranes such as neuronal membranes (Isaac et al., 2006) strongly underlines the possibility that accumulation of sulfatides impacts more cellular systems. The involvement of sulfatides in additional non-myelin deficits may be better appreciated in late-onset forms of the disease. For example, late-infantile patients showed decreased cerebral grey matter volume compared with age-matched controls (Groeschel et al., 2012). Adult MLD often presents with cognitive psychiatric disabilities years before major motor deficiency is noted (Kolodny and Fluharty, 1995; Shapiro et al., 1994). Interestingly overexpression of CGT or CST enzymes in neurons using the Thy1.2 promoter showed that increasing sulfatides levels in neurons lead to lethal audiogenic seizures in mice (van Zyl et al., 2010), a feature also observed in MLD patients and the MLD mouse model (Hess et al., 1996). This implicates deficits in sulfatide metabolism in myelin and non-myelin lead to variegated pathogenic responses. Furthermore, recent work has shown signs of dysfunction in MLD microglia even in areas where myelin lesions are not evident (Bergner et al., 2019). These findings also reveal that changes in sulfatide homeostasis (Safaiyan et al., 2016) are pathogenic for microglia much earlier than previously considered. This new aspect of MLD pathophysiology indicates a central role for microglia in disease progression and is aligned with growing evidence for similar roles for this immune cell type in a number of other LSD.

6.2. Sulfatides in oligodendrocyte differentiation and myelination

Although sulfatides are enriched the plasma membrane of most cells (Inui et al., 1988) and exert pleiotropic functions (for a complete review please read (Takahashi and Suzuki, 2012)), their biological function(s) remain largely unknown. When we think about the function of lipids in biological membranes, the first role that comes into consideration is as molecules that provide structural scaffolding to membrane associated proteins. Expectedly, sulfatides, like many other sphingolipids, are largely located on the outer leaflet of the plasma membrane. There is evidence that sulfatides may act as “receptors” for the interaction with extracellular molecules. One of these interactions is that with laminin and tenascin-R to promote signalling through integrin and dystroglycan receptors (Li et al., 2005). Interference of this interaction using antibodies anti-sulfatides blocks downstream signalling causing a negative regulation of oligodendrocyte maturation (Baron et al., 2014).

In the nervous system, sulfatides are crucial components of myelin, a specialized membrane produced centrally by oligodendrocytes and peripherally by Schwann cells. Sulfatides constitute one fifth of all galactosylceramides and 4–7% of the dry weight of lipids in myelin (Norton and Cammer, 1984). Reports have shown that, although in low quantities,

neurons, astrocytes and neural precursors also synthesize sulfatides (Isaac et al., 2006; Pituch et al., 2015).

The role of sulfatides in myelination was mainly studied using knockout (KO) mice null for CST (Honke, 2013; Ishibashi et al., 2002; Takano et al., 2012) or ARSA (Hess et al., 1996). Deficiency of sulfatides in CST KO mice revealed sulfatides' contribution to the stability of myelin, particularly that of the paranodal regions. Interestingly, while CST KO mice do not show any major cellular problem (Honke, 2013; Ishibashi et al., 2002; Takano et al., 2012), increased number of oligodendrocytes in the spinal cord are detected (Shroff et al., 2009), apparently due to an increased survival. These findings supported a theory that sulfatides are negative regulators of oligodendrocyte differentiation (Bansal et al., 1999; Hirahara et al., 2004).

On the other hand, the ARSA-KO mouse has increased levels of total sulfatides (Hess et al., 1996) but does not completely recapitulate the infantile human disease but shows mild demyelination and neurodegeneration. Interestingly, overexpression of sulfatides in oligodendrocytes of the ARSA KO via CST genetic manipulation causes demyelination and neurological signs (Ramakrishnan et al., 2007). This finding underscores the importance of lipid levels in triggering sufficient myelin instability to cause demyelination.

Although long acyl chain (>C18) sulfatides are the main isoforms expressed in mature myelinating cells (supporting their role(s) in myelination), the finding of short acyl chain (<C18) sulfatides at earlier premyelinating developmental times underlines additional roles for these lipids. Sulfatides are present during embryonic development in the spinal cord (colocalizing with Olig-2+ oligodendrocyte progenitors, (Hirahara et al., 2017)), sciatic nerves (Li et al., 2005) and telencephalic neural precursor cells (Pituch et al., 2015) well before myelination. The expression of short acyl chain sulfatides before myelin synthesis also suggests additional functions of sulfatides in precursor cells, which may not involve a structural role in myelin membranes but rather, related to sulfatides' association with lipid rafts (see below).

6.3. Sulfatides in neurons and immune cells

Few studies have addressed the role of sulfatides in neurons. Sulfatides with short acyl fatty chains are present in neurons and astrocytes and are mainly associated with endosomal vesicles. Previous studies have shown that sulfatides inhibit neurite outgrowth in cultured neurons via Rho signalling (Winzeler et al., 2011) and if over-expressed in neurons of the ARSA null mouse, sulfatides facilitate motor and cortical hyperexcitability (Eckhardt et al., 2007). Sulfatides are also known for their involvement in immune cell signalling. Blomquist demonstrated that although many sulfatides have promiscuous effects on antigen presenting cells (APC), lysosulfatides and the C24:1 sulfatide isoform induced the strongest stimulation (Blomqvist et al., 2009). Sulfatides also stimulate type II NK T-cells in the content of MIH class I (Jeon et al., 2008). Although this study was done under in vitro conditions, it clearly demonstrated that sulfatides induce the production of inflammatory mediators in microglia and astrocytes. Sulfatides but not galactosylceramides can trigger the phosphorylation of p38, ERK and JNK via a L-Selectin dependent-mechanism (Jeon et al., 2008). In view that sulfatides are enriched in myelin, these finding underlines a possible role for these

lipids during demyelination and immune responses in the brain. In fact, type II NK T-cells recognize myelin derived sulfatides during experimental allergic encephalomyelitis (EAE) (Maricic et al., 2014), while activation of sulfatide reactive type II NK T-cells by sulfatides reduces EAE (Jahng et al., 2004).

Likely related to non-myelin functions, sulfatides have been found dysregulated in neurodegenerative diseases like PD (Fabelo et al., 2011), AD (Haughey, 2010) and Multiple Sclerosis (Marbois et al., 2000; Moyano et al., 2016; Moyano et al., 2013). Whether this reflects a generalized and non-specific response to brain damage or due to specific sulfatide functions beside those in myelination remains unclear. Together, these findings reinforce the pleotropic roles that sulfatides have in the nervous system, and that a better understanding of the pathophysiological mechanisms associated with this important class of sphingolipids will contribute to understand pathogenic mechanisms in multiple neurodegenerative conditions.

7. Krabbe's disease: a psychosine lysosomal storage disease

7.1. Genetics and pathophysiology

Patients with a diffuse and lethal sclerosis of the brain were first described by Knud Haraldsen Krabbe, a Danish neurologist in 1916 (Krabbe, 1916). KD (also known as globoid cell leukodystrophy or GLD) is an autosomal recessive condition caused by mutations in the gene encoding for galactosylceramidase (GALC). GALC is a lysosomal hydrolase that catalyses the removal of galactose from psychosine and galactosyl-ceramides (Table 1). GALC deficiency leads to the progressive accumulation of psychosine in multiple organs, but particularly in the nervous system. The high levels of psychosine elicit a toxic environment for myelinating cells, promoting diffuse global demyelination, accompanied by gliosis, and neuronal dysfunction. Most Krabbe patients are infants with a rapid and invariably fatal course, carrying the 502 T/del mutation, which removes a 30 kb segment in the 3′ region of the gene (Wenger et al., 2019). The disease can manifest as early infantile (most cases), juvenile or adult onset forms, with over 110 mutations described (Wenger et al., 2019). The disease affects both sexes indistinctly and generally starts with hyperirritability, limb stiffness, and continues with rapid and severe motor and mental deterioration and early death (Suzuki, 2003). Although hematopoietic stem cell (HSC) transplantation (HSCT) is a well-established protocol for hematopoietic replacement, which slows disease progression when administered in presymptomatic Krabbe babies, it is compounded with significant morbidity and mortality. Although HSCT clearly protracts disease, HSCT-patients recur with significant paralysis and death during the teen years (Escolar et al., 2005; Galbiati et al., 2009; Krivit et al., 1998; Luzi et al., 2005; Reddy et al., 2011; Yagi et al., 2005). Promising gene therapy pre-clinical trials using AAV vectors have shown their efficacy to better control disease in animal models, and underline the possibility for combination with HSCT (Bradbury et al., 2018; Karumuthil-Melethil et al., 2016; Marshall et al., 2018a; Qin et al., 2012; Reddy et al., 2011). However, several key aspects of the pathogenic mechanisms in KD remain unanswered, which has limited advancing a cure for patients.

7.2. Signalling and mechanisms targeted by psychosine

Psychosine is a sphingolipid with known pleiotropic pathogenic characteristics. Being a myelin disease, it is not surprising that psychosine targets the activation of pro-apoptotic pathways in oligodendrocytes and Schwann cells, which leads to cell death and presumably to myelin loss. Numerous studies have used using a variety of cell model systems to determine how psychosine induces apoptosis of oligodendrocytes and various mechanisms have been identified. Psychosine interferes with mitochondrial potential, activation of caspases including caspase 3 and 9, release of toxic levels of cytochrome C, aberrant signalling through AMPK, phospholipase A2, connexin 43, extracellular calcium and membrane damage (Cho et al., 1997; Giri et al., 2008; Giri et al., 2006; Graziano et al., 2016; Haq et al., 2003; Hawkins-Salsbury et al., 2013; Inamura et al., 2018; Smith et al., 2011; Voccoli et al., 2014; White et al., 2011; White et al., 2009; Won et al., 2013; Zaka and Wenger, 2004). In addition to these, psychosine was shown to promote inflammatory responses in glial cells, including microglia, astrocytes and macrophages (Claycomb et al., 2014; Ijichi et al., 2013; Kondo et al., 2011; LeVine and Brown, 1997; Ohno et al., 1993; Snook et al., 2014).

Although psychosine has historically been studied only in myelinating cells, various studies demonstrated that neurons are particularly sensitive to this lipid. For example, Cantuti-Castelvetri and coll. Found that axons in Krabbe's disease suffer of axolemmal swelling, and undergo rapid atrophy with segmentation fitting the dying back neuropathy model (Castelvetri et al., 2011; Smith et al., 2011). Further studies demonstrated that axonopathy was accompanied by exacerbated psychosine-sensitive phosphatase activity, primarily via PPI and PP2A, promoting abnormal levels of dephosphorylated neurofilaments, which likely contributes to the thinning of axons diameter (Duchen et al.,1980). Axonopathy and dying back neuropathy are highly linked to how the axon is capable to sustain healthy communication between the neuronal body and the axonal terminal. Optimal rates of axonal transport are key to support this communication and factors that reduce axonal transport inevitably will undermine neuronal connections. In this regard, Cantuti-Castelvetri and coll. were the first to demonstrate that psychosine is sufficient to reduce anterograde and retrograde axonal transport modes (Cantuti Castelvetri et al., 2013), which established the basis of dying-back neuropathy in KD. Interestingly, the mechanism by which psychosine facilitated this pathogenic response in axonal transport was not mediated by myelin, plasma membrane or even neuronal and/or oligodendroglial components. By using axolemma-free preparations of squid axoplasm, these authors demonstrated that psychosine is sufficient to stimulate a PP1-GSK3β aberrant phosphorylation of motor proteins in the axon, which leads to reduced transport rates (Cantuti Castelvetri et al., 2013). These findings underlined the possibility that some of the pathogenic responses of psychosine might not need a direct involvement of membranes but rather, intermolecular interactions. In this regard, psychosine was found to directly bind to negatively charged amino-acids in the carboxi-terminus of α-synuclein (Abdelkarim et al., 2018), promoting the aberrant formation of α-synuclein aggregates in neurons of the Krabbe brain (Smith et al., 2014).

Although many additional pathogenic processes have been described in KD, with the exception of the study of Abdelkarim and coll. demonstrating a direct interaction between

psychosine and α-synuclein (Abdelkarim et al., 2018), all other studies reported to date have not been able to answer a common question: how do membrane-bound glycosphingolipids such as psychosine operate to trigger cellular and signalling responses which occur in the cytoplasm? This question, shared in other lipidoses such as Niemann-Pick types A, B, C, MLD, and GD, is further discussed below.

8. Lipid rafts: membrane tethered signalosomes affected in lipidoses

Emerging evidence has shown that most biological membranes have the property of reorganizing specific sets of lipids into limited nanometric domains known as lipid rafts (Carquin et al., 2016; Lingwood and Simons, 2010; Simons and Ikonen, 1997; Singer and Nicolson, 1972) (Fig. 6A). Lipid rafts are small (10–250 nm in diameter) dynamic platforms that operate by enabling transient or stable associations between specific lipids including cholesterol and several classes of sphingolipids and raft-associated proteins, including receptors, scaffold proteins and signalling intermediates. Lipid raft domains may be flat but they may also fold contributing to the formation of caveola.

There are three major lipid groups largely present in all plasma membranes: 1) cholesterol, which is a non-polar sterol molecule inserted within the membrane bilayer, exposing a single hydroxyl group above the membrane surface; 2) glycerophospholipids (i.e. phosphatidylcholine) composed by saturated/unsaturated fatty acyl chains and a polar head-group and 3) sphingolipids composed by a hydrophobic sphingoid base (sphingosine), in most cases acylated with fatty acids to form ceramide, which is linked to head-groups such as choline (sphingomyelin), sugars (galactosylceramide, glucosylceramide) or even more complex and larger head-groups (i.e. sulfatides; gangliosides). Many of these traditional glycosphingolipids have also lysophingolipid versions, composed by sphingosine and the corresponding sugar (i.e. galactosylsphingosine or psychosine). Rafts are important for membrane curvature. The shapes of lipids significantly influence how much a membrane can bend, a fundamental property for maintaining cell shape, endocytosis and exocytosis. The molecular volume of the head-group and composition of the fatty acyl chains (i.e. saturated vs unsaturated) greatly convey steric features that shape each lipid species. For example, most glycerophospholipids have cylindrical shapes, while cholesterol appears more like a planar molecule with a minimal head-group, sphingomyelin shows more a truncated inverted-cone shape, and most glycosphingolipids (galactosylceramides, sulfatides) and their lysosphingolipid versions (psychosine, sulfopsychosine) are inverted cones where the ceramide/sphingoid tail is topped with outward large sugar heads (Fig. 6A). Thus, the type and abundance of a particular lipid significantly influence the architecture of the raft, and consequently, modify membrane behavior (McMahon and Boucrot, 2015), including bending (Cooke and Deserno, 2006), surface tension and force sensing (Mollinedo and Gajate, 2015) and cell signalling (Gomez-Mouton et al., 2004; Iwabuchi et al., 2010).

The formation of lipid rafts is greatly determined by the melting temperature of the lipids. For example, glycerophospholipids have low-melting temperature while glycosphingolipids and cholesterol have higher-melting temperature (de Almeida et al., 2003). Hence, at physiological temperature, cholesterol and sphingolipids tend to coalesce in more rigid domains that “raft” within the more fluid non-raft areas of the cell membrane composed

by low-melting point glycerophospholipids (Bagatolli et al., 2010). Therefore, one can intuitively and easily understand that the lipid composition of the membrane as a whole and of lipid rafts in particular is crucial in the formation, maintenance and dynamics of raft behavior. Evidence for the existence of lipid rafts (Ramstedt and Slotte, 2002) has been provided by multiple studies using planar lipid systems (Fidorra et al., 2006), giant unilamellar vesicles (Dietrich et al., 2001; Kahya et al., 2003; Pinto et al., 2008) and cell-derived PM (Baumgart et al., 2007; Bernardino de la Serna et al., 2004; Plasencia et al., 2007).

The physicochemical characteristics of lipid rafts enable to envision local semi-rigid membrane areas where signalling pathways operate at optimal rates (Fig. 6A). For example, transduction of the IGF signal involves binding of IGF to the IGF-receptor, and activation of a complex cascade of events, involving multiple steps occurring at the membrane such as production of PIP3 via PI3K, which is needed for the subsequent phosphorylation of AKT (Sural-Fehr et al., 2019). Similarly, other signalling pathways key for neural cells such as those mediated by PDGFRα, transferrin receptor, EGF receptor and Notch receptor are also associated with lipid rafts. Hence, lipid rafts act as true “signalosomes” with the capacity to regulate multiple vital signalling pathways (Marin et al., 2013).

Thus, because of their architecture, it is easy to understand how even small changes in lipid raft components may exert large detrimental effects on cells through deregulation of specific raft-associated signalling pathways. In fact, in most lipidoses, alteration of lipid homeostasis leads to changes in the physiological and structural architecture of the membrane and lipid rafts. Altering lipid composition highly impacts on membrane fluidity and curvature, two properties that influence successful interactions between the cell and its environment. Fluidity reflects the average membrane viscosity generated by the rotational and lateral mobility of individual molecules and their interactions with surrounding molecules (Lenaz, 1987). Fluidity is a key property that greatly modifies positioning of proteins and lipids within the membrane. For example, short and unsaturated lipids tend to increase fluid membranes while long and saturated fatty acid chains of sphingolipids as well as cholesterol tend to decrease fluidity. Expectedly, gangliosides (Nishio et al., 2004), sphingomyelin (Galvan et al., 2008; Koike et al., 1998; von Einem et al., 2012), sulfatides (Givogri & Bongarzone, unpublished), and psychosine (D’Auria et al., 2017; Hawkins-Salsbury et al., 2013; White et al., 2011; White et al., 2009) seem to decrease fluidity leading to abnormal spatial distribution of lipid raft components and limiting the proper mobility of raft-proteins and lipids (Fig. 6B). This effect may negatively regulate the interaction of partners of a given signalling pathway. For example, sulfatides are preferentially segregated to detergent resistant membranes or lipid rafts (Moyano et al., 2014). In MLD, the sharp increase of raft sulfatides causes dysregulation of the tyrosine receptor PDGFRα (Pituch et al., 2015), interfering with proper activation of downstream AKT after stimulation of with PDGF, (Pituch et al., 2015). Likewise, the accumulation of psychosine in lipid rafts of Krabbe’s disease alters multiple signalling pathways including PKC (Hawkins-Salsbury et al., 2013; White et al., 2011; White et al., 2009), IGF-receptor (Sural-Fehr et al., 2019), phosphatases (Cantuti Castelvetri et al., 2013; Cantuti-Castelvetri and Bongarzone, 2016; Cantuti-Castelvetri et al., 2012; Castelvetri et al., 2011) and Akt (Cantuti-Castelvetri et al., 2015). As we see, the abnormal accumulation of lipid species in a given lipidosis may elicit

multiple secondary cascades of pathogenic mechanisms by affecting membrane fluidity and decreasing signal transduction efficacy. The consequence of this has the potential to affect multiple cellular responses such as remyelination, inflammation, neurodegeneration, synaptic activity and cognition.

In addition to fluidity, membrane curvature is crucial to regulate membrane processes, such as cell shape, vesicular secretion or synaptic activity. Not surprisingly, lipid shapes have a significant effect on membrane bending. Changes in membrane curvature may have a direct contribution to some of the morphological alterations observed in sphingolipidoses by promoting the physical loss of key signalling components (Fig. 5C). For example, accumulation of psychosine not only affects the composition of lipid rafts (White et al., 2009) but also promotes the vesiculation or shedding of membranes (D'Auria et al., 2017). This exacerbated membrane shedding may be significant to understand axonal swelling (Castelvetri et al., 2011) and demyelination in KD and other lipodoses. For example, neurons from GM1 and GM2 gangliosidoses also show large axonal and dendritic swellings (Purpura, 1978; Purpura and Baker, 1977), which could be directly caused by abnormal vesiculation of the membrane.

In conclusion, lipid rafts are crucial to the structure, shape, and function of the cell membrane and pathological changes of their components such as those seen in several lipidoses may have dire consequences including abnormal rigidity, excessive bending, swelling and vesiculation and triggering of pathogenic responses.

9. Final remarks

Since the first description of LSDs, there has been a remarkable effort to understand their pathophysiology. The generation of animal models that recapitulate human disease was key to achieve this goal. Although new cellular and signalling pathways have been linked to dysfunctional neural cells in these pathologies, there is still much to be discovered on how deregulation on the homeostasis of sphingolipids and cholesterol affect the nervous system and specifically neurons and glial cells. New animal models incorporating human mutations and the use of human iPS cells from affected patients will be important paradigms to study pathogenic mechanisms and to test treatments. Importantly, models that resemble adult forms of LSD are largely missing and will be greatly needed to reveal new cellular pathogenic mechanisms underpinning late onset neurodegeneration.

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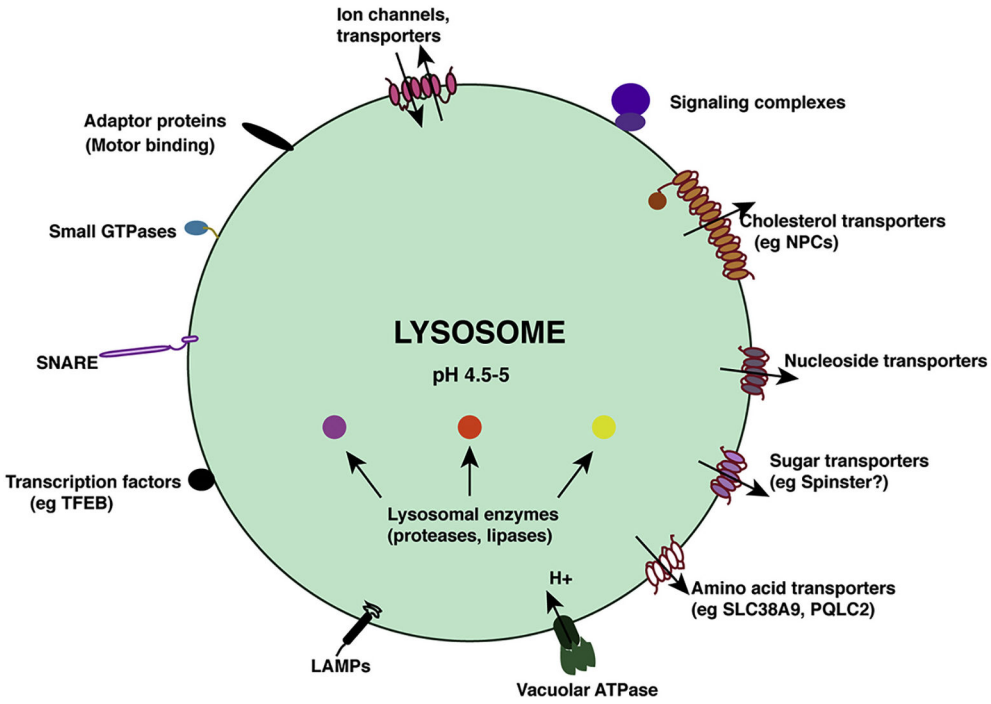

Fig. 1.

Lysosomal components and properties. Lysosomes are composed of soluble proteins (includes numerous enzymes such as cathepsins), membrane proteins as well as peripherally associated proteins (on its cytosolic surface). Lysosomes have a highly acidic pH that is essential for the action of many of its enzymes. The pH is maintained by the activity of the vacuolar proton pump. Lysosomal membrane proteins include the highly glycosylated LAMP1 and LAMP2 proteins that form a glycocalyx lining the organelle. Other membrane proteins include the cholesterol and amino acid as well as ion transporters. Peripherally associated proteins include small GTPases such as Rab7 (involved in its movement, tethering to other organelles as well as fusion with other membranes).

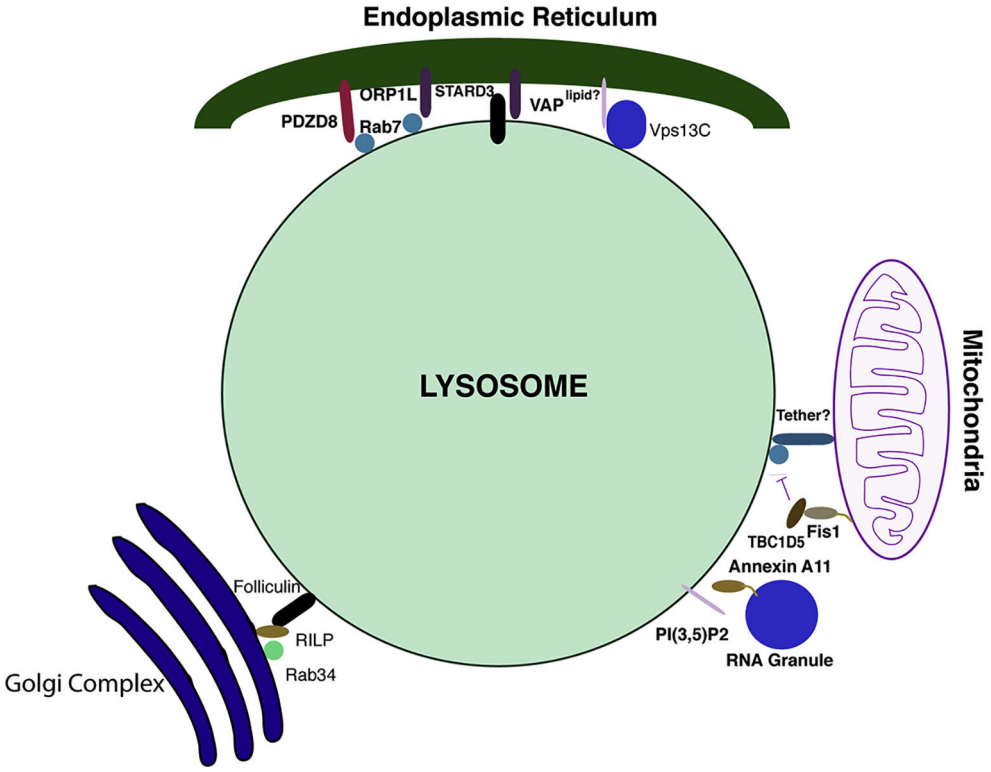

Fig. 2.

Membrane contact sites between lysosomes and other organelles. Lysosomes form numerous contacts with other organelles. These contact sites are populated by specific proteins, and aid in many different processes. Lysosome contacts with ER play a key role in lipid transfer and metabolism. The small GTPase, Rab7 is involved in lysosome contacts with ER and mitochondria. Lysosomes also form contacts with RNA granules and aid in their transport. Lysosome contacts with the Golgi complex have been implicated in their perinuclear localization.

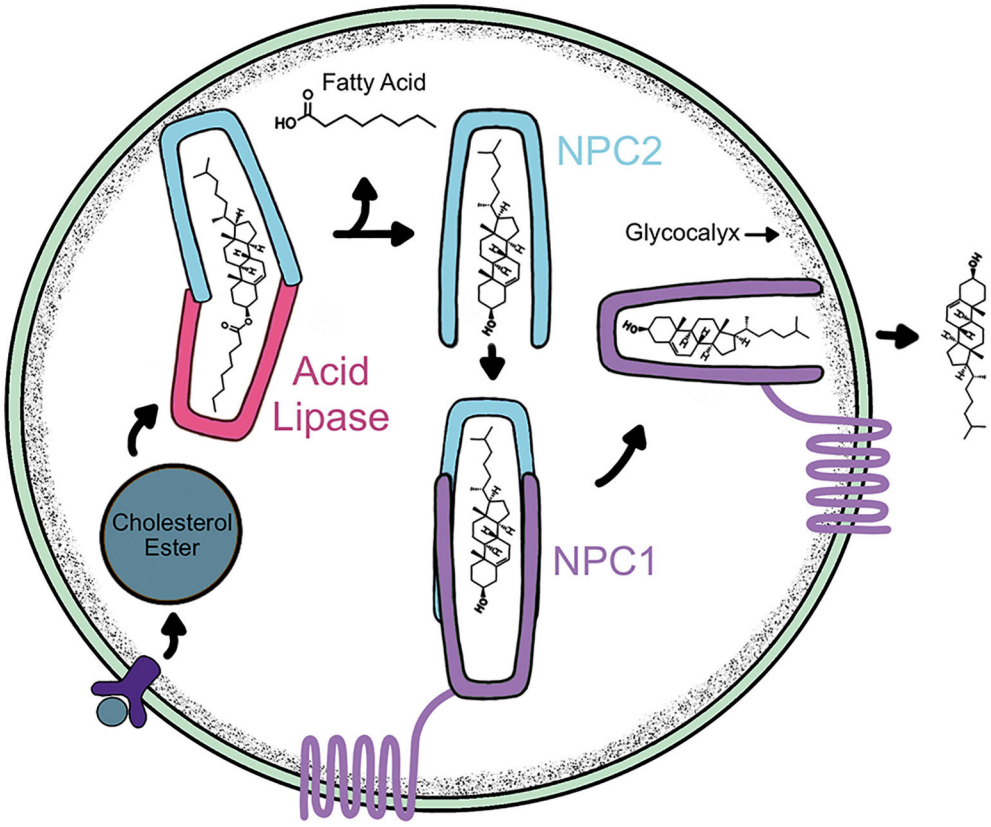

Fig. 3.

The lysosome serves as a recycling hub for cholesterol. Receptor-mediated uptake of lipoproteins results in binding of cholesterol by the NPC2 lysosomal protein and the fatty acid is cleaved by acid lipase. The free cholesterol is then handed off to the large, lysosomal membrane protein, NPC1. Cholesterol is then egressed out of the lysosome to the ER or other destinations.

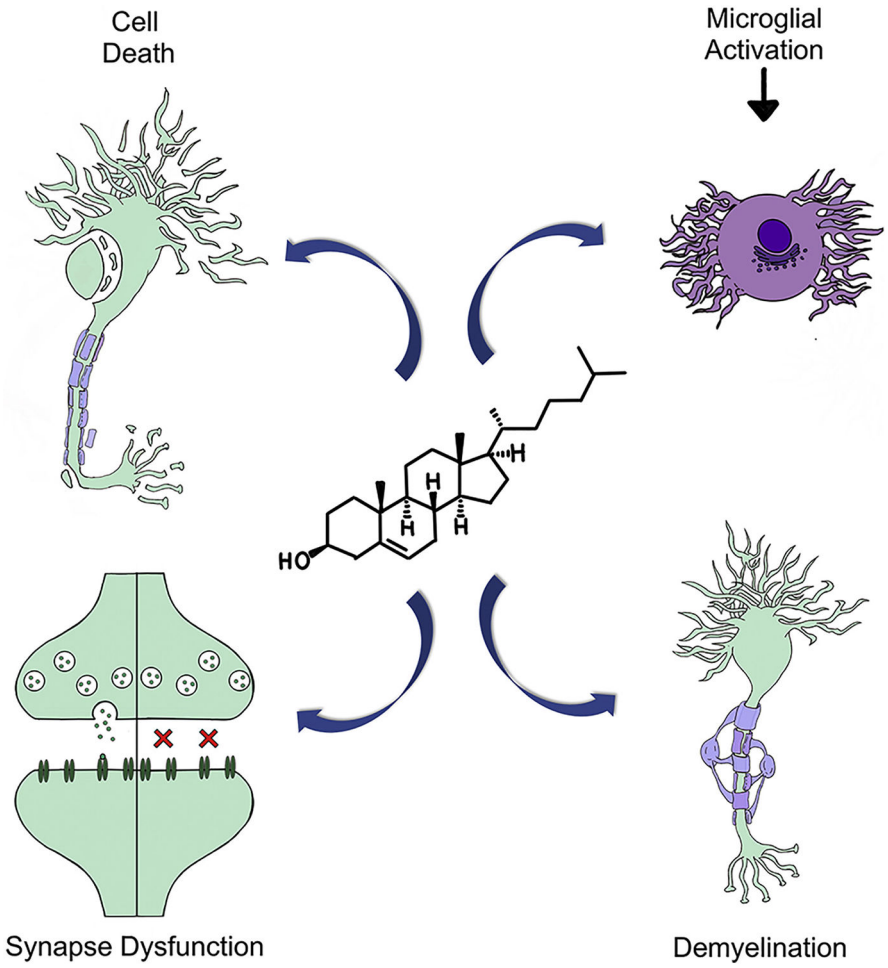

Fig. 4.

Cholesterol in neurodegeneration. Cholesterol is disrupted in many neurodegenerative conditions and plays a role in neuronal cell death, demyelination, microglial activation and synapse dysfunction.

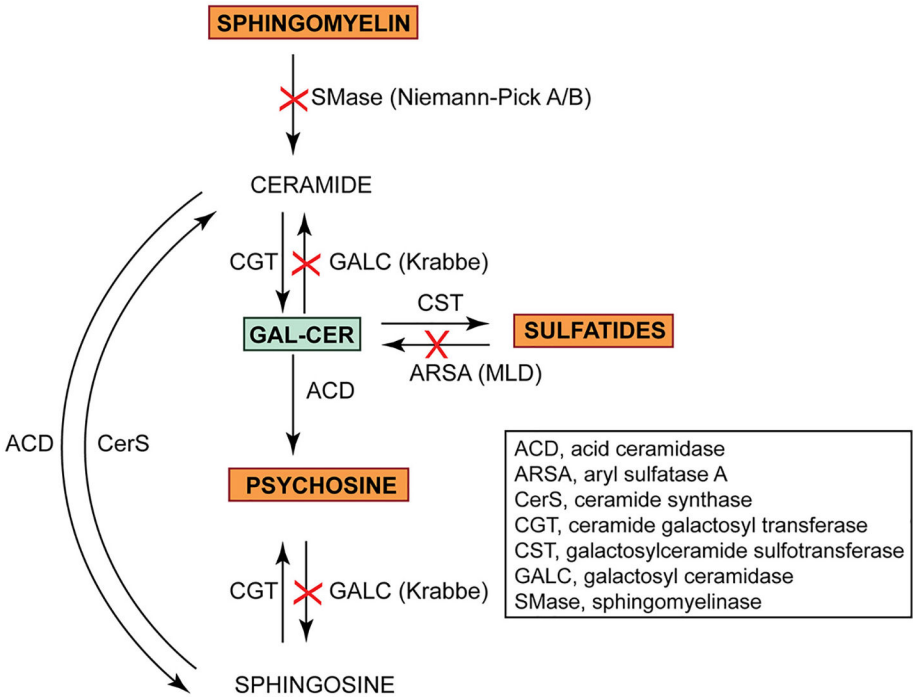

Fig. 5.
Main pathways of the glycosphingolipid metabolism.

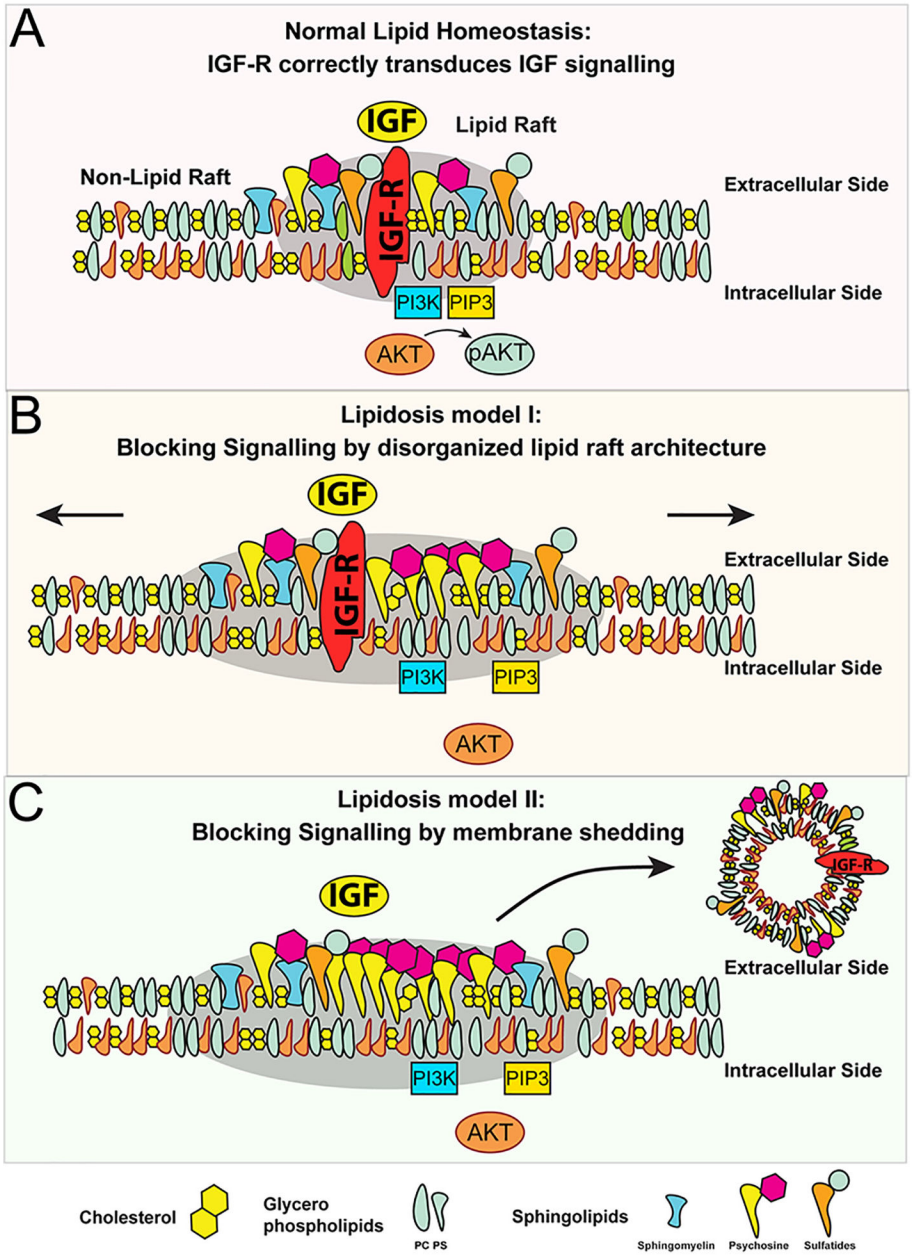

Fig. 6.

Models of signalling disruption in lipidoses. A) Under physiological conditions, cholesterol and glycosphingolipids tend to coalesce in more rigid lipid raft domains, which provide platforms where multiple components participating in signalling may interact with optimal efficiency. B) In lipidoses, the abnormal accumulation of glycosphingolipids or cholesterol in lipid rafts alter the fluidity and lateral mobility of raft-associated components, reducing or blocking the transduction of cell signalling. In this example, even though all components participating in the IGF pathway are essentially not altered, deformation of the raft interferes with their proper interaction, blocking downstream activation of AKT. C) A complementary

model to explain dysfunctional signalling in lipidoses involves the shedding or vesiculation of membranes leading to the loss of key components and blockage of the signal.

Table 1

Examples of Lysosomal storage diseases.

Enzyme	Disease	Inheritance	Symptoms	Affected lipid
Galactosylceramidase	Krabbe's disease	Autosomal recessive	Muscle weakness, stiff limbs, trouble walking, vision and hearing loss, muscle spasms, seizures.	Psychosine
Arylsulfatase A	Metachromatic leukodystrophy	Autosomal recessive	Loss of feeling in hands and feet, seizures, trouble walking and talking, vision and hearing loss.	Sulfatides
Acid sphingomyelinase (Type A, B); NPC1 and 2 (Type C1 and C2 respectively)	Niemann-Pick disease (A–C)	Autosomal recessive	hepatosplenomegaly, jaundice, slow development, trouble moving eyes up and down, breathing problems, heart disease.	Cholesterol and glycolipids
Glucocerebrosidase	Gaucher's Disease	Autosomal recessive	Anemia, hepatosplenomegaly, easy bleeding and bruising, tiredness, bone and joint pain, seizures.	Glucocerebroside
α-Galactosidase A	Fabry's Disease	X-linked	Pain, numbness, tingling n hands and feet, ringing in the ears, trouble breathing, dizziness, abnormal heart rhythms, stroke.	Glycosphingolipids
α-L-iduronidase (I); Iduronate sulfatase (II); *N*-acetyl galactosamine-4 sulfatase (VI); Heparan sulfamidase (III A); *N*-acetylglucosaminidase (III B); β-galactosidase (IVB); β-glucuronidase (VII); Hyaluronidase (IX)	Mucopoly-saccharidosis (MPS I-IX)	Most Autosomal recessive except MPS II (Hunter Syndrome) which is X-linked.	Intellectual disability, learning difficulties (I, II), Skeletal dysplasia (IV, VI, VII), motor dysfunction (III, IV, VI), trouble hearing and speaking, heart issues, trouble breathing and depression.	Heparan sulfate (I, II, III, VII), Dermatan sulfate (I, II, III, VI, VII), Keratan sulfate (IV, V) and Chondrotin sulfate (IV, VII).
α-Glucosidase	Pompe's disease	Autosomal recessive	Poor muscle tone, severe muscle weakness, enlarged heart, liver, tongue.	Glycogen
Hexosaminidase A	Tay Sachs' disease	Autosomal recessive	Progressive cognitive and motor deterioration resulting in seizures, intellectual disability, paralysis and death by age 5 years. Vision and hearing loss, red spot in the back of the eye are also common.	GM2 Ganglioside
Hexosaminidase A and B	Sandhoff's disease	Autosomal recessive	Progressive cerebral degeneration beginning at 6 months, accompanied by blindness, red macular spot, hyperacusis. Almost indistinguishable from Tay Sachs except visceral involvement.	GM2 Ganglioside
Lysosomal acid lipase	Wolman's disease	Autosomal recessive	Manifests within first few weeks of life with poor feeding, vomiting, abdominal distention secondary to hepatosplenomegaly; calcification of adrenal gland	Cholesteryl esters and triglycerides

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