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The strategic function of the P5-ATPase ATP13A2 in toxic waste disposal

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ABSTRACT

The P-type ATPase ATP13A2 protein was originally associated with a form of Parkinson's Disease (PD) known as Kufor Rakeb Syndrome (KRS). However, in the last years it has been found to underlay variants of neuronal ceroid-lipofuscinoses and hereditary spastic paraplegia. These findings expand the clinical and genetic spectrum of ATP13A2-associated disorders, which are commonly characterized by lysosomal dysfunction. Nowadays it is well known that lysosomes are not merely related to the degradation and recycling of cellular waste, but are also involved in fundamental processes such as secretion, plasma membrane repair, signaling, energy metabolism and autophagy. The essential role of lysosomes in these cellular processes has significant implications for health and disease. ATP13A2 is localized in lysosomes and late endosomes and its mutation leads to lysosome dysfunction, diminishes the exosome secretion and impairs autophagic flux. In this review, we first describe ATP13A2-associated disorders and their relation with the endolysosomal pathway. We then describe the ATP13A2-involvement in iron homeostasis and its potential linkage with new pathologies like cancer, and finally, we consider the putative role of ATP13A2 in lipid processing and degradation, opening the interesting possibility of a broader role of this protein providing protection against a variety of disease-associated changes affecting cellular homeostasis.

1. Introduction

Parkinson's Disease (PD) and neuronal ceroid-lipofuscinoses (NCLs) are neurological diseases usually described as separate clinical entities. However, at the cellular level they show similar alterations of the endolysosomal pathway and autophagic flux. Both of these pathologies are characterized by the accumulation of toxic products. PD is characterized by the presence of Lewy Bodies formed by the cytosolic aggregation of α-synuclein protein (α-syn), while NCLs are a group of neurological disorders produced by the accumulation of autofluorescent material (ceroid-lipofuscin) within lysosomes. Several monogenic forms in which the inheritance of a mutated gene causes PD or NCL are well established. Notably, mutations of the *ATP13A2* gene, also known as *PARK9*, were initially associated with a form of PD known as Kufor Rakeb Syndrome (KRS) (Ramirez et al., 2006), but more recently they were also found to underlay a form of NCL (CNL12) (Bras et al., 2012; Kollmann et al., 2013) and of hereditary spastic paraplegia (SPG78) (Estrada-Cuzcano et al., 2017). The ATP13A2 gene codes for a protein that features all the essential structural domains that are characteristic of the family of P-type ATPases, These proteins comprise a large group of enzymes that couple active substrate transport with the hydrolysis of ATP, and form a phosphorylated intermediate during their reaction cycle. The best known members of this family of proteins are the Ca^{2+}-ATPase from sarcoendoplasmic reticulum or SERCA and the Na^{+}-K^{+}-ATPase (Palmgren and Nissen, 2011). P-ATPases have been classified into five subfamilies termed P1-P5 (or type I-V) according to their similarity in primary structure (Axelsen and Palmgren, 1998). The P5 subfamily remains the most poorly understood P-type ATPases for which a putative transported substrate has not yet been identified. Five genes named *ATP13A1-ATP13A5* that belong to the P5-ATPase group are present in humans, while two P5-ATPases named Cod1p (or Spf1p) and Ypk9p were found in the yeast *Saccharomyces cerevisiae*. By protein sequence alignment it was shown that this type V ATPases are divided in two groups named P5A and P5B; the mouse ATP13A1

Abbreviations: CHO cells, Chinese hamster ovary cells; EE, Early Endosome; LE, Late Endosome; KRS, Kufor Rakeb Syndrome; MVB, Multi-Vesicular Body; NCL, Neuronal Ceroid Lipofuscinosis; PD, Parkinson's Disease; TGN, Trans-Golgi Network.

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and the yeast Cod1p (or Spf1p) are members of the first group, while the mouse ATP13A2-ATP13A5 and the yeast Ypk9p are clustered into the second one (Mollerup Sørensen et al., 2010). P5A_ATPases have been identified in the endoplasmic reticulum and seem to have basic functions in protein maturation and secretion; while P5B-ATPases localize to vacuolar/lysosomal or apical membranes and in animals play a role in hereditary neuronal diseases (Ramirez et al., 2006; Bras et al., 2012; Kollmann et al., 2013; Estrada-Cuzcano et al., 2017). The *ATP13A2* gene codes for a transmembrane protein named ATP13A2 strategically located in lysosomes and late endosomes (LEs), a late endosomal compartment located at the convergence point of the endosomal and autophagic pathways. Dysfunction of ATP13A2 diminishes lysosomal degradation (Dehay et al., 2012a, 2012b; Usenovic et al., 2012; Gusdon et al., 2012), autophagic flux (Dehay et al., 2012b; Usenovic et al., 2012; Gusdon et al., 2012), exosome externalization (Kong et al., 2014), and induces an accumulation of fragmented mitochondria (Gusdon et al., 2012; Grünewald et al., 2012; Ramonet et al., 2012). Moreover, ATP13A2 is present in Lewy Bodies, and studies using various cellular models have shown that its overexpression reduces the intracellular α-syn levels by increasing α-syn externalization in exosomes (Dehay et al., 2012a; Usenovic et al., 2012; Kong et al., 2014); although the link between ATP13A2 and α-syn externalization in mice is less clearly established (Kett et al., 2015). Altogether, these findings point to a key role of ATP13A2 in the function of the endolysosomal and autophagic pathways.

2. The endolysosomal and autophagic pathways

Lysosomes and LEs are cellular organelles that receive and degrade macromolecules from the secretory, endocytic, autophagic, and phagocytic membrane-trafficking pathways. They are involved not only in degradation, but also in fundamental processes such as secretion, plasma membrane repair, signaling, and energy metabolism. Because they are responsible for the physiologic turnover of cell constituents, defects in their function lead to the development of a complex set of disorders with often-severe consequences for human health (Huotari and Helenius, 2011). Briefly, the cargo internalized by ongoing endocytosis in mammalian cells first arrives to an early endosome (EE), where most receptors are returned to the plasma membrane via the recycling endosomes. Cargo destined for degradation is retained in the EE, which through a process involving exchange of material and multiple fusion events, converts into a late endosome. LEs are also called multi-vesicular bodies (MVBs) since they contain intraluminal vesicles (Huotari and Helenius, 2011; Hyttinen et al., 2013). LEs also can fuse with autophagosomes to form amphisomes; autophagosomes are the primary double-membrane vacuoles that engraft cytoplasmic proteins and organelles in autophagy (Fig. 1). In LEs, cargo undergoes further sorting and is transported to other organelles such as *trans*-Golgi network (TGN) or can fuse with the plasma membrane to release extracellular vesicles termed exosomes that have the potential of intercellular communication and have recently been implicated in a number of neurodegenerative diseases (Huotari and Helenius, 2011; Schneider and Simons, 2013; Appelqvist et al., 2013). Macromolecules such as complex lipids and oligosaccharides that are constitutively degraded into their building blocks are delivered from LEs to lysosomes, together with new lysosomal hydrolases and membrane proteins from the TGN. The resulting catabolites are exported to the cytosol and reused in cellular metabolism. In view of the foregoing, it is clear that the specific transport, distribution and processing of cargo is an inherent function of the endolysosomal system and its malfunction

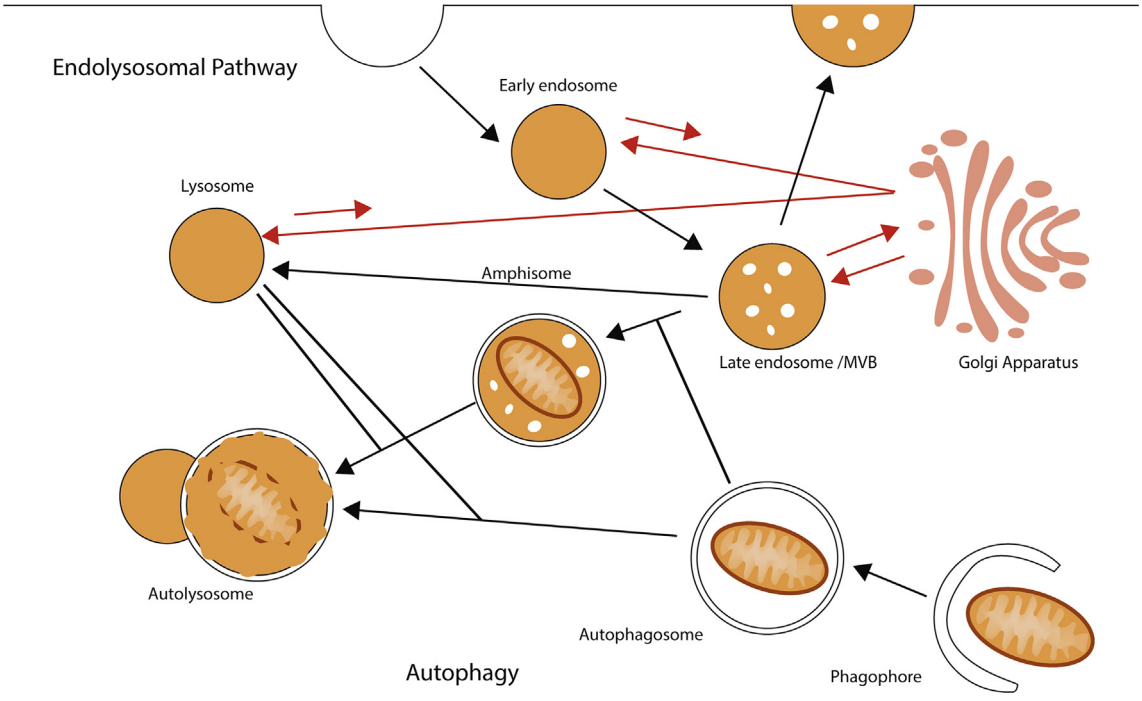

Fig. 1. The endolysosomal and autophagic pathways. The primary endocytic vesicles deliver their contents and their membrane to early endosomes (EEs) in the peripheral cytoplasm. EEs convert into LEs or MVBs through multiple fusion events and are characterized by the presence of intravesicular bodies (ILVs, white circles). The traffic between endosomes and the *trans*-Golgi network (TGN) is a continuously ongoing process responsible for the delivery of lysosomal and removal of endosomal components during endosome maturation (red arrows). In LEs, cargo can be transported to other organelles such as the TGN or can fuse with the plasma membrane to release exosomes. However, macromolecules that have to be degraded are delivered from LEs to lysosomes, together with new lysosomal hydrolases and membrane proteins from the TGN. The autophagy process initiates with the phagophore and autophagosome formation followed by fusion of autophagosomes either directly to lysosomes to form autophagosomes, or to LEs to give amphisomes that subsequently fuse with lysosomes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

promotes the accumulation of undegraded material.

Although the lipofuscin-like compounds found in NCL and Parkinson's Lewy Bodies have a distinct composition, both are diminished by endolysosomal-mediated clearance where ATP13A2 meets its function. In this line, it was recently shown that ATP13A2 regulates crucial steps of cargo trafficking and sorting processes in the endocytic system independently of its ATPase catalytic activity by a scaffolding role of its cytosolic N-terminal domain. The N-terminal domain of the protein requires the interaction with the signaling lipid $PI(_{3,5})P2$ to potentiate the release of cytoplasmic cargo through nanovesicles export to the extracellular space (Demirsoy et al., 2017). This discovery suggests that ATP13A2 may develop a key function in the endolysosomal clearance of toxic compounds through vesicle secretion.

3. Iron in toxic waste formation

Alterations in iron metabolism has been associated with several neurodegenerative diseases (Berg and Youdim, 2006). Lysosome function plays a key role in iron handling in normal and pathological conditions (Kurz et al., 2011). Even under normal conditions, iron-catalyzed peroxidation takes place intralysosomally, resulting in the oxidative modification of the autophagocytosed material that becomes resistant to the hydrolytic activity of lysosomal enzymes. If cells do not divide, this material progressively accumulates within the lysosomal compartment in the form of lipofuscin inclusions (Kurz et al., 2011; Brunk and Terman, 2002). Although progressive lipofuscin accumulation is a normal aging event, exacerbation of this process has been implicated in numerous age related diseases such as Alzheimer disease, PD and macular degeneration pathologies (Kurz et al., 2011). There is a wide variety of lipofuscin-like materials and their composition differ according to the pathology. Most frequently, the term “ceroid-lipofuscin” refers to the lipofuscin-like lipopigment that accumulates in the lysosome as a result of a pathological condition like NCL, and its composition differs from the age-related lipofuscin (Seehafer and Pearce, 2006). However, regardless of the chemical composition of the accumulated material, it is clear that iron-induced lipid peroxidation is a common prime event in its formation and the exacerbation of this phenomenon drives to an endo-lysosomal flux malfunction (Kurz et al., 2011).

Intralysosomal iron-chelating agents like the polyamines spermidine and spermine are able to reduce lipofuscin formation (Løvaas, 1996; Marzabadi and Løvaas, 1996). Cells containing larger LEs and lysosomes, equipped with more iron-chelating agents may be more resistant to the iron-catalyzed lysosome membrane permeabilization (LMP) (Kurz et al., 2011). Noteworthy, chinese hamster ovarian (CHO) cells stably expressing the human ATP13A2 protein exhibit a higher accumulation of spermidine (de La Hera et al., 2013; de Tezanos Pinto et al., 2012). Likewise, the iron content and the cytotoxicity induced by iron exposure is reduced in ATP13A2-expressing CHO cells (Rinaldi et al., 2015). Moreover, ATP13A2 expression causes an enlargement of acidic vesicles and a reduction of the iron-induced LMP (Rinaldi et al., 2015). These results suggest that ATP13A2 overexpression improves the lysosome and LE function by protecting the membrane integrity against the iron-induced damage.

4. ATP13A2-gene regulation

It was recently reported that the promoter region of the human *ATP13A2* gene contains hypoxia response elements that can bind to the hypoxia-inducible factor 1α (HIF-1α) (Xu et al., 2016), a transcription factor associated with tumor growth, angiogenesis and metastasis in various carcinomas (Jokilehto et al., 2006). HIF1α induces the transcription of cellular stress genes, including several involved in iron metabolism like transferrin and transferrin receptor 1. Hydroxylation of HIF1α by prolyl hydroxylase domain protein 2 (PHD2) results in its proteasomal degradation. Hence, the pharmacological inhibition of PHD2 increases the expression of ATP13A2 by diminishing HIF1α degradation (Rajagopalan et al., 2016). Knockdown of ATP13A2 expression within human dopaminergic cells results in elevations in cytosolic ferrous iron levels and eliminates the restoration of cellular iron homeostasis induced by PHD2 inhibition (Rajagopalan et al., 2016). These findings support the idea that the regulation of ATP13A2 by the PHD2-HIF1α signaling pathway not only affects the cellular iron homeostasis but also is involved in the hypoxic stress response.

Interestingly, the polyamine transport system is also up-regulated through the HIF1α pathway and is associated with cancer cell survival during hypoxic stress (Svensson et al., 2008). In this line, is noteworthy that a recent publication suggests the involvement of another P5B-ATPase isoform -ATP13A3-in polyamine transport in human pancreatic cancer. In the mentioned study, high levels of ATP13A3 expression were detected in tumors where the endogenous polyamine biosynthesis was inhibited (Madan et al., 2016), suggesting a compensatory mechanism for increasing the uptake of polyamines from the media. As the native polyamines, putrescine, spermidine and spermine are key resources required by mammalian cells for growth and proliferation, polyamine homeostasis have been shown to be clinically useful for both the chemoprevention and treatment of human cancers (Meyskens and Gerner, 1999; Samal et al., 2013). Although is only speculative at this time, because ATP13A2 increases polyamine uptake -possibly in an indirect way at the level of the plasma membrane- and its expression is regulated through the HIF1α pathway -both facts clearly related to cancer progression-opens the possibility that P5B-ATPases could play a role in this pathology.

5. ATP13A2 in endolysosome homeostasis

ATP13A2 contributes to the integrity of the endo/lysosome vesicles by promoting the accumulation of chelating agents like spermidine inside acidic vesicles. However, there is no data showing that ATP13A2 protein is directly responsible of the active accumulation of polyamines into the vesicles of the late endocytic compartment. Moreover, this possibility seems unlikely since the expression of ATP13A2 did not produce a significant change in the apparent affinity of the cells for spermidine (de La Hera et al., 2013). Several alternative mechanisms explaining the observed effects of ATP13A2 overexpression may be considered. The pH gradient that exists between the lysosomal lumen and the cell cytosol is responsible for driving the accumulation of many small-molecular-weight amine-containing molecules through a process referred to as ion trapping (Goldman et al., 2009). Thus, if ATP13A2 would act as an active H^+ transporter, it would improve the existing pH gradient across the vesicle membrane favoring the uptake of polycations. Although some publications support this possibility, ATP13A2 expression was unable to revert the increase of lysosomal/endosomal pH induced by chloroquine (CQ) treatment, suggesting that it cannot replace the function of the lysosomal proton pumps (de La Hera et al., 2013). Nevertheless, the possibility of ATP13A2 may somehow collaborate to maintain the acidic environment in the endolysosomal systems cannot be discarded. Moreover, it must be take into account that CQ is also a polycationic diamine and probably is being accumulated at a greater extent inside the acidic vesicles of ATP13A2-expressing cells, a fact that may explain the lack of differences observed in the lysosomal pH of CQ treated ATP13A2-expressing cells.

Several studies using cellular and mice models have shown that

ATP13A2 also plays a crucial role in the control of Mn^{2+} and Zn^{2+} homeostasis. In the absence of ATP13A2, the cells contain lower amounts of these ions and are more sensitive to the toxicity of external Mn^{2+} and Zn^{2+}, presumably because they have a reduced capacity to sequester these ions into acidic vesicles (Kong et al., 2014; Gitler et al., 2009; Schmidt et al., 2009; Tan et al., 2011; Park et al., 2014; Tsunemi and Krainc, 2013). Is worth mention that as suggested above for iron, the effect of ATP13A2 on Mn^{2+} and Zn^{2+} homeostasis may be mediated by increasing the metal chelating capacity of lysosomes and/or contributing to metal clearance by exosome releasing. Finally, the steady-state phosphorylation levels of ATP13A2 pump were unaffected by $MnCl_2$ or $ZnCl_2$, indicating that ATP13A2 is unlikely to directly transport Mn^{2+} or Zn^{2+} (Holemans et al., 2015).

Because phylogenetically P5-ATPases are closest to the P4-ATPases phospholipid transporters, it has been suggested that they also function as flippases (Graham, 2004; VanVeen et al., 2014). In this case, the observed protection of lysosome-membrane integrity by ATP13A2 could result from modifications in the composition or distribution of lipids in the lysosomal membrane. Unfortunately, data supporting this hypothesis are still lacking. On the other hand, the constitutive degradation of membrane components that takes place in intraendosomal membranes formed in LEs requires a lipid-sorting process during which cholesterol is sorted out of the inner membranes and their content in the anionic phospholipid bis(monoacylglycero)phosphate (BMP) increase. This process allows the binding of hydrolases like acid sphingomyelinase and acid ceramidase -which are water-soluble polycations at a lysosomal pH of less than 5.0- to the negatively charged inner membranes. In those inner bodies, these hydrolases become protected against proteolysis and are able to degrade their membrane-bound substrates. Amine-containing amphiphilic compounds disturb the binding of these hydrolases to the inner membranes causing their rapidly detachment and proteolysis (Kolter and Sandhoff, 2010). This phenomenon characterized by an intracellular accumulation of undigested material and the concurrent development of concentric lamellar bodies is known as drug-induced phospholipidosis, and was considered as a “molecular mimicry” of lysosomal storage disorders like NCL (Kolter and Sandhoff, 2010; Anderson and Borlak, 2006; Schulze and Sandhoff, 2011; Shayman and Abe, 2013). However, this idea is based principally on the fact that multilamellar bodies are observed under microscopic examination in both circumstances and doesn't imply the same molecular origin. Interestingly, it was recently shown that the degradative capacity of ATP13A2-expressing cells was significantly reduced after proteasomal inhibition (Demirsoy et al., 2017). Importantly, this effect did not require the catalytic activity of the pump and suggests that ATP13A2 overexpression affects the cell digestion capacity by a scaffolding function.

6. Vesicle clearance as a defense mechanism

At first glance, the ATP13A2-induced lysosomal accumulation of polycations like spermidine should hamper the lipid digestion process. However, lamellar bodies induced by phospholipidosis have been observed to reach the extracellular space by exocytosis (Anderson and Borlak, 2006). It was shown that by releasing the LEs/lysosome content via exocytosis, the cell bypasses excessive production of reactive oxygen species, eliminates undigested material and protein aggregation, thereby preventing undue stress (Anderson and Borlak, 2006). Moreover, the induction of lysosomal exocytosis by transcription factor EB (TFEB)-overexpression rescues the pathologic storage and restores normal cellular morphology in LSDs (Medina et al., 2011), suggesting that lysosomal exocytosis may directly modulate cellular clearance. This idea is supported by a recent publication showing that cells trigger a lysosome-biogenesis activation after basic-amines or cationic-amphiphilic drugs treatment, and this would be a lysosomal adaptation that helps the cell to bypass the lysosome dysfunction induced by these lysosomotropic compounds (Lu et al., 2017). Importantly, TFEB not only regulates lysosomal biogenesis and function but also induces the expression of HIF1α (Palmieri et al., 2011), which as indicated above upregulates ATP13A2 transcription. These results suggest that the alteration of the lipid digestion process by amine accumulation may stimulate the LE/lysosome exocytosis with the concomitant diminution of intracellular toxic compounds.

Interestingly, ATP13A2 has been shown to regulate exosome biogenesis through functional interaction with the endosomal sorting complex required for transport machinery (ESCRT) (Tsunemi et al., 2014), promoting α-syn (Kong et al., 2014) and ubiquitinated-proteins (Demirsoy et al., 2017) externalization. The strategic localization of ATP13A2 in LEs and its involvement in exosome externalization suggest that this protein could play a key role in a clearance mechanism mediated by lysosome/exosome

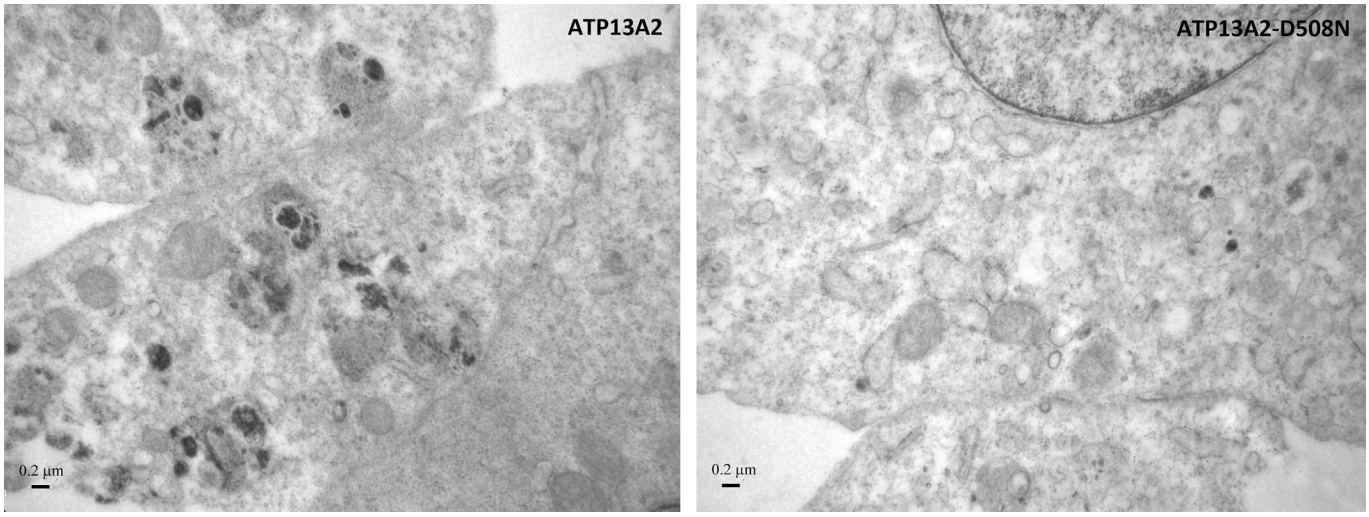

Fig. 2. Electron microscopic photographs of CHO cells stably expressing the human ATP13A2 or the unfunctional mutant ATP13A2-D508N stained with osmium tetroxide. Note in ATP13A2-expressing cells the lysosome-like structures containing electrodense granular deposits suggesting phospholipidosis.

exocytosis. In this line, it was observed that the loss-of-function of ATP13A2 leads to decreased density of ILVs in LEs (Tsunemi et al., 2014). Accordingly, the amine-accumulation induced by ATP13A2 would favor the formation of intravesicular bodies similar to those observed during drug-induced phospholipidosis (Anderson and Borlak, 2006). Favoring this idea, we have observed by electron microscopic examination that CHO cells stably expressing ATP13A2, contain enlarged multivesicular structures with internal granular deposits similar to those produced by drug-induced phospholipidosis (Fig. 2) (Rinaldi et al., 2015). This hypothesis is also supported by a recently demonstration that ATP13A2 increases cargo export through nanovesicles formation, although by a catalytic-independent manner (Demirsoy et al., 2017). Usenovic et al. reported an increase in the size puncta and number of LAMP1 and LysoTracker positive vesicles in ATP13A2 mutant fibroblasts and by ATP13A2 knock down in primary cortical neurons. On the other hand, Demirsoy et al. did not see changes in the expression of LAMP1/LAMP2 after ATP13A2 overexpression or knock down. At present, the reason of this discrepancy is not obvious however, it is possible that ATP13A2 silencing increases the LAMP1+ lysosomes and LEs, while overexpression also increases or relocalizes LAMP1+ in order to promote the exocytosis of toxic compounds.

7. Concluding remarks

Most of the studies have shown that loss-of-function of ATP13A2 promotes lysosomal dysfunction with the concomitant accumulation of undigested material (Dehay et al., 2012a, 2012b; Usenovic et al., 2012). On the other hand, a reduced digestion capacity was also observed in ATP13A2-overexpressing cells (Demirsoy et al., 2017). One would expect that both scenarios have opposing effects, however, both of them alter lysosome homeostasis; a fact that may explain reports of similar phenotypes associated with the loss- or gain-of-function of ATP13A2 (Ramonet et al., 2012). It was also shown that by increasing the expression of ATP13A2, the cell is able to eliminate -by exosome-release- toxic compounds whose production is increased under conditions of cellular stress (Kong et al., 2014; Tsunemi et al., 2014). Accordingly, ATP13A2-function seems to be essential for cells under stress conditions (Gusdon et al., 2012; Ramonet et al., 2012; Demirsoy et al., 2017). We believe that the amine accumulation produced by ATP13A2 expression could reduce the lipid digestion capacity while increasing the endolysosome/exosome exocytosis, in a way similar to that observed during drug-induced phospholipidosis (Anderson and Borlak, 2006; Lu et al., 2017). In this line, overexpression of this protein under basal conditions would result in an excessive zinc and/or iron chelation that would be also harmful for endolysosome homeostasis. This possibility would explain why ATP13A2-overexpression was slightly toxic to cells under basal conditions (Park et al., 2014). Consistent with the phenotype found in NCL and KRS, these observations highlight the proposed function of ATP13A2 as a remodeler of the endocytic pathway toward export, mainly under cellular stress conditions.

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