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Lysosome motility and distribution: Relevance in health and disease

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ABSTRACT

Lysosomes are dynamic organelles, which can fuse with a variety of targets and undergo constant regeneration. They can move along microtubules in a retrograde and anterograde fashion by using motor proteins, kinesin and dynein, being main players in extracellular secretion, intracellular components degradation and recycling. Moreover, lysosomes interact with other intracellular organelles to regulate their turnover, such as ER, mitochondria and peroxisomes.

The correct localization of lysosomes is relevant in several physiological processes, including appropriate antigen presentation, neurotransmission and receptors modulation in neuronal synapsis, whereas hepatic lysosomes and autophagy are master regulators of nutrient homeostasis.

Alterations in lysosome function due to mutation of genes encoding lysosomal proteins, soluble hydrolases as well as membrane proteins, lead to lysosomal storage diseases (LSDs). Lysosomes containing undegraded substrates are finally stacked and therefore miss positioned inside the cell, leading to lysosomal dysfunction, which impacts a wide range of cellular functions.

1. Introduction

Lysosomes are intracellular organelles involved in a myriad of cellular processes, including degradation and processing of macromolecules and metabolites, secretion, plasma membrane repair and signaling. Indeed, the manner in which lysosomes are viewed has changed markedly in recent years and they are no longer considered merely as cellular garbage disposal organelles, but rather as central organelles for the maintenance of cellular homeostasis [1].

Lysosomes contain approximately 60 different soluble hydrolytic enzymes, responsible for the degradation and processing of macromolecules and metabolites. At the lysosome membrane, proteins such as transporters, ion channels and SNAREs participate in different aspects of lysosome function [1]. An important component is the vATPase complex, which mediates lysosomal acidification and generates an internal acidic environment with a pH of approximately 4.5–5.0, required for the optimal activity of hydrolases. In addition to these integral membrane proteins, an increasing number of proteins and protein complexes have been identified that are associated with the surface of the lysosome, depending on the metabolic conditions. These proteins and complexes, which include mTOR and their regulatory proteins, can regulate the function of lysosomes and can also be regulated by lysosomal metabolites. Therefore, lysosomes emerge as organelles that can be regulated by diverse cellular conditions, thereby impacting lysosome associated functions.

Lysosome biogenesis is a complex process that involves the maturation of early endosomes to late endosomes, the fusion between late endosomes and pre-existing lysosomes and the delivery of newly synthesized lysosomal proteins to endosomes via the Mannose-6-Phosphate receptor (M6PR) and other destination pathways [2,3].

Lysosomes are dynamic organelles, able to fuse with a variety of targets and to be re-formed after fusion events. Its substrates can originate from the extracellular milieu by endocytosis and from autophagy of macromolecules or intracellular organelles such as mitochondria. In turn, lysosomes can deliver their content to the extracellular environment through secretion, which is key in membrane repair and internally by the formation of the autophagolysosomes. In addition, lysosomes are able to interact with other organelles such as peroxisomes, endoplasmic reticulum and mitochondria through specialized membrane regions between the apposing organelles, allowing the exchange of metabolites

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and signaling molecules [4,5]. For all these functions and lysosomal interactions their motility and cellular distribution are key, as we will see in more detail in this review.

Lysosomal biogenesis, as well as lysosome secretion and autophagy are coordinately regulated by the TFEB transcription factor and TFEB in turn, is regulated by mTORC1 [4,6–10]. Under a normal nutritional status, mTOR is activated and phosphorylates TFEB, retaining this transcription factor in the cytosol, specifically at the cytosolic surface of lysosomes. During starvation and mTOR inactivation, TFEB is dephosphorylated and translocates to the nucleus where it can promote the expression of its target genes, enhancing lysosome biogenesis, exocytosis and autophagy and increasing cellular clearance [4,6,9–11]. Thus, mTOR-TFEB axis can act as a nutrient sensor [8,12].

Mutations in genes encoding for proteins involved in lysosomal function cause lysosomal storage diseases (LSDs), which are characterized by the progressive accumulation of undegraded substrates inside the lysosome, perturbing its normal function [13–15]. Over 50 LSDs have been described and although they are individually rare, collectively they can be considered a common group of pathologies, affecting 1/5000 living births [14,16]. At present, attention has been focused on how lysosome distribution and motility, as well as autophagy, are altered in these diseases [17]. Remarkably, lysosome functionality has also been found to be crucially involved in a variety of conditions, such as neurodegenerative diseases, obesity, and cancer [18]. Therefore, a better comprehension of lysosomes function, distribution and motility; and the cellular mechanisms involved in the regulation of these phenomena is essential for development of new therapeutic approaches for such devastating diseases.

The role of lysosomes as recycling organelles of cellular components as well as its contribution to cellular homeostasis has been extensively reviewed elsewhere [2,3,19,20]. Here we will focus our attention to the emerging concept of lysosome dynamics, distribution and motility as a coordinated process in several physiological conditions [21,22], such as exocytosis, phagocytosis or autophagy. Also, we will highlight the interaction of lysosomes with other organelles e.g. phagosomes or endoplasmic reticulum. We will also analyze how lysosome distribution and motility are altered in several LSDs.

Therefore, this review is organized in the following contents: (I) Lysosomal distribution and motility; describing the proteins involved in the associations between microtubule-based motor proteins and lysosomes or late endosomes, as well as the interaction between lysosomes and the actin cytoskeleton. (II) Coupling lysosomal functions to their distribution and dynamics, with special emphasis on the physiological relevance in the Immune System, the Central Nervous System (CNS) and the liver (III) Alterations in lysosome dynamics, motility and distribution in LSDs, particularly; Mucopolysacharidoses, Niemann-Pick diseases types A (NPA), B (NPB) and C (NPC), and Gaucher Disease (GD) and their consequences. (IV) Finally we will outline the relationship between LSDs and human neurodegenerative disorders.

2. Lysosomal distribution and dynamics

Similar to other organelles, lysosomes move across the cell in a tightly orchestrated manner. For long distances lysosomes move fast ($\approx$1 μm/s) along the microtubule (MT) network, whereas shorter distances involve slower movements ($\approx$0.1 μm/s) along actin microfilament arrangements [23]. Microtubules are usually oriented from microtubule organizing center (MTOC), nearby the nucleus, to the plasma membrane. In most cells, vesicle transport along MTs can be anterograde (from nucleus to plasma membrane) or retrograde (from plasma membrane to the nucleus) (Fig. 1). The highly regulated mechanisms for lysosomes distribution and motility inside the cell rely on their interaction with motor proteins, regulators and adaptors.

In general, motor proteins (kinesins for anterograde movement and dyneins for retrograde movement) mediate organelles movement along MTs. The interactions between motor proteins and *endo*-lysosomes are complex: In mammals there are several isoforms of kinesins and there is not a one-to-one organelle-kinesin relationship. For instance, lysosomes and late endosomes can bind many different kinesin heavy chains: kinesin-1 KIF5B [24], kinesin-2 KIF3A [25], kinesin-3 KIF1A/KIF1Bβ [26] and kinesin-13 KIF2A [27] and a same kinesin type (kinesin-1 KIF5B) can serve as a motor protein for different organelles inside the cell (lysosomes, late endosomes, melanosomes and proto-lysosomes) [24]. Furthermore, specific small GTPases and other *cargo* adaptor molecules and membrane phospholipids mediate the binding of the organelle to the kinesins. In particular, recruitment of KIF5B and also KIF1A/KIF1Bβ to the lysosomes and late endosomes depends on the small GTPase Arl8 and the multisubunit complex BORC [21,28,29]. This interaction also involves the participation of SKIP, which connects Arl8 and kinesin-1 [30].

Similarly, lysosome rearward movement relies on the interaction of lysosomes with the retrograde motor protein dynein, bound trough the multisubunit complex dynactin. This interaction is usually mediated by a Rab-GTPase. Rab7GTPase, and its effector protein, the Rab interacting lysosomal protein (RILP) mediate the interaction of dynein with late endosomes and lysosomes, as well as the retrograde movement. RILP interacts with dynein and specifically with the p150Glued dynactin complex subunit [31,32].

Actin cytoskeleton and myosin motor proteins also regulate lysosome movement and positioning, including the participation of the small GTPases and adaptor proteins (Fig. 1). The interaction between lysosomes and actin cytoskeleton is particularly relevant for its fusion to the plasma membrane, for example, during dendritic cell (DC) maturation [33]. Among all the different arrangements of actin microfilaments, endosomes and lysosomes are usually bound to actin-based comet tails [34], allowing their propulsion through the cytoplasm. Here, the Wiskott-Aldrich Syndrome Protein and Scar Homolog (WASH) complex have a critical role. WASH complex C-terminus is involved in Arp2/3 activation and its N-terminus interacts with BLOS2, a subunit of BLOC-1 complex, involved in lysosomes-endosomes formation and trafficking. Additionally, WASH and BLOS2 co-localize with γ–tubulin, suggesting that they could regulate MTOC-associated functions. Therefore, WASH may have a role in lysosome-endosome transport by connecting actin and MTs cytoskeletons [35,36]. On the other hand, loss of WASH function disturbs phagocytic and autophagic clearance due to increased lysosomal acidification, along with cell spreading and cell migration defects in macrophages [37].

3. Coupling lysosomal functions to its distribution and dynamics: physiological relevance

As mentioned above, lysosomes fulfill several functions that are physiologically relevant including degradation and processing of macromolecules, secretion and plasma membrane repair. In addition, lysosomes are key for completing autophagy and the degradation of intracellular macromolecules as well as old organelles. Furthermore, lysosomes are actively involved in metabolic signaling. For all these functions lysosomes must dynamically move and distribute inside the cell.

Thus, for the degradation of extracellular and intracellular components lysosomes must fuse with endocytic vesicles and with autophagosomes, respectively. Autophagy can be classified into three categories: *Macro-autophagy* (hereafter referred to as autophagy for the purpose of this review); which involves a multistep process with several vesicular fusion events, *Micro-autophagy*; in which lysosomes are directly involved in engulfing and digesting small molecular content, and *Chaperone-mediated autophagy* (CMA). The main difference between these three categories is how the cellular content is directed to lysosomes for degradation. Here we will focus our attention in the first category [38]. Autophagy comprises the formation of a *phagophore* that surrounds cellular components targeted for degradation. The phagophore membrane could come from several sources: the endoplasmic

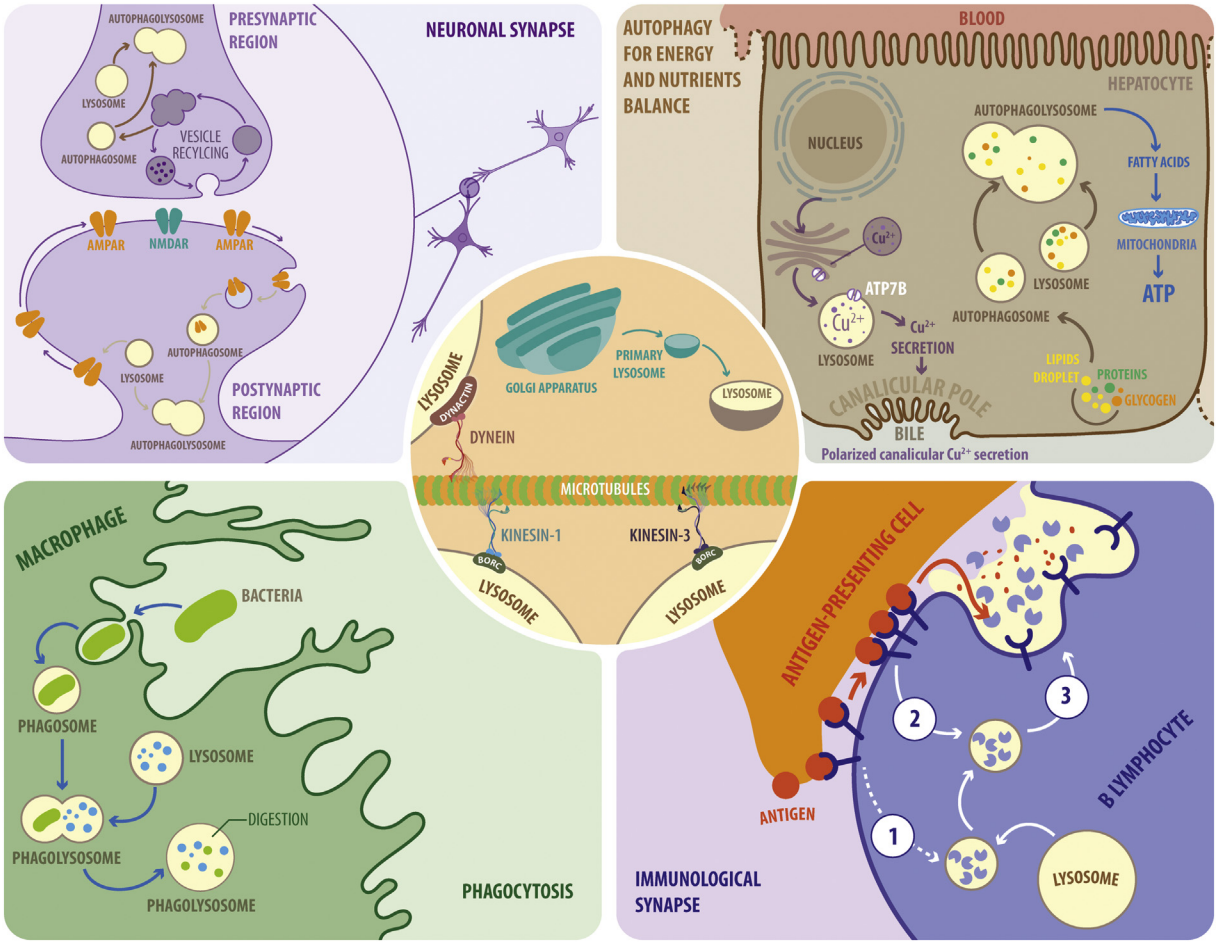

Fig. 1. Lysosomal positioning and function varies among different cell types. The relevance of lysosomes in neuronal synapse, hepatocytes autophagy for energy and nutrients balance and Cu^{2+} biliary secretion, macrophage phagocytosis and B lymphocyte immunological synapse is shown. In neurons, at the presynaptic region, lysosomes and autophagosomes are involved in vesicles and neurotransmitters recycling, meanwhile at the postsynaptic region, they participate on receptors turn over and recycling. In hepatocytes, they are responsible for degradation of macromolecules and recycling of sugars, amino acids and fatty acids and for excess of Cu^{2+} secretion into bile. In macrophages lysosomes degrade macrocomponents engulfed at plasma membrane (phagocytosis). In the immunological synapse B-lymphocytes recognize antigens presented by the antigen presenting cells through their B-cell receptor and the antigen-BCR complexes is endocytosed and targeted to endolysosomal compartments (1 and 2) where antigen processing and peptide loading onto MHC-II molecules takes place. After, the MHC-II-peptide complexes could be presented at the B-lymphocyte surface (3). Kinesin and dynein motor proteins mediate anterograde and retrograde movements of lysosomes respectively, along the MTs (central image).

reticulum (ER), the mitochondria, the ER-Golgi-Intermediate compartment (ERGIC), as well as from the ER-mitochondria contact sites and can expand forming a double membrane organelle named *autophagosome*. This LC3-II positive organelle fuses with a late endosome and is then called *amphisome*, which is beclin-1 positive, and finally fuses with a lysosome becoming an *autolysosome* [39], a process that absolutely depends on lysosome positioning [40].

Final completion of the autophagic process requires the fusion of the autophagosome with the lysosome, which mainly occurs in the perinuclear region in most cells. This process is facilitated through physical proximity of the organelles, slowing of vesicular trafficking and positioning of these degradative compartments in the vicinity of the nucleus in a microtubule-dependent manner [41,42]. Although the minus-end-directed motor protein dynein mediates the centripetal trafficking of autophagosomes, it is not known whether it also determines the perinuclear location of autophagosomes and lysosomes.

Lysosomal secretion or exocytosis requires two sequential steps [11]. In the first one, lysosomes are recruited close to the proximity of the plasma membrane. In the second, the pool of pre-docked lysosomes fuse with the plasma membrane in response to lysosomal Ca^{2+} release via the transient receptor potential mucolipin 1 (TRPML1). Lysosomal exocytosis is relevant in several physiological processes such as plasma membrane repair, bone resorption, and in the immune response [1,43]. For both processes lysosome positioning has been proved to be a crucial condition. Thus, it is of special interest to understand the regulatory mechanisms of lysosomal positioning across the cell.

As highlighted before, lysosome positioning in cells is dynamically regulated. For example, starvation induces dynein/dynactin-dependent perinuclear clustering of LAMP1 vesicles. Following starvation-induced lysosomal Ca^{2+} efflux dynein activation depends on the enhanced interaction between the TRPML1-associated calcium sensing protein, ALG-2, and the dynactin component, dynamitin [44].

Interestingly, and as we will mention below, TFEB has not only been implicated in the regulation of lysosome biogenesis, but also in their positioning inside the cell in response to metabolic status. An example of TFEB dependent regulation of lysosomal positioning is the expression of TMEM55B, which can recruit dynein adaptor JIP4, promoting dynein-dependent retrograde transport of lysosomes [45]. It is also important to mention that, at the same time, this entire complex interacts with the cholesterol sensor ORP1L [21]. Accordingly, studies have shown that an increase in intracellular cholesterol levels promotes reverse transport of lysosomes increasing their perinuclear clustering, which is particularly relevant in lysosomal storage disorders (LSD) such as NPC [46]. In different LSD, mucolipidosis type IV, point mutations

have been described in the Ca^{2+} channel TRPML1. Therefore, Ca^{2+} can regulate lysosome motility. It has been demonstrated in fibroblasts that TRPML1 and its main endogenous agonist, PtdIns (3,5)P_2, are required for retrograde transport of lysosomes in a Rab7-RILP-ORP1L independent way [44].

Next, we will describe how different lysosomal functions are coupled with the motility and distribution of the lysosomes in three systems/tissues that are particularly relevant from a physiological point of view: the immune system, the CNS and the liver.

3.1. Lysosome functions and dynamics in cells of the immune system

3.1.1. Role of lysosomes in antigen processing and presentation

One of the prominent functions of lysosomes is to process extracellular antigens up taken by cells of the immune system. Professional antigen presenting cells, such as macrophages, B-lymphocytes and dendritic cells capture foreign antigens and target them to endolysosomal compartments, where their degradation takes place. Within these compartments, antigenic peptides are generated and mounted on MHC-II molecules for further delivery to the cell surface for presentation to T helper lymphocytes [47]. Thus, coordinating the uptake of antigens and their fusion with lysosome compartments is a critical process to achieve an efficient adaptive immune response.

In this context, the convergence of lysosomes with antigen-containing endosomal compartments has been well studied in both phagocytosis and during the formation of an immunological synapse (Fig. 1).

Phagocytosis is defined as cellular ingestion of bulk particles ($> 0{,}5\,\mu M$), such as pathogens and apoptotic bodies. The process requires the recognition of certain structures of the phagocyted body by specific membrane receptors, such as the mannose receptor, complement receptor and scavenger receptors [48–50]. The invaginated plasma membrane surrounding the phagocyted body gives rise to a phagosome, a transient organelle that becomes mature prior to its fusion with lysosomes for degradation of its content [51].

The immune synapse (IS) is a tight communication between lymphocytes and antigen presenting cells (APC). In this context, polarization of the centrosome or MTOC coordinates lysosome proximity to the IS [52]. An example of this is the immune synapse between B-lymphocyte and an APC, where B-lymphocytes recognize antigens presented by the APC through their B-cell receptor (BCR) [53]. This interaction promotes the establishment of a polarized phenotype in B-cells, where organelles such as MTOC and lysosomes are mobilized towards the IS [54–56]. Further secretion of the lysosomal content into the synaptic space, has been suggested to facilitate antigen extraction, by locally liberating hydrolases [57]. Antigen-BCR complexes are further endocytosed and targeted to endolysosomal compartments where antigen processing and peptide loading onto MHC-II molecules takes place [58]. MHC-II-peptide complexes are presented to T-lymphocytes $CD4^+$, which in turn can stimulate B-lymphocyte maturation, giving rise to antibody-producing plasma B-cells as well as B-memory cells [59].

Observations made in both T and B-lymphocytes have shown that the recruitment of lysosomes to the immune synapse is tightly coupled to the repositioning of the MTOC at the synaptic membrane [60]. In both cases the microtubule-based motor protein, Dynein plays a role in transporting lysosomes towards the MTOC [61]. During the activation of cytotoxic-T-lymphocytes, Rab7 was shown to bind dynein through RILP and thereby recruit secretory lysosomes (also known as lytic granules) towards the MTOC, which concomitantly translocates to the synaptic membrane.

In dendritic cells transcriptional regulation of lysosomal specific membrane proteins by TFEB has also been described. TFEB was shown to act as a molecular switch between MHC-I restricted cross-presentation and antigen presentation involving MHC-II. Up-regulation of TFEB during Dendritic cell maturation reduces cross-presentation while enhancing lysosome degradation of up-taken antigens, thereby favoring MHC-II presentation [62]. Thus, lysosome activation has a direct impact on antigen presentation and thus on immune effector functions.

3.2. Lysosomal functions, distribution and dynamics in the CNS

In neurons, the lysosomes receive their substrates from autophagic and endocytic pathways and have degradative and signaling functions very similar to non-neuronal cells. However, the long distance between the cell body and distal ends of dendrites, and specially axons, makes the neuronal lysosomal system highly dependent of an efficient transport system. Indeed, lysosome dysfunction, defective trafficking and maturation in neurons underlie several neurodegenerative conditions.

Lysosomes biogenesis is tightly linked to neuron metabolic status. Anabolic conditions activates mTORC1 pathway, through RagA/B GEF activation, leading to TFEB phosphorylation and retaining in the cytosol, turning off lysosome biogenesis. On the other hand, catabolic conditions activate the AMPK pathway, promoting TFEB dephosphorylation and translocation to the nucleus where it enhances expression of genes involved in lysosomal biogenesis [63]. This is also related to the pH gradient and lysosomes movement direction. Under normal nutrient conditions (more alkaline pH), anterograde movement of lysosomes by kinesins is promoted. But under starvation (lower pH) Ca^{2+} efflux through TRPML1 not only enhances TFEB dephosphorylation and nuclear translocation, but also promotes dynein transport leading to perinuclear localization of lysosomes [64]. Regarding synaptogenesis, the role of mTOR has been already established [65], but the incidence of TFEB function remains to be elucidated.

The maturation of endocytic-vesicles to endolysosomes and mature lysosomes is highly coupled to their retrograde transport, with a decreasing pH gradient from the distal to the proximal axon and matures lysosomes mostly concentrated in the cell body [66,67]. Neuronal lysosomes receive substrates mainly from the autophagic pathway, that works constitutively clearing damaged organelles and cellular waste and preventing the accumulation of toxic molecules [68]. In the CNS, autophagy is a constitutive neuronal process that occurs normally under physiological conditions. For example, it has been reported that autophagy regulates lipid metabolism within hypothalamic neurons modulating neuropeptide levels [69]. Therefore, it is expected that disturbances in constitutive autophagy lead to neurodegeneration. In fact, impaired autophagy has been implicated in several neurodegenerative disorders, among them Alzheimer's disease (AD) [70], Parkinson's disease (PD) [71] and Amyotrophic Lateral Sclerosis (ALS) [72].

Autophagosomes and endocytic vesicles mature to amphisomes and late endosomes by fusion with more acidic compartments acquiring endolysosomal markers such as LAMP1 and Rab7 [73,74] and endosome-specific phosphoinositides [75] allowing its association of late endosome-motor proteins of [76] and then long-range retrograde transport, acidifying and maturing into lysosomes, in the cell body [74,76,77]. Thus, although the autophagosomes are continually formed, mostly at distal ends of axons [77,78], they are efficiently transported and cleared in the cell body.

Under normal conditions, there is a basal rate of autophagy that maintains cell homeostasis, but under adverse conditions, such as depletion of nutrients or oxidative stress, autophagy is induced, allowing the degradation of macromolecules and the efficient removal of damaged organelles and cytoplasmic protein aggregates [79]. Although autophagy is a constitutive process in neurons, the number of autophagosomes in a given moment is not high. Autophagosomes, autophagic vesicles (AVs) or amphisomes are rarely observed in neurons unless lysosome function is disrupted [80]. This could indicate that neuronal autophagy is quite an efficient process, so autophagosomes do not accumulate under normal physiological conditions [81].

In neurons, autophagosomes are mainly synthesized in the axonal terminal compartment. Although they can move in either direction, there is a preferential retrograde transport along the axons e.g. from

terminal to the soma, where they can fuse with lysosomes to form auto lysosomes allowing cargo degradation and recycling [82].

Neuronal synapses are highly dynamic structures. Recent evidence has revealed that autophagy is capable of regulating synaptic function in presynaptic and postsynaptic terminals. In this sense, the autophagy rate is inversely correlated with synaptogenesis and directly related with synaptic elimination. More explicitly, autophagy participates in the weakening and elimination of the synapses removing redundant or inappropriate synaptic connections. Also, autophagy participates in synaptic transmission regulating in the presynaptic, the number of synaptic vesicles and, the turnover of neurotransmitters receptors, in the postsynaptic [83]. For example, inhibition of autophagy increases spine density in neurons, and in postsynaptic terminals autophagy contributes to AMPARs degradation [84]. Several presynaptic proteins, such as Endophilin-A and Synaptojanin-1, promote autophagy meanwhile Bassoon represses autophagy. Moreover, Presenilin-1 and palmitoyl-protein thioesterase-1, are directly involved in lysosome acidification and are also implicated in presynaptic function [85]. Also, the structure and maintenance of dendritic spines is interrelated with the lysosomal function. Synaptic activity induces the mobilization of LAMP-1 vesicles towards the activated dendritic spines contributing to synaptic protein turn over and the maintenance of the synaptic structure [86].

Several gene mutations related to proteins involved in lysosome function have been identified in AD, FTD and PD, linking LSDs and these neurodegenerative diseases. Interestingly, lysosome alkalization is a common feature among all these neurodegenerative disorders [87]. In particular, in AD as well several LSDs, there is evidence of swollen axons and AVs and accumulation of multivesicular bodies (MVBs). These lead to anterograde transport disruption, enhanced by undegraded protein and their accumulation [87,88].

Additionally, in pathological conditions perturbations in autophagy occur not only in neurons but also in glial cells. For example in GD, the most prevalent LSD, there is evidence for impairment of mitophagy in neurons as well as in astrocytes [89].

3.3. Lysosomal functions, distribution and dynamics in the liver

3.3.1. Role of lysosomes in the regulation of autophagy during starvation

Most of the knowledge we have about lysosome function and particularly autophagy comes from studies in the liver. In this organ, autophagy has a central role in the balance of energy and nutrients, removing either physiologically or pathologically misfolded proteins, inducing lipids and glycogen catabolism as well as turnover of several other organelles, especially ER and mitochondria.

Although the identity of proteins degraded by autophagy in the liver under normal physiological conditions is still matter of debate, some hints may emerge from studies of autophagic degradation of miss folded proteins under pathophysiological conditions [90].

More recently, several groups have demonstrated that autophagy of lipids or lipophagy is especially relevant in hepatocytes [91,92]. In this context, lysosomes are involved in the degradation of lipid droplets (LD), an intracellular storage depot for neutral lipids; among them triglycerides (TGs), diacylglycerol (DG) and cholesterol ester (CE), surrounded with a polar phospholipid monolayer membrane and a variety of proteins including, Rab proteins and perilipins [93]. Removal of perilipins is necessary for cytosolic lipases and autophagy factors to gain access to the lipids in the core of the LD.

Regulation of liver autophagy is clearly visualized in conditions of nutrient deprivation, in which three general responses are observed (Reviewed in 89): i) Recycling of cellular proteins, lipids and sugars. Early in starvation, autophagy of cytosolic proteins and organelles predominates, generating an important source of amino acids. If nutrient deprivation persists, there is a switch towards glycogen and LD as preferential cargos, contributing to an increase in glucose and free fatty acids that can be used to sustain a positive energetic balance; ii) Regulation of mitochondrial number and quality control. By mitophagy the liver would not only eliminate nonfunctional mitochondria, but also would control mitochondrial mass through a coordinated balance with mitochondrial biogenesis and iii) Selective removal via CMA of enzymes that induce metabolic pathways such as glycolysis or lipogenesis. In addition, CMA would also induce hepatic lipolytic capacity through degradation of perilipins on the surface of LD [39,91]. In regard to the hierarchical selectivity for autophagic substrates, organelle and protein selectivity have been clearly demonstrated. However, the selectivity determinants for lipids or glycogen are still matter of debate [91].

It is well-known that autophagic flux decreases in an age-dependent manner in the liver [94,95] which would be related mainly with a decrease in the maturation of autophagosomes to autophagolysosomes [96]. Interestingly, a recent report shows that hepatocytes from old mice display lower association of autophagosomes and lysosomes with the microtubule-based minus-end-directed motor proteins, dynein and KIFC3 respectively [97].

As previously described, TFEB is a master regulation of lysosome function, exocytosis and autophagy. In this context, it is not surprising that there is an inverse correlation between TFEB activation and steatosis severity and injury in the liver of mice and patients with non-alcohol and ethanol-induced fatty liver diseases [98].

3.3.2. Role of lysosomes for management of metals and alterations in LSDs

Overload of metals such as iron and copper leads to multiple lesions in liver cells [99–101]. The studies from Polishchuk et al. [99] demonstrated that an increase in Cu concentration induced a direct trafficking of the Cu^+ATP7B pump from the TGN to a subset of lysosomes. ATP7B would mediate Cu import in the lumen of these lysosomes and through the interaction with the p62 subunit of the dynactin complex the polarized exocytosis at the canalicular surface of hepatocytes of these lysosomes Cu-overloaded (Fig. 1). This study demonstrates the relevance of lysosomes and their polarized distribution on copper homeostasis.

Alterations in copper levels and distribution have been reported in NPC patients and mouse models [102–104]. Interestingly, we have described that increased copper content in the liver correlated with decreased copper levels in the bile of NPC mice [103,104], suggesting a decrease in the polarized exocytosis of lysosomes at the canalicular pole.

Additionally, lysosomes and their role in autophagy are critical to reduce the hepatic toxicity of either copper [105] or iron [106] in Wilson Disease or hemochromatosis respectively, as well as in the mobilization of iron from ferritin stores [107].

4. Pathologies associated to defective lysosome distribution and dynamics

Considering that lysosomes display critical functions in many different processes, it has become increasingly clear that alterations in their localization and distribution would be implicated in the pathophysiology of several diseases where autophagy is involved. Among these pathologies are Alzheimer's disease, Down Syndrome [108], non-alcoholic fatty liver disease (NAFLD) [109,110] and particularly several LSDs. It is important to mention that in these diseases, not only is autophagy impaired, but also disturbances in the general normal function of the lysosomes are present.

Several LSDs are associated to mutations in genes whose products are involved in lysosomal positioning and/or motility [111]. Among others, MPS type IV and TRPML1 mutation [44], Danon Disease and LAMP2 mutation [112], Charcot-Marie-Tooth 2B and Rab7 mutation [113], Charcot-Marie-Tooth 2A and KIF1Bb3-Q98L mutation [26]. Some other LSDs are not only associated to defects in these types of proteins, but also lead to alterations in lysosome distribution.

In this section, we discuss LSDs; beginning with Gaucher Disease (GD), where not only autophagy impairment seems to be relevant but

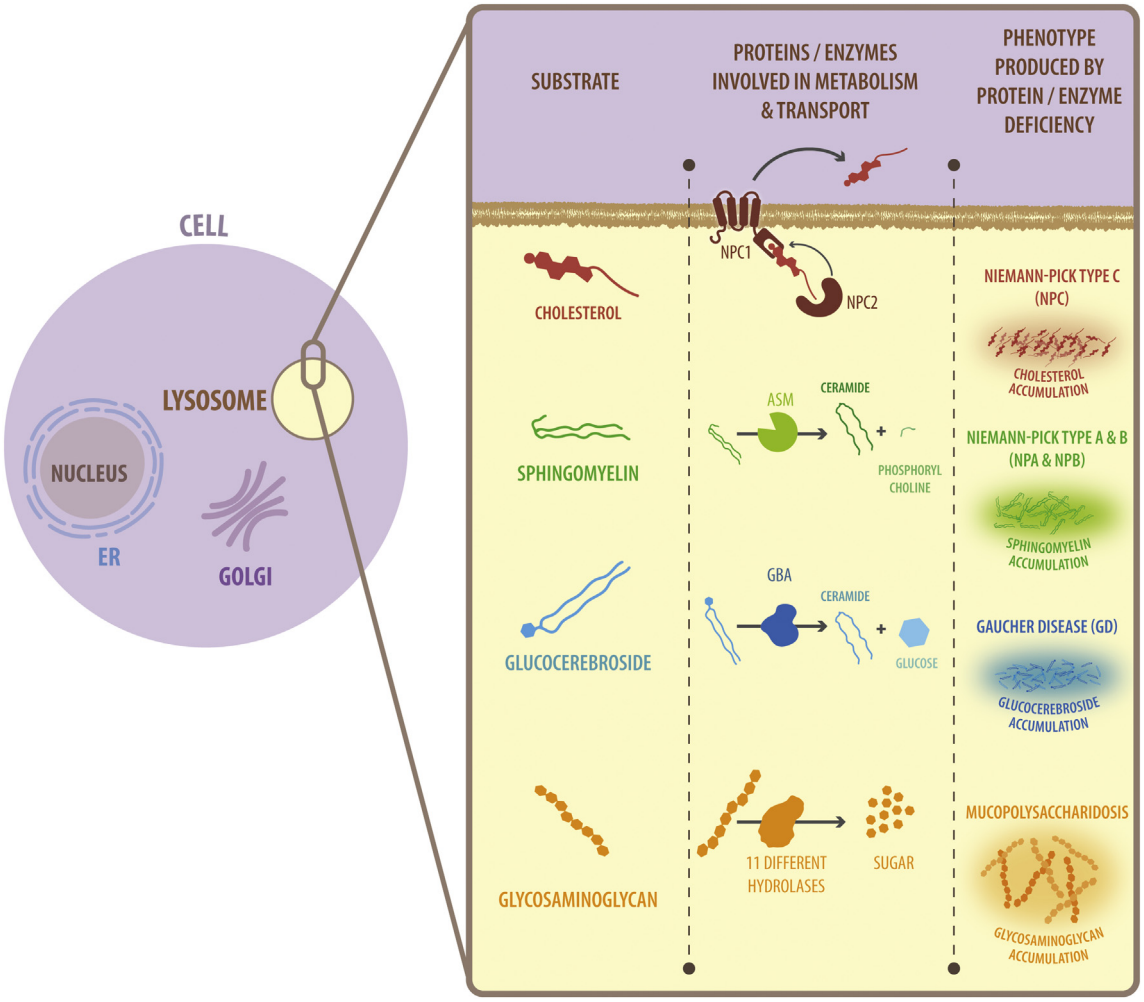

Fig. 2. Lysosome storage disorders. Gaucher Disease (GD), mucopolysaccharidosis, Niemann-Pick A, B and C (NPA, NPB and NPC) LSDs are depicted, indicating the membrane protein or soluble enzymes altered or miss functioning. These defects lead to abnormal accumulation of substrates that cannot be transported out of the lysosome or degraded by enzymes. Lysosomes accumulating non-degraded substrates display defects in movement, positioning and therefore function are impaired.

also lysosomes mislocalization is involved in the pathophysiology of the disease. We will further describe Mucopolysacharidoses, Niemann-Pick type A (NPA), type B (NPB) and type C (NPC) diseases, where alterations in the relationship between lysosome dysfunction and autophagy become progressively clearer. Finally, we include an analysis concerning the connection between LSDs and neurodegenerative disorders and the immune system.

4.1. Gaucher disease

GD is a recessive autosomic inherited disorder where over 300 mutations [114] on the GBA1 gene that encodes the lysosomal hydrolase β-glucocerebrosidase (GCase) have been described (Fig. 2). β-Glucocerebrosidase loss of function leads to glucosylceramide and glucosylsphingosine accumulation inside the lysosomes with the consequent lysosome dysfunction [115]. GD can be classified into three types: Type I; adult onset non-neuropathic or visceral, Type II; severe early childhood neurodegeneration or acute and Type III; late onset ataxia with myoclonic seizures or chronic [116]. Lysosomal miss localization has been proposed as an early event, prior to neuronal loss and microglia activation. This is supported by miss localization of Limp-2 puncta and loss of Lamp-1 puncta [117]. Interestingly, transport of β-glucocerebrosidase from ER to lysosomes is mediated by Limp-2 instead of mannose-6-phosphate receptor as for most of the other lysosomal hydrolases [118]. As well as in other LSDs, lysosomes malfunction in GD results in autophagy disruption. Blocking retrograde transport disrupts normal autophagic fusion essential for adequate endosomal degradation by lysosomes. Therefore, along with the accumulation of β-glucocerebrosidase substrates there is also an increase of Lamp-2 and p62, an autophagy adaptor protein responsible for cargo delivery of ubiquitinated substrates [119,120]. This has been supported not only by GAB1 KO mice model but also by a non-mammal model, Drosophila [121].

4.2. Mucopolysaccharidosis

Mucopolysaccharidosis represents a quarter of all LSDs [122]. They are caused by progressive accumulation of undegraded glycosaminoglycans (Fig. 2), among them dermatan, chondroitin, heparan and keratan sulfate and hyaluronic acid, the main components of the extracellular matrix where they normally interacts with collagen fibrils. There are several pathologies within this group, comprising specific enzyme deficiencies, caused by mutations in 11 different genes. Likewise the rest of the LSDs, MPS are autosomal recessive traits with the sole exception of MPS-II, also known as Hunter syndrome, which is an X-linked condition.

It has been described in mucopolysaccharidosis type IIIA (MPS-IIIA) as well as in multiple sulfatase deficiency (MSD) an increased number of autophagosomes, suggesting an activation of the autophagic response. However, in mouse models of these diseases, there is evidence

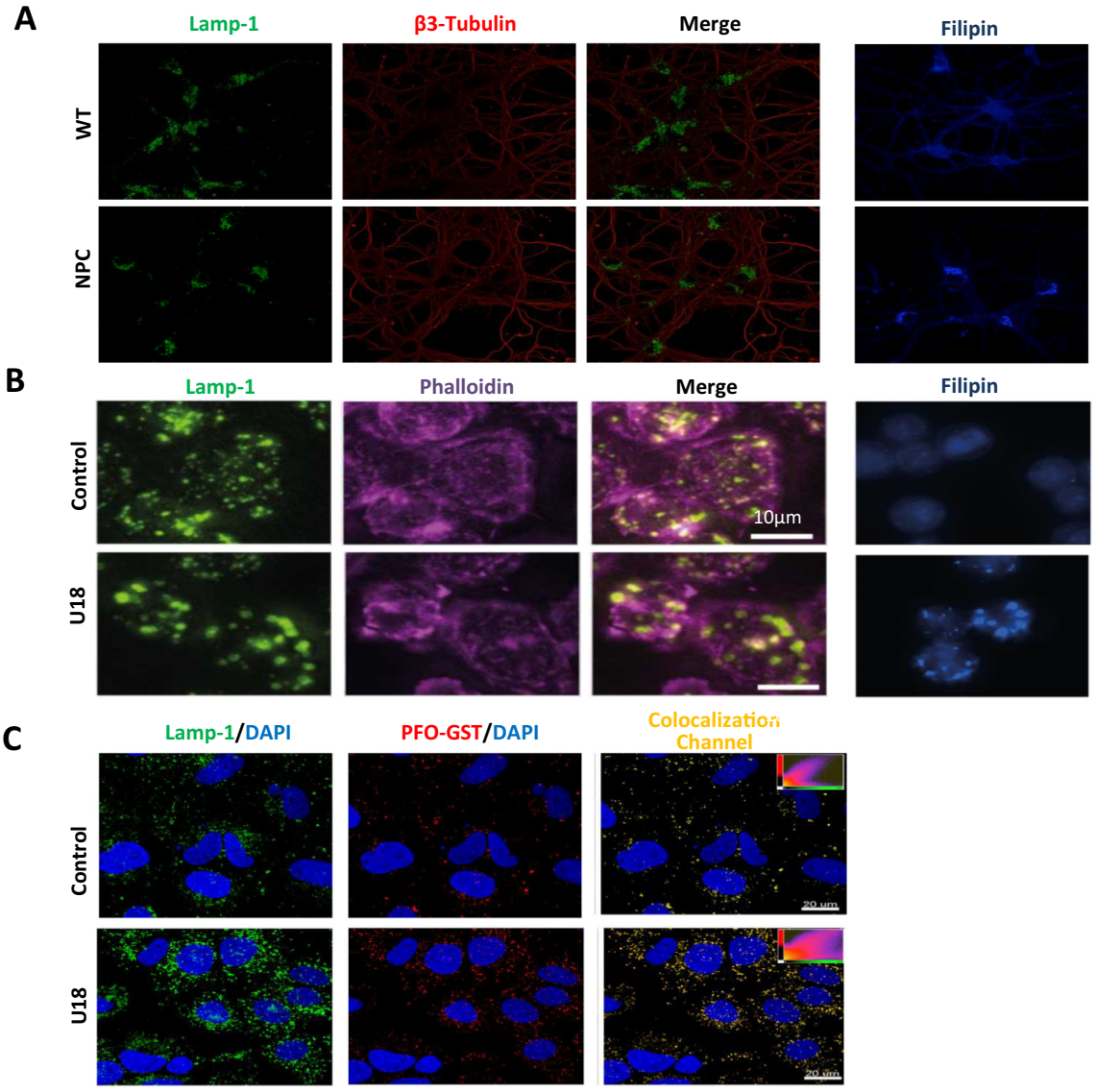

Fig. 3. Lysosomes altered distribution and cholesterol accumulation in NPC cells.
(A) Lamp-1, β-tubulin and cholesterol staining using Lamp-1 and β-tubulin immunofluorescence and filipin are shown for primary hippocampal neurons obtained from wild-type (WT) and *Npc1*$^{-/-}$ (NPC) mice.
(B) Lamp-1, phalloidin and cholesterol staining using Lamp-1 and phalloidin immunofluorescence and filipin are shown for the B lymphocyte cell line IIA1.6 incubated with U18666A (U18) 0.5 μg/ml or vehicle (control) for 24 h. Activation of B lymphocyte was performed using a BCR positive ligand.
(C) Lamp-1, nucleus and cholesterol staining using Lamp-1 immunofluorescence, DAPI and perfringolysin O-glutathione S-transferase (PFO-GST) immunofluorescence against GST are shown for Huh-7cells incubated with U18666A (U18) 1 μg/ml or vehicle (Control) for 24 h.

supporting the idea that this is due to impairment of autophagosomes and lysosome fusion. Consequently, cells (neurons and fibroblasts were both analyzed) diminish their ability to degrade proteins and other cellular content, leading to accumulation of polyubiquitinated proteins. And there is also an accumulation of dysfunctional mitochondria [123]. Similar evidence has been reported for MPS type VI, also known as Maroteaux-Lamy syndrome [124]. Both reports suggest, as a potential therapy, inhibition of autophagy rather than autophagy induction considering that a proper autophagy response requires “healthy” lysosomes. In addition, a study with the first mouse model for MPS-IIIC (or Sanfilippo disease type C) did not clearly conclude that autophagy is actually impaired, but presents evidence of mitochondrial alterations [125].

It is also noteworthy to mention that in some MPS, where disturbances in the CNS are involved, alterations in lysosome positioning and motility have been described. In this scenario, enlarged lysosomes with undegraded substrates are a consequence of mutations in lysosomal membrane proteins. Particularly, in neuronal ceroid lipofuscinosis type 3 (CLN3) and mucolipidosis type IV (ML-IV), these oversized lysosomes are located nearby the nucleus [18]. On the other hand, in a neurodegenerative diseases such as AD, it has been described that inhibition of lysosomal proteolysis disrupts axonal transport leading to the accumulation of late endosomes, lysosomes and autolysosomes in dystrophic axons, a well-known characteristic of AD [74]. Further studies are needed to elucidate how mis or altered function of lysosomal hydrolases cause the observed disturbances in their motility and positioning.

4.3. Niemann-Pick disease types A and B

Niemann-Pick disease types A (NPA) and B (NPB) are due to loss of function or decreased function mutations of SMPD1 gene, encoding for

acid sphingomyelinase (ASM). ASM is a lysosomal hydrolase responsible for sphingomyelin (SM) conversion into ceramide. Therefore, in both diseases there is an accumulation of SM inside the lysosome (Fig. 2). NPA patients develop severe neurological damage ending in early death, whereas NPB is a milder disorder with more pronounced hepatic damage but longer life expectations [126].

The analysis of fibroblasts as well as neuronal cells of a murine model of NPA (ASM KO mice) lead the authors to conclude that autophagy impairment occurs at later stages, compare to what was reported for mucopolysaccharidosis. That is, autophagosome formation and autophagosome-lysosome fusion indeed occurs, but the final cargo degradation is inhibited. Additionally, they showed that SM accumulation inside the lysosome and not cholesterol accumulation induces autophagy interruption. Treatment with dexamethasone, inducing neutral sphingomyelinase activity reduces SM lysosome accumulation and also alleviates lysosome membrane permeabilization, being the possible explanation for the autophagic dysfunction observed [127].

The first report on autophagy dysfunction in NPB disease describes impaired autophagy at initial and later stages, leading finally to specific alterations in mitophagy (mitochondria autophagy) [128]. Unpublished results of our laboratory (Zanlungo et al) show that NPA/B cells have an increase in the signal of lysosomal markers and an altered lysosome distribution, which accumulate in the juxtanuclear area, similarly to the described phenomena in NPC cells, as explained below.

4.4. Niemann-Pick type C disease

Niemann-Pick type C disease is another recessive inherited neurovisceral disorder, caused by mutations in either *NPC1* (95% of the clinical cases) or *NPC2* gene [129,130]. Clinical symptoms are cerebellar ataxia, cognitive impairment, seizures, supranuclear gaze palsy, dysphagia, hepatic disease, and death typically by 20 years of age [131–133]. NPC1 and NPC2 proteins are both involved in free cholesterol and glycosphingolipids efflux from the endosome/lysosome compartment to other cellular destinations [134,135]. Therefore, a loss of function of one protein or another causes lysosomal accumulation of unesterified cholesterol (Fig. 3) and glycosphingolipids and also disrupts the export of cholesterol derived from lipoproteins [132]. The lysosomes of NPC cells show a typical and concentrated perinuclear pattern, different from that of normal cells, suggesting that their cellular distribution and/or motility are altered (Fig. 3).

To date, there are two major animal models to study this disease: spontaneous NPC1 null mice due to a deletion/insertion mutation in the *Npc1* gene [136] and a cat model homozygous for an *Npc1* missense mutation [137] which has been widely used for putative therapeutic assays with 2-hydroxypropyl-β-cyclodextrin (CYCLO) intrathecal administration.

Regarding CYCLO administration, in 7-day old NPC1 deficient mice, it restores unesterified cholesterol efflux from lysosomes to other cellular organelles where it is required, bypassing the blockage produced by NPC1 loss of function in this murine model. This positive effect of CYCLO treatment was remarkably more effective in liver than in the brain, probably due to difficulty for CYCLO to cross the brain blood barrier [138]. In the feline model, biweekly intrathecal administration of CYCLO normalizes LC3-II and p62 levels, and this effect correlates with diminished Purkinje cell loss suggesting a restoration of normal autophagic response. This phenomenon seems to be restricted to NPC disease and not for other LSDs such as MPSIV, MLII or AMD [139]. Unfortunately, the current clinical trial of CYCLO in NPC patients has not yielded the expected results [140].

It is already known that NPC1 deficiency disturbs autophagic flux, evidenced by accumulation of autophagic vacuoles [141–143]. Therefore, it has been proposed that there is an increase in autophagy in NPC disease. In fact, autophagy markers LC3-II and beclin-1 are increased in the cerebellum and hippocampus of NPC1 deficient mice, although this could be due to accumulation of autophagosomes. There are also an increased number of secondary lysosomes [144]. Another study with NPC1 deficient and wild type cultured neurons shows that in fact LC3-II puncta were increased indicating an elevated number of autophagosomes per neuron compared to wild type condition. Most of these LC3-II puncta colocalize with the acidic compartment in this *Npc1*$^{-/-}$ cultured neurons, clearance of autophagosomes by lysosomal digestion is delayed, explaining the autophagic flux disturbance [145]. In this scenario, therapeutic approaches should be focused on selectively lowering the abnormal lipid load in the lytic compartment in addition to increasing the autophagic flux [17,145].

4.5. The connection between neurodegenerative disorders and LSDs

Several human neurodegenerative disorders such as AD, PD, HD, ALS are characterized by abnormal aggregation of miss folded proteins, e.g. amyloid–β peptide, α-synuclein, hungtington and SOD respectively [146], and of course deregulation of autophagy is a common pathogenic mechanism [147] as well as alterations of the proteasome-ubiquitin system [148] and apoptosis [149]. Besides autophagy, an additional link between these neurodegenerative disorders and LSDs is cathepsin D. Cathepsin D is a lysosomal hydrolase highly ubiquitous in the CNS and has an important role in proper degradation of misfolded and aggregated proteins mentioned above: amyloid-β peptide, α-synuclein and hungtington [150].

In neurons, tight regulation of lysosome dynamics is particularly relevant due to their asymmetric and variably long morphology, e.g., axons and dendrites. In fact, mutations in components of the lysosome-positioning machinery are syndicated as causative of several neurological disorders [18]. Besides the already mentioned alterations in Charcot–Marie–Tooth disease types 2A and 2B, single nucleotide polymorphisms have also been identified that cause increased expression of the diaskedin (BORCS7) subunit of BORC as a major risk factor for schizophrenia [151]. Also, other components of this machinery are mutated in several neurological disorders, among them p150-glued subunit of dynactin in ALS, KIF5A in hereditary spastic paraplegia type 10, KIF5C in cortical dysplasia with other brain malformations type 2 and up regulation of KLC2 is the cause of spastic paraplegia, optic atrophy and neuropathy (SPOAN) syndrome. Finally, it is also necessary to consider that some neurodegenerative diseases can also be due to mutations of proteins that indirectly influence lysosome motility and positioning, by modulating physiological or pathological conditions [18].

The most prominent link between neurodegenerative disorders and LSDs includes PD and GD. In fact, mutations in the *GBA1* gene have been indicated as a risk factor to develop PD [152]. Heterozygous GBA variants have five-fold high risk to develop PD. It also correlates with an earlier disease onset, higher cognitive impairment and accelerated disease progression [153]. Moreover, GCase deficiency seems to be specific in inducing α–synuclein aggregation. And α–synuclein aggregation may interfere with normal GCase function in PD, resembling GD, although the precise mechanism is still unknown. Therefore, a potential bidirectional pathogenic loop between GD and PD arises, in which an increase in the levels of aggregated α–synuclein leads to a decrease in lysosomal GCase activity and a further increase of α-synuclein aggregates [154].

There are some other potential risk factors connecting LSDs with PD: cathepsin B, ATPase H^+ transporting V0 subunit a1 and galactosylceramidase [155]. Growing data of overlapping disease mechanisms including cholesterol accumulation, mitochondrial dysfunction and autophagic alterations, open a window of opportunity to develop new therapeutic strategies common for both diseases [156]. Furthermore, several other LSDs present a potential correlation with PD: GM1 gangliosidosis, GM2 gangliosidoses (Tay-Sachs and Sandhoff), Mucopolysacharidoses II and IIIB, NPC and NPB, among others.

4.6. Alteration of immune functions and autophagy in LSDs

Given the fundamental importance of lysosomes in immune effector functions, it is not surprising to find altered immune responses in LSDs, where several defects, ranging from immunosuppression to inflammation have been reported. For instance NPC patients frequently present perinatal respiratory infections [157] and GD patients have a poor response to bacterial infections [158], but with high levels of circulating inflammatory cytokines dependent on the inflammasome such as IL-1β and IL-6 [159]. Patients with GD present hepatosplenomegaly, anemia, thrombocytopenia, bone manifestations [160] and display defects in phagocytosis of apoptotic bodies [161]. Meanwhile, NPC patients display deficient elimination of pathogens mediated by macrophages [162]. Altogether, these studies highlight that how defects in lysosome content, as those observed in LSDs can impact lysosome function in phagocytosis during innate immune responses. Such defects can also be extrapolated to adaptive immune responses. In mucolipidosis II, mannose-6-phosphate deficiency, generates an incorrect destination of lysosomal enzymes to the extracellular space. As a consequence, cells accumulate non-degraded molecules within lysosomes. Notably, it has been reported that B-lymphocytes obtained from these patients are less capable of extracting antigens and presenting them to T-lymphocytes [163]. *Npc1*$^{-/-}$ mice, display a lack of the main NK T-lymphocytes population, the subclass Vα14-Jα18 [164]. On the other hand, APCs from patients with metachromatic leukodystrophy, who accumulate sulfatides due to a deficiency in arylsulfatase-A, directly activate invariant NKT cells [165]. These sulfatides can be linked to CD1 inside the lysosomes, where it accumulates, and thereby enhances iNKT cell activation. It is also noteworthy to mention recent evidence supporting a role of TRPML2, an isoform of TRPML1 which is altered in mucolipidosis type IV, in the antigenic peptide transfer to MHC-II in B lymphocytes and APC [166].

In summary, Gaucher, Fabry and NPC disease along with mucopolysaccharidosis type IV and α–mannosidosis can be classified as immune suppressor disorders, with an increase in circulating proinflammatory cytokines. Additionally, GM2 gangliosidosis, Krabbe disease and juvenile neuronal ceroid lipofuscinosis are associated to an over-stimulated immune system and autoimmunity [167,168]. Regarding NPC disease in particular, there seems to be an activation of the innate immune system, including the microglia and astrogliosis in the *Npc1*$^{-/-}$ mice, before symptomatic manifestations [169]. However, their direct impact on the pathophysiology of each disorder still remains to be elucidated [167].

Autophagy, which is tightly coordinated with lysosome positioning, plays a fundamental role in immune system by regulating cell signaling and antigen processing. When autophagosomes are generated, they are transported in a dynein dependent manner to the centrosome at the perinuclear area where lysosomes are concentrated to facilitate the fusion of autophagosomes with lysosomes [40]. Moreover, redistribution of lysosomes from perinuclear area to periphery can increase mTOR activity, which inhibits autophagy, and vice versa [64,170]. Additionally, danger signals sensed by pattern recognition receptors termed Toll-like Receptors (TLRs) in macrophages, can induce an increase in lysosomal biogenesis to support processes such as phagocytosis and xenophagy by the up regulation of transcription factor TFEB which boosts the expression of lysosomal genes. This enhances lysosomal degradation and bacterial killing [171,172]. TLR trafficking to the autophagosome-lysosome pathway also regulates their signaling. For instance, in B-cells TLR9 and BCR signaling can be enhanced by the fusion of endosomes with autophagosome-like compartments [173]. Also, in macrophages LC3 decorated endosomal vesicles are required to transduce interferon regulatory elements after the stimulation with CpG, a TLR9 ligand [174]. However, fusion of lysosomes with autophagosomes containing TLRs, such as TLR4 and TLR9, is also necessary to terminate signaling. This is highlighted in B-cells, where the absence of ATG5 or LC3 increases TLR signaling, thereby promoting B-cell activation and proliferation [175]. Thus, the interplay between of autophagosome and lysosomes plays an important role in promoting or terminating TLR signaling, which can tune immune responses.

In innate immunity, autophagy is involved in processes such as phagocytosis and cytokine production. Intracellular pathogens that have escaped from endocytic pathway can be recognized by the protein adaptor p62 and targeted to autophagosomes in a mechanism termed xenophagy [176,177]. Additionally, ingested pathogens can be eliminated through LC3 associated phagocytosis or LAP, which relies on the formation of a single membrane vesicle and depends on Rubicon instead of ULK1, among others [178,179]. Nevertheless, independently of the mechanisms used for protein assembly to promote autophagy, both pathways rely on their convergence with lysosomes to complete the process. Thus, the fusion of autophagosomes with lysosome compartments is a critical step, where Rab-GTPases, such as Rab7 [180] and SNAREs, including syntaxin17, SNAP29 and VAMP8 [181,182] have been described to regulate this process. Whether the association and/or activation of GTPases and SNARE proteins are altered in lysosome storage diseases and are related to the defective immune responses and autophagy observed in such diseases remains to deexplored.

Understanding the mechanisms that govern lysosome functions and as well as their connection with different cellular pathways, such as autophagy can provide valuable insight on how to manipulate cellular responses under pathological conditions for therapeutic means.

5. Concluding remarks

Lysosomes are membranous intracellular organelles that contain over 60 different soluble hydrolases, enabling them to degrade every macromolecule in a living cell. Our current view on lysosomes has shifted from considering them garbage disposals to being critical organelles involved in cellular homeostasis. Lysosomes are dynamic organelles, able to fuse with a variety of targets and to be re-formed after fusion events. In this way, lysosomes are main players in extracellular secretion, intracellular components degradation and recycling. Given their highly dynamic nature and capacity to interact with other intracellular organelles, such as ER, mitochondria and peroxisomes, it is clear that defects associated to lysosome functions can have diverse functional consequences.

In general terms, lysosomes move in anterograde direction attached to MTs by kinesin motor proteins and in retrograde direction by dynein. Nevertheless, actin microfilaments are also involved in the correct positioning and movement of lysosomes. Fine regulation of these interactions directly regulates also an adequate autophagic process.

From a physiological point of view, there are at least three systems or organs where adequate lysosome motility, positioning and function along with autophagy, have a determinant role. Those are the Immune System, the Central Nervous System and the liver; all of them extensively described in this review. In summary, the correct localization of lysosomes determines an appropriate immune synapse between lymphocytes (B- or T-cells) and APCs, such as dendritic cells. At the CNS, lysosomes function is essential for synapsis. In the presynaptic compartment they are involved in vesicle secretion and in the postsynaptic terminal they are fundamental for neurotransmitters receptors degradation and/or recycling. Studies of lysosome function and motility in the liver have been the main source of knowledge in the regulation of autophagy. Liver, and therefore hepatic lysosomes, is the master regulator of nutrients and metal ions levels. In the three contexts described above, misfunction of lysosomes lead to severe pathologies.

We have described here how alterations of lysosomes due to mutation of genes coding for lysosomal proteins (soluble hydrolases as well as membrane proteins) lead, in general terms to LSDs. Lysosomes saturated with undegraded substrates are finally stacked and therefore miss positioned inside the cell. And misregulation of lysosome movement and positioning mechanisms lead to the accumulation of undegraded molecules inside lysosomes. These alterations are also seen in

more common pathologies of the liver, CNS and the immune system. In fact, there is a cross talk between diseases, the most remarkably example of this is GD, a LSD and PD a neurodegenerative disorder. One way or another, lysosome function and specially autophagy are compromised and pathology emerges.

Conflicts of interest

The authors declare that they have no conflicts of interest. The corresponding author is responsible for sharing this document with all co-authors.

Transparency document

The Transparency document associated with this article can be found, in online version.

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