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Lysosomal Calcium in Neurodegeneration

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Abstract

Lysosomes are the central organelles responsible for macromolecule recycling in the cell. Lysosomal dysfunction is the primary cause of lysosomal storage diseases (LSDs), and contributes significantly to the pathogenesis of common neurodegenerative diseases. The lysosomes are also intracellular stores for calcium ions, one of the most common second messenger in the cell. Lysosomal Ca^{2+} is required for diverse cellular processes including signal transduction, vesicular trafficking, autophagy, nutrient sensing, exocytosis, and membrane repair. In this review, we first summarize some recent progresses in the studies of lysosome Ca^{2+} regulation, with a focus on the newly discovered lysosomal Ca^{2+} channels and the mechanisms of lysosomal Ca^{2+} store refilling. We then discuss how defects in lysosomal Ca^{2+} release and store maintenance cause lysosomal dysfunction and neurodegeneration.

Keywords

Lysosomes; Calcium Channels; TRPML1; Refilling; Lysosomal Storage Diseases; Neurodegenration; NPC

INTRODUCTION

Lysosome is the cell's recycling center that mediates the degradation of macromolecules from intracellular (via autophagy) or extracellular (via endocytosis and phagocytosis) sources (Luzio et al., 2007). Armed with more than 60 hydrolases and 50 membrane proteins, lysosomes degrade proteins, polysaccharides, and lipids into their "building blocks" which are transported out of lysosomes via specific transporters or vesicular membrane trafficking, for energy or re-use (Kolter and Sandhoff 2005; Schwake et al., 2013; Xu and Ren 2015). Lysosome function thus plays a pivotal role in maintaining cellular homeostasis. Defects in lysosomal degradation, exporting, or trafficking can cause accumulation of undigested biomaterials in the lysosome. This represents lysosomal storage diseases (LSDs) (Platt et al., 2012; Boustany 2013; Xu and Ren 2015). Most LSDs exhibit neurological pathologies, suggesting that the nervous system is particularly vulnerable to

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lysosome dysfunction (Boustany 2013). On the other hand, common neurodegenerative diseases such as Alzhermer's Disease (AD), Parkinson's Disease (PD), and Huntington's Disease (HD) are intimately associated with lysosome dysfunction (Fraldi et al. 2016).

Ca^{2+} is one of the most common second messenger involved in a variety of intracellular signaling events, which in turn control a vast array of cellular processes, including gene expression, exocytosis, cell growth, proliferation, differentiation, cell motility, cell death, and muscle contraction (Clapham 2007; Berridge 2012). Hence mammalian cells are equipped with specific channel and transporter proteins to tightly control intracellular Ca^{2+} levels ($[Ca^{2+}]_i$). Inappropriate Ca^{2+} signaling and abnormal Ca^{2+} levels are found to be associated with many cellular defects, contributing to a broad spectrum of clinical disorders, including heart disease, AD, and stroke (Bojarski et al., 2008; Berridge 2012). $[Ca^{2+}]_i$ undergoes dynamic changes in response to stimulation by cellular and environmental cues in animal cells. At resting conditions, free cytosolic $[Ca^{2+}]_i$ is maintained at a very low level (~100 nM), which is about 20,000-fold lower than extracellular $[Ca^{2+}]$, and about 5,000-fold lower than the intracellular Ca^{2+} stores such as endoplasmic reticulum (ER) and lysosomes (Berridge et al., 2000; Christensen et al., 2002; Clapham 2007). Upon stimulation by hormones, neurotransmitters, or membrane depolarization, $[Ca^{2+}]_i$ increases dramatically through passive Ca^{2+} flow down the electrochemical gradient from extracellular space and/or from intracellular Ca^{2+} stores. Intracellular Ca^{2+} signals display spectacular spatiotemporal complexity, which may encode the nature and intensity of the stimulus. The information carried by Ca^{2+} signaling is reliably decoded by a long list of Ca^{2+} effector proteins, such as calmodulin and synaptotagmins, relaying to fulfill diverse cellular functions. Upon signal termination, cytosolic Ca^{2+} returns to the resting value, mainly through Ca^{2+} pumps and transporters localized at the plasma membrane (e.g., PMCA) and on intracellular membranes (e.g., SERCA in the ER) (Berridge 2012).

Besides ER, lysosomes have also emerged as intracellular Ca^{2+} stores (Christensen et al., 2002; Churchill et al. 2002; Patel and Docampo 2010). While the importance of Ca^{2+} homeostasis in neurodegeneration is well recognized (Marambaud et al., 2009; Bezprozvanny 2010), the role of lysosomal Ca^{2+} homeostasis in neurodegeneration is largely unexplored. In this review, we will summarize the current knowledge on the key players and mechanisms in the regulation of lysosomal Ca^{2+} signaling. We will then discuss how de-regulation of lysosomal Ca^{2+} causes lysosomal dysfunction and neurodegeneration.

LYSOSOMAL CALCIUM HOMEOSTASIS

The Ca^{2+} concentration in lysosome lumen ($[Ca^{2+}]_{iy}$): is estimated to be about 500 μM (Christensen et al., 2002; Patel and Cai 2015), which could be released by intracellular cues, for example, nicotinic acid adenine dinucleotide phosphate (NAADP), one of the most potent Ca^{2+}-mobilizing second messenger (Christensen et al., 2002; Calcraft et al., 2009). Like the plasma membrane and ER, lysosomes are also believed to be equipped with ion channels and transporters to control Ca^{2+} flux across lysosome membranes (Dong et al., 2010; Xu et al., 2015; Xu and Ren 2015). The local Ca^{2+} release from lysosomes is crucial for lysosome function, but may also be involved in global Ca^{2+} signaling by interacting with ER Ca^{2+} signaling (Kilpatrick et al., 2013; Morgan et al., 2013; Kilpatrick et al., 2016;

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Raffaello et al., 2016) With the development of organelle-specific physiological and imaging approaches, for example, the whole-lysosomal patch-clamp technique, the single-organelle planar patch-clamp and live imaging with genetically encoded Ca^{2+} indicators (Dong et al., 2008; Dong et al., 2010; Schieder et al., 2010; Shen et al., 2012, Wang et al., 2012, Cang et al., 2015; Cao et al., 2015), an expanding number of lysosomal ion channels, including some Ca^{2+}-permeable ones, have been identified recently. We will briefly review these channels as well as their physiological importance. In addition, we will also discuss the mechanisms by which lysosomal Ca^{2+} is taken up or refilled after release.

Lysosomal Ca^{2+} Channels

TRPMLs—TRPML proteins belong to the mucolipin subgroup of TRP ion channel family (Ramsey et al., 2006; Nilius et al., Scientific Publishers 2007). There are three TRPML isoforms in mammals: TRPML1, TRPML2, and TRPML3. Whereas TRPML1 is widely expressed and predominantly localized on the late endosomes and lysosomes, TRPML2 and TRPML3 are expressed on the early/recycling endosomes in addition to late endosomes and lysosomes (see Fig. 1). TRPML1 is a Ca^{2+}-permeable, non-selective cation channel that can be activated by phosphatidylinositol 3,5-bisphosphate [$PI(3,5)P_2$], a phospholipid enriched on the late endosomal and lysosomal membranes (Dong et al., 2010). Mutations in human *TRPML1* have been associated with Mucolipidosis type IV disease (ML-IV), an LSD characterized by accumulation of various lipids in lysosomes. TRPML1-mediated lysosomal Ca^{2+} release may fulfill diverse physiological functions, which includes lysosomal exocytosis (Medina et al., 2011; Samie et al., 2013; Park et al., 2016), membrane repair (Cheng et al., 2014), autophagy (Medina et al., 2015), nutrient sensing (Wang et al., 2015), oxidative stress sensing (Zhang et al., 2016), lysosome motility, and lysosome tubulation and reformation (Li et al., 2016).

P2X4—P2X4 is an ATP-gated cation channel that belongs to the ionotropic P2X–family ATP receptors (North 2002). In addition to its expression on the plasma membrane, P2X4 was also found on the lysosomal membranes (Qureshi et al., 2007). Whole-lysosome patch-clamp studies revealed that lysosomal P2X4 was functional (Huang et al., 2014) (see Fig. 1). Interestingly, ATP, the natural ligand of P2X4 was found to accumulate in lysosomes (Cao et al., 2015; Zhong et al., 2016). However, even with the presence of ATP, P2X4 activity was inhibited by acidic pH of lysosome lumen (Huang et al., 2014). Luminal alkalization could counteract this inhibition thus allow lysosomal Ca^{2+} release through P2X4 (Huang et al., 2014), which was shown to be involved in lysosomal membrane fusion in a calmodulin-dependent manner (Cao et al., 2015).

TPCs (Two-Pore Channels)—TPCs contain two tandem six-transmembrane domains (2X:6 TM) which might be evolutionary intermediates between 6 TM and 4X 6TM voltage-gated ion channels (Rahman et al., 2014). Whereas TPC1 is expressed in both early endosomes and lysosomes, TPC2 is predominantly present on the lysosomal membranes (see Fig. 1) (Calcraft et al., 2009). TPCs were proposed to be the long-sought NAADP receptor that mediates NAADP-induced Ca^{2+} release from the lysosome (Brailoiu et al., 2009; Calcraft et al., 2009; Zong et al., 2009; Lloyd-Evans et al., 2010; Penny and Patel 2015). Consistent with this hypothesis, TPC overexpression increased NAADP binding

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(Calcraft et al., 2009). The Ca^{2+}-permeability of TPC2 was also supported by calcium imaging experiments and confirmed by electrophysiological studies (Brailoiu et al., 2010; Pitt et al., 2010; Schieder et al., 2010; Grimm et al., 2014, Ruas et al., 2015; Penny et al., 2016). However, several recent studies showed that TPC2 is a Na^+-selective channel with a low Ca^{2+} permeability (Wang et al., 2012; Cang et al., 2013). The crystal structures of *Arabidopsis thaliana* TPC1 (AtTPC1), a non-selective cation channel, have been resolved recently (Guo et al., 2016; Kintzer and Stroud 2016). Structure-guided mutagenesis studies revealed the molecular determinants for the Na^+-selectivity (Guo et al., 2017).

Despite the controversies on the biophysical properties of TPCs, they are suggested to have important physiological roles (Patel 2015). For example, TPC2 may regulate Ebola virus infection (Sakurai et al., 2015), pigmentation in melanocytes (Lin-Moshier et al., 2014; Ambrosio et al., 2016), autophagy regulation in cardiomyocytes (Pereira et al., 2011; Garcia-Rua et al., 2016), and physical endurance during nutrition restriction (Cang et al. 2013).

TRPM2—TRPM2 is a member of the melastatin family of the TRP family (Ramsey et al., 2006; Nilius et al., 2007). TRPM2 is a Ca^{2+}-permeable channel gated by ADPR, ADPR-2′-phosphate (ADPRP), and Ca^{2+} (Toth et al., 2015). In addition to acting as a channel on the plasma membrane, TRPM2 is also functional as a lysosomal channel in pancreatic β-cells and dendritic cells. The Ca^{2+} release through TRPM2 contributes to H_2O_2-induced β-cell death, and is critical for the maturation and chemotaxis of dendritic cells (Lange et al. 2009; Sumoza-Toledo et al., 2011).

P/Q Type Voltage-Gated Ca^{2+} Channels (VGCCs)—VGCCs are a group of voltage-gated ion channels predominately reside on the plasma membrane of excitable cells (e.g., muscle cells, neurons, etc.) with a high permeability to Ca^{2+} (Catterall et al., 2005). VGCCs are activated by depolarization, allowing Ca^{2+} influx and coupling of electrical activity with intracellular Ca^{2+} signaling (Catterall 2011; Buraei and Yang 2015). Activation of P/Q-type VGCCs triggers neurotransmitter release in neurons (Luebke et al., 1993; Takahashi and Momiyama 1993). Unexpectedly, a recent study reported the presence of P/Q-type VGCCs in the lysosomes of neurons, in both fruit flies and mice (Tian et al., 2015). Loss of pore-forming α1A subunit or auxiliary α2δ (encoded by *Cacna1a* and *Cacna2d2* respectively), leads to defects in autophagosome-lysosome fusion (Tian et al., 2015).

TRPA1—TRPA1 is a Ca^{2+} permeable nonselective cation channels mainly expressed on primary afferent nociceptors and could be activated by diverse noxious compounds, such as mustard oil and tear gas (Bandell et al., 2004; Jordt et al., 2004; Bautista et al., 2006; Julius 2013). Recently, Shang et al., reported the functional expression of TRPA1 in the peripheral lysosomes of dorsal root ganglion (DRG) neurons (Shang et al., 2016). Ca^{2+} imaging studies has shown before that allyl isothiocyanate (AITC) could induce a TRPA1-dependent intracellular Ca^{2+} release (Bandell et al., 2004; Jordt et al., 2004). With pharmacological and immunohistochemical analyses, Shang et al., found the presence of TRPA1 proteins in the lysosomes of DRG neurons. Electrophysiology and immunoassay also showed that lysosomal Ca^{2+} efflux through TRPA1 could trigger vesicle exocytosis and neuropeptides

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(NPY, CGRP) release. Furthermore, behavior analysis indicated the physiological function of intracellular TRPA1 channel in nocifensive sensation.

In summary, multiple Ca^{2+} channels have been found on the lysosomal membrane in the past few years. It should be noted, however, that direct electrophysiological studies of TRPM2, P/Q VGCCs, and TRPA1 are still lacking. Outstanding questions such as what their endogenous activation mechanisms are, and what the roles of these channels are in lysosomal physiology and diseases remain to be answered.

Lysosomal Ca^{2+} Refilling

The storage capacity of intracellular stores is limited. Thus Ca^{2+} release from stores must be followed by Ca^{2+} refilling. ER Ca^{2+} refilling is mediated by a process termed the store-operated calcium entry (SOCE) (Putney 2007), the molecular mechanism of which have been delineated recently (Clapham 2007; Berridge 2012). In contrast, the refilling mechanisms for lysosomal stores are largely unknown. It's been proposed that lysosome Ca^{2+} refilling is a pH-dependent process based on two observations (Morgan et al., 2011). First, lysosomal pH gradient dissipation, either by v-ATPase inhibitors or by alkalizing reagents such as NH4Cl, lead to the loss of lysosomal Ca^{2+} stores (Christensen et al., 2002; Lloyd-Evans et al., 2008; Calcraft et al., 2009; Dickson et al., 2012; Shen et al., 2012). Second, in yeast and plant vacuoles, the lysosome equivalents in these organisms, the Ca^{2+}–H^{+} exchanger (CAX) is required for their Ca^{2+} store maintenance (Morgan et al., 2011; Pittman 2011). This hypothesis was further emphasized by recently cloned CAXs from two non-placental mammalian: the platypus and the Tasmanian devil (Melchionda et al., 2016).

However, a recent study by Garrity et al. suggested an alternative mechanism (Garrity et al., 2016). In this study, a physiological assay was developed using GCaMP3-tagged TRPML1 and its specific cell-permeable agonist ML-SA1 (Shen et al., 2012). The lysosomal Ca^{2+} stores of TRPML1 stable cells were depleted by a brief ML-SA1 application. Unexpectedly, pH dissipation by v-ATPase inhibitors bafilomycin-A or concanamycin-A did not abolish the refilling, suggesting a dispensable role of lysosomal pH gradient. Instead, the ER store was found to be required for lysosomal Ca^{2+} refilling. Depleting ER Ca^{2+} store by either thapsgargin (a SERCA inhibitor) or TPEN (a luminal Ca^{2+} chelator operating at neutral pH) abolished the refilling. Furthermore, IP3-receptors (IP3Rs) but not Ryanodine receptors (RyRs) on the ER are required for the refilling. Inhibition of IP3Rs caused lysosome dysfunction and LSD-like phenotype. Furthermore, the critical role of ER for lysosomal calcium refilling is also supported by the intimate spatial localization of ER and lysosomes (also see (Kilpatrick et al., 2013; Aston et al., 2017; Kilpatrick et al., 2017)). Overall, this new study provided a new platform to study the mechanism of lysosomal Ca^{2+} refilling. Further test of the ER-refilling hypothesis may require the identification of new players including the involved lysosomal Ca^{2+} sensor(s) and pump(s), as well as the ER-lysosome tether(s) (see Fig. 1).

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LYSOSOMAL CALCIUM HOMEOSTASIS DEFECTS AND NEURODEGENERATION

Diminished Lysosome Ca^{2+} Store in Neurodegeneration

Several studies suggest a correlation between diminished lysosomal Ca^{2+} stores and neurodegeneration. Niemann-Pick disease type C (NPC) is an autosomal recessive LSD caused by loss of function mutations in NPC1 or NPC2 genes (Carstea et al., 1997; Sleat et al., 2004). NPC1 is a membrane protein that resides on the limited membrane of lysosomes, while NPC2 is a soluble protein in the lysosome lumen (Infante et al., 2008; Kwon et al., 2009). NPC1 and NPC2 transport un-esterified cholesterol outside of lysosome lumen through lysosome membranes (Kwon et al., 2009). It was reported that in $NPC^{-/-}$ cells have reduced lysosomal Ca^{2+} stores, presumably due to inhibition of Ca^{2+} uptake or refilling by sphingosine accumulation in NPC cells (Lloyd-Evans et al., 2008).

A role of lysosomal Ca^{2+} was suggested in Familial Alzheimer's disease (FAD), which is caused by mutations in presenilin1 (PS1), presenilin2 (PS2) or amyloid precursor protein (APP) (Campion et al., 1999). PS1 and PS2 are key components of γ-secretase, a protein complex resides on plasma membrane that cleaves APP to amyloid-β (Aβ peptides (Bertram and Tanzi 2008). Two recent studies both showed that deletion of PS(s) caused a decrease in lysosome Ca^{2+} stores (Coen et al. 2012; Lee et al., 2015). Whether this is linked with lysosomal acidification defect, as reported earlier (Lee et al., 2010), still remains controversial. In Coen et al.'s study, PS(s) knock-out cells appear to have similar pH as Wt cells (Coen et al., 2012). Lee et al., however, reported that impaired lysosomal acidification leads to lysosomal Ca^{2+} homeostasis in a TRPML1-dependent manner (Lee et al., 2015). Further investigation is thus needed to clarify whether lysosomal acidification is defected and contribute to the decreased lysosomal Ca^{2+} store in PS(s)-deficient cells.

One of the genetic risk factors for Parkinson's disease (PD) is *GBA1*, a gene that encodes lysosomal hydrolase β-glucocerebrosidase that degrades glucocerebroside to glucose and ceramide (Gan-Or et al., 2015). Recessive mutations of *GBA1* cause Gaucher disease (GD), either neuropathic (type II and III) or non-neuropathic (type I) depending on mutations (Nagral 2014). A recent study showed that fibroblasts from GD type I patients or PD patients carring *GBA1* mutation have enlarged lysosomes and reduced Ca^{2+} release induced by GPN (Kilpatrick et al., 2016), suggesting a decreased lysosomal Ca^{2+} store. Besides *GBA1*, mutation of Leucine-rich repeat kinase 2 (LRRK2) is another most common genetic risk factor of PD, that may also play a role in lysosome function and autophagy (Gan-Or et al., 2015). A recent study reported that primary fibroblasts from an LRRK2-G2019S PD patient contained enlarged and clustered lysosomes with elevated NAADP-induced Ca^{2+} release (Hockey et al., 2015). Very intriguingly, the abnormal lysosome morphology can be reversed by inhibiting TPC2 or applying a fast Ca^{2+} chelator, BAPTA-AM, but not a slow Ca^{2+} chelator, EGTA-AM, suggesting a dysregulation of lysosomal Ca^{2+}.

Defects in key elements of lysosomal Ca^{2+} refilling, such as IP3Rs and proteins that mediate ER-lysosome contact, may also potentially affect lysosomal Ca^{2+} stores. For example, in HD, an autosomal recessive genetic disease caused by the expansion of a trinucleotide CAG

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repeat in *HTT* gene (MacDonald et al., 1993; Bates et al., 2015), mutant Htt (mHtt) but not the wild type Htt sensitize IP3Rs' response to IP3 (Tang et al., 2003). Reduced ER Ca^{2+} store was also observed in an HD mouse model (Wu et al., 2016). Similarly, spinocerebellar ataxia (SCA), another neurodegenerative disease caused by CAG repeat expansion in SCA genes, often features altered IP3Rs expression and IP3 responses (Brown and Loew 2014). Given that IP3Rs are required for lysosome Ca^{2+} refilling, it is possible that impaired lysosomal Ca^{2+} signaling may underlie neurodegenerative diseases with defective IP3R function (Takada et al., 2016).

ER-lysosome contact sites are still poorly understood in mammalian cells (Kilpatrick et al., 2013; Kilpatrick et al., 2017). The yeast counterparts, ER-vacuole contact sites, are much more clearly defined in the involving players, which may therefore shed light on disorders caused by mutation in their human homolog genes (Hariri et al., 2016). For example, deficiency in human sorting nexin 14 (Snx14) is linked with pediatric cerebellar ataxia and intellectual disability (Thomas et al., 2014; Akizu et al., 2015). Study in its yeast homolog Mdm1, an ER-vacuole tether protein, revealed that the patient allele of *SNX14* disturbs sphingolipid synthesis when expressed in yeast (Henne et al., 2015). It is possible that impaired lysosomal Ca^{2+} signaling may underlie related human diseases.

Impaired Lysosome Ca^{2+} Release and Neurodegeneration

Besides diminished lysosomal Ca^{2+} store, defects in key components of Ca^{2+} releasing machineries such as Ca^{2+} channels could also lead to lysosomal Ca^{2+} dysregulation. The most direct link between lysosomal Ca^{2+} release defects and human disease came from ML-IV, an autosomal recessive LSD that manifests severe neurodegeneration caused by loss of function of TRPML1 (Berman et al., 1974; Slaugenhaupt 2002). In ML-IV cells, lysosomal Ca^{2+} store might remain unchanged (Lloyd-Evans and Platt 2011) or accumulated (Wong et al., 2012; Cao et al., 2015), and NAADP-induced Ca^{2+} release also not affected (Yamaguchi et al., 2011). However, enlarged lysosomes lysosomal storage are observed in TRPML1-deficient cells (Dong et al., 2008; Venkatachalam et al., 2015), suggestive of lysosomal dysfunction. Given the roles of TRPML1 in autophagy, lysosomal exocytosis, and oxidative stress sensing, it is of no surprise that ML-IV is a neurodegenerative disease (Andersen 2004; Menzies et al., 2015). Neurodegeneration in ML-IV patients is likely a result of defects in multiple ML1-dependent processes required for maintaining cellular homeostasis.

Defective TRPML1 signaling might be a common feature for many LSDs. In NPC cells, TRPML1-mediated lysosomal Ca^{2+} release is much reduced, which may be caused by Sphingomyelins (SMs) storage (see Fig. 1). Boosting TRPML1 activity genetically or pharmacologically may reduce lysosome storage and cholesterol accumulation (Shen et al., 2012). Similarly, TRPML1-:m ediated Ca^{2+} release is also compromised in Niemann-Pick disease type A (NPA) and Fabry disease (Shen et al., 2012; Zhong et al., 2016).

In HD, mHtt expression can cause increased perinuclear lysosome accumulation and decreased lysosome mobility (Erie et al., 2015). Acute activation and chronic inhibition of TRPML1 can both result in lysosome perinuclear accumulation (Li et al., 2016). It remains to be investigated whether altered TRPML1 activity underlies HD.

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Cacna1a mutant neurons are defective in autophagosome-lysosome fusion. Inhibition of CACNA1A Ca^{2+} channel function in the lysosome but not PM led to the lysosomal fusion defects (Tian et al., 2015). Human mutations in *Cacna1a* are also associated with neurological diseases including Episodic ataxia type 2 (EA2), Familial hemiplegic migraine-1 (FHM1), and pinocerebellar ataxia type 6 (SCA6) (Rajakulendran et al., 2012). It is possible the lysosomal Ca^{2+} defects may contribute to these diseases. P2X4 is involved in epilepsy and amyotrophic lateral sclerosis (ALS) (Saez-Orellana et al., 2015). Whether these functions are mediated by lysosomal P2X4 is still unclear.

Other than mutations of the channels, the impairment of lysosomal Ca^{2+} release could also be the result of other causes such as decreased activation or increased inhibition of channel activity, or other environmental cues (summarized in Fig. 1). Taking TRPML1 as the example, mutations in key components of $PI(3,5)P_2$ synthesis, such as *FIG4* and *PIKfyve*, are associated with neurological disorders (Jin et al., 2016). Inhibition of TRPML1 is observed in NPC cells (by SMs) (Shen et al., 2012) or adenosine deaminase (ADA)-deficient cells (by adenosine) (Zhong et al., 2017). TRPML1 can also be activated by ROS (Zhang et al., 2016), which is closely linked with neurodegenerative diseases (Barnham et al., 2004; Niedzielska et al., 2016).

CONCLUDING REMARKS

Diverse biological processes crucial for maintaining cellular homeostasis require Ca^{2+} release from lysosomes. Given the importance of lysosomal Ca^{2+} in lysosomal functions and the importance of lysosome function in neuronal health, studies on direct links between lysosomal Ca^{2+} and neurodegeneration are surprisingly few (summarized in Table I, II). The ER-refilling studies suggest that Ca^{2+} dysregulation in ER may subsequently affect Ca^{2+} homeostasis in lysosomes. Common defects in TRPML1-mediated lysosomal Ca^{2+} release in multiple LSDs suggest that pharmacologically manipulating its functions may be a potential general strategy in alleviating lysosome storage and neurodegeneration.

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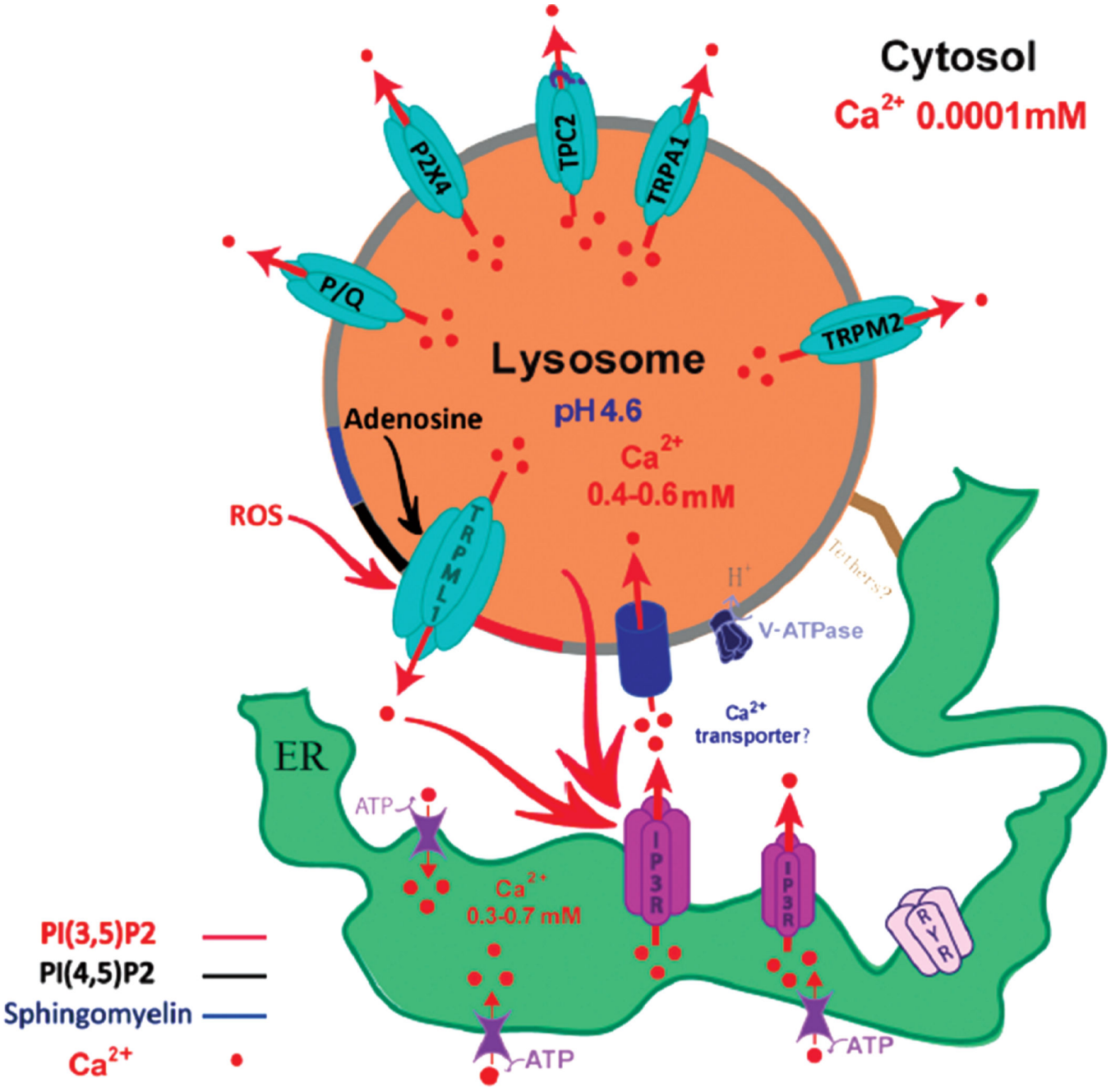

Figure 1.

Lysosomal Ca^{2+} release channels and store refiling mechanisms. Several Ca^{2+}-permeable channels may be present on the lysosomal membranes. Activation of the channels trigger Ca^{2+} release from lysosomal Ca^{2+} stores. Among them, the gating mechanisms are most well-established for TRPML1. The lysosome-enriched phosphoinositide $PI(3,5)P_2$ (red) can activate the channel, while plasma-membrane-enriched phosphoinositide $PI(4,5)P_2$ (black) can inhibit TRPML1. Additionally, TRPML1 can be activated (red arrow) by reactive oxygen species (ROS), and ROS-induced lysosomal Ca^{2+} release may induce lysosomal biogenesis (Zhang et al., 2016). In addition, accumulated materials such as sphingomyelin

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(blue) and adenosine may inhibit (black arrow) TRPML1. While TPC-mediated lysosomal Ca^{2+} release can be triggered by NAADP or sphingosine (Calcraft et al., 2009; Zong et al., 2009; Lloyd-Evans et al., 2010; Hoglinger et al., 2015) (whether TPC2 serves as the Ca^{2+} channel still remains convtroversial, indicated by the question mark), activation mechanisms for other lysosomal Ca^{2+} channels are less clear. Upon lysosomal Ca^{2+} channel activation, lysosome stores are largely depleted, which is expected to trigger a refilling mechanism. In refilling mechanism 1, a putative Ca^{2+}–H^{+} exchanger may transport Ca^{2+} ions into lysosome lumen in an H^{+}-dependent manner (Morgan et al., 2011). Alternatively, Garrity et al. suggest that in the ER-lysosome membrane contact sites, IP3Rs–mediated ER release Ca^{2+} may allow an unidentified Ca^{2+} transporter to transport Ca^{2+} to lysosomes. In this model, possible tether proteins may link ER membrane proteins directly with lysosomal membrane proteins at ER-lysosome membrane contact sites. Reprinted with permission from Garrity, A. G., et al. (2016). The endoplasmic reticulum, not the pH gradient, drives calcium refilling of lysosomes. *Elife* 5, e15887. © 2016, eLife/CC BY 4.0.

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Table I

Summary of neurodegenration with defected calcium store.

Disease	Model	Ca^{2+}_{ly} **store**	Ref.
NPC	Human B	Decreased	Lloyd-Evans et al., 2008
	lymphoblasts & Human fibroblast	Decreased	
FAD	PSENdKO MEF	Decreased	Coen et al., 2012
	PSEN $^{-/-}$ neuron	Decreased	
	PSEN1 KO murine blastocyst	Decreased	Lee et al., 2015
PD + GBA1	Human fibroblast	Decreased	Kilpatrick et al., 2016

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Table II

Summary of neurodegenration with impaired lysosomal calcium release.

Disease	Model	Ca^{2+}_{ly} efflux	Ref.
NPA	Human fibroblast	TRPML1-mediated, decreased GPN-induced, unchanged	Shen et al., 2012
	Human fibroblast	TRPML1-mediated, decreased GPN-induced, unchanged	Zhong et al., 2016
NPC	Human B lymphoblasts & Human fibroblast	GPN-induced, decreased	Lloyd-Evans et al., 2008
	$NPC^{-/-}$ CHO & Humam fibroblast	TRPML1-mediated, decreased GPN-induced, unchanged	Shen et al., 2012
ML IV	Unpublishied SKBR3 cell transfected with channel dead TRPML1	TRPML1-mediated, missing NAADP-induced, unchanged	Peterneva et al., Yamaguchi et al., 2011
Fabry disease	Human fibroblast	TRPML1-mediated, decreased GPN-induced, unchanged	Zhong et al., 2016
FAD	PSENdKO MEF & $PSEN^{-/-}$ neuron	GPN-induced, decreased	Coen et al., 2012
	PSEN1 KO murine blastocyst	GPN-induced, decreased	Lee et al., 2015
PD + GBA1	Human fibroblast	GPN-induced, decreased	Kilpatrick et al., 2016
PD	LRRK2 G2019S human fibroblast	NAADP-induced, increased	Hockey et al., 2015
EA2, FHM1, SCA6	Cacna1a mutant mouse	$VGCC_{ly}$-mediated, missing	Tian et al., 2015