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Review
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Deviant Lysosomal Ca^{2+} Signalling in Neurodegeneration. An Introduction

Sandip Patel

Department of Cell and Developmental Biology, University College London, London WC1E 6BT, UK

Lysosomes are key acidic Ca^{2+} stores. The principle Ca^{2+}-permeable channels of the lysosome are TRP mucolipins (TRPMLs) and NAADP-regulated two-pore channels (TPCs). Recent studies, reviewed in this collection, have linked numerous neurodegenerative diseases to both gain and loss of function of TRPMLs/TPCs, as well as to defects in acidic Ca^{2+} store content. These diseases span rare lysosomal storage disorders such as Mucolipidosis Type IV and Niemann–Pick disease, type C, through to more common ones such as Alzheimer and Parkinson disease. Cellular phenotypes, underpinned by endo-lysosomal trafficking defects, are reversed by chemical or molecular targeting of TRPMLs and TPCs. Lysosomal ion channels therefore emerge as potential druggable targets in combatting neurodegeneration.

Keywords: Ca^{2+}, Lysosomes, Acidic Ca^{2+} Stores, TPCN1, TPCN2, MCOLN1, NAADP, Phosphatidylinositol-3,5-Bisphosphate, Neurodegeneration.

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INTRODUCTION

According to the textbook, Ca^{2+} stores are synonymous with the endoplasmic reticulum (ER). And, certainly by volume, the ER is no doubt the largest store of Ca^{2+} oft mobilised to regulate numerous cellular events (Berridge, 2002). But acidic organelles such as lysosomes have also emerged as important Ca^{2+} stores despite their relatively small volume (Christensen et al., 2002; Morgan et al., 2011; Patel and Docampo, 2010).

Lysosomes are H^{+}- and Ca^{2+}-replete organelles—that together with lysosome-related organelles, endosomes, secretory vesicles and the more distantly related acidocalcisomes and vacuoles (found in organisms outside of the animal kingdom)—constitute the acidic Ca^{2+} stores (Patel et al., 2010; Patel and Muallem, 2011). Like the ER, lysosomes express Ca^{2+}-permeable channels and transporters (Patel and Cai, 2015). Strategic positioning of these organelles in close proximity to the ER (allowing Ca^{2+} signals to be amplified or tempered) and other acidic organelles (facilitating vesicular fusion) offers an alternative, versatile means to regulate Ca^{2+}-dependent output (Kilpatrick et al., 2013; Lopez-Sanjurjo et al., 2013; Melchionda et al., 2016; Pryor et al., 2000; Yamasaki et al., 2004).

Befitting widespread functional roles for lysosomes (Xu and Ren, 2015), evidence is now accumulating that links dysregulated lysosomal Ca^{2+} channel function to neurodegenerative disease (Fig. 1). This collection of reviews summaries this contemporary literature.

DRUGGING ENDO-LYSOSOMAL Ca^{2+}-PERMEABLE CHANNELS

The archetypal lysosomal ion channel is TRP mucolipin 1 (TRPML1). This channel has attracted much attention because it is mutated in the childhood neurodegenerative lysosomal storage disorder, Mucolipidosis Type IV (MLIV) (Bargal et al., 2000). The two-pore channels TPC1 and TPC2 are endo-lysosomal ion channels that have entered the limelight more recently (Galione et al., 2009; Grimm et al., 2017; Patel, 2015). Both TRPML1 and TPC2 are targeted to lysosomes via dileucine motifs (Brailoiu et al., 2010; Vergarajauregui and Puertollano, 2006) and

E-mail: patel.s@ucl.ac.uk

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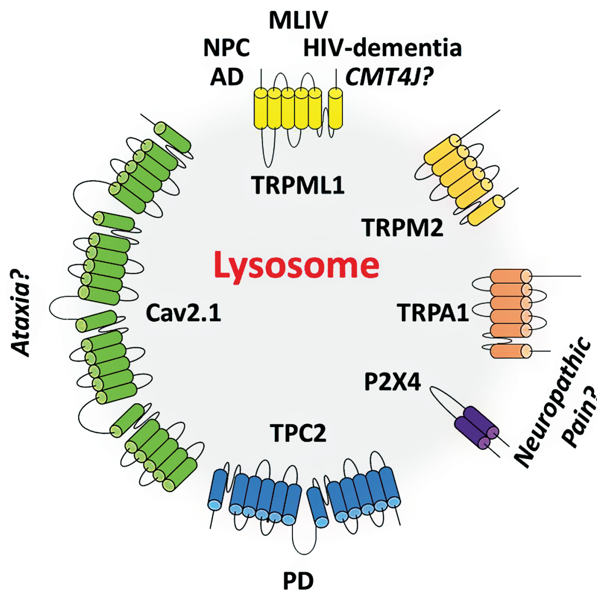

Figure 1. *Deviant lysosomal Ca^{2+} signalling in neurodegeneration.* Schematic relating dysfunction of Ca^{2+}-permeable channels in lysosomes (inner perimeter) to neurodegenerative disease (outer perimeter).

both are Ca^{2+}-permeable (LaPlante et al., 2002; Schieder et al., 2010). It is however interesting that the ion selectivity of these channels has been subject to controversy (Marchant and Patel, 2013; Puertollano and Kiselyov, 2009) likely related to the special challenges associated with characterizing intracellular as opposed to plasma membrane-targeted channels.

Here, Grimm (2016) discusses the rapidly advancing pharmacology of TRPMLs, in particular the identification of TRPML agonists and antagonists (Chen et al., 2014; Grimm et al., 2010; Samie et al., 2013). The pharmacology of TPCs is relatively poorly characterised and limited to modifiers of voltage-gated Ca^{2+} and Na^{+} channels (Rahman et al., 2014; Sakurai et al., 2015). Nevertheless indirect inhibitors such as the antagonists of the Ca^{2+} mobilising messenger NAADP, a TPC activator, are proving useful (Davidson et al., 2015; Naylor et al., 2009).

As discussed throughout the reviews in this issue, chemical tools targeting TRPMLs and TPCs are providing new insights into the function and dysfunction of these channels in various neurodegenerative contexts.

TRPML1 AND NEURODEGENERATION

The role of TRPML1 in MLIV has been well reviewed and the reader is referred to recent articles (Ahuja et al., 2016; Bach et al., 2010; Grimm et al., 2012; Venkatachalam et al., 2015; Wang et al., 2014). Grimm covers work demonstrating correction of lysosomal storage in MLIV fibroblasts by synthetic TRPML agonists (Chen et al., 2014; Grimm, 2016). This is significant as it opens up new therapeutic options for forms of the disease where TRPML1 activity is not completely lost. Notably, growing evidence suggests that TRPML1 function might also be compromised in disorders such as Niemann–Pick disease, type C (NPC) (Shen et al., 2012), a distinct lysosomal storage disorder, and Alzheimer's disease (Lee et al., 2015) amongst others. Here, reviews by Lloyd-Evans (2016) and Feng and Yang (2016) provide overviews of the relevant literature.

It was using various models of NPC that a clear link between lysosomal Ca^{2+} and lysosomal storage was uncovered (Lloyd-Evans et al., 2008). Lysosomal Ca^{2+} levels measured directly (using endocytosed Ca^{2+} indicators) or indirectly (through cytosolic Ca^{2+} signals in response to the lysosomotropic agent GPN) suggested that they were lower in NPC, and that lysosomal Ca^{2+} depletion was an early step in the pathogenesis. Although supported by independent studies (reviewed by Lloyd-Evans (2016)), more recent findings suggest that TRPML1 channels are inhibited by the accumulation of sphingomyelins in NPC rather than a reduction in stored Ca^{2+} (Shen et al., 2012). However, whether reductions in total Ca^{2+} were masked by secondary ER Ca^{2+} release (Kilpatrick et al., 2013) remains a formal possibility. Nevertheless, both studies concur that lysosomal Ca^{2+} signalling is inhibited in the disease (Lloyd-Evans et al., 2008; Shen et al., 2012). Importantly, boosting activity of endogenous TRPML1 with a synthetic TRPML agonist in NPC reversed lysosomal storage (Shen et al., 2012). Chemical activation of TRPML1 has also been reported to clear lysosomal amyloid β-peptides and sphingomyelin in cellular models of HIV dementia (Bae et al., 2014). However, in these cells TRPML channels appeared to be hyperactive. It is worth mentioning that TRPML1 activity in these studies (Bae et al., 2014; Shen et al., 2012) was measured using a genetically-encoded Ca^{2+} indicator fused to TRPML1 (Zhong et al., 2016b). Although elegant, the approach requires overexpression of TRPML1 which as shown recently triggers Ca^{2+} influx and ER Ca^{2+} release (Kilpatrick et al., 2016b). Such coupling might confound interpretation of the resulting signals.

Both TRPMLs and TPCs are regulated by the endo-lysosomal phosphoinositide, phosphatidylinositol-3,5-bisphosphate ($PI(3,5)P_2$) (Dong et al., 2010; Jha et al., 2014; Wang et al., 2012). Levels of this lipid are governed by PIKfyve and FIG4 (Dove et al., 2009). Mutations in the gene encoding FIG4 lower $PI(3,5)P_2$ levels and are associated with Charcot-Marie-Tooth peripheral neuropathy type 4J (CMT4J) (Chow et al., 2007) as well as a number of other disorders. In FIG4 knockout cells, lysosomal Ca^{2+} levels measured using Calcium Orange were elevated (Zou et al., 2015). As in NPC and HIV dementia models, chemical activation of TRPMLs normalised lysosomal dysfunction. These findings again suggest compromised TRPML activity, presumably due to $PI(3,5)P_2$ deficiency that results

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in Ca^{2+} accumulation within lysosomes. Elevated lysosomal Ca^{2+} levels upon FIG4 depletion are reminiscent of the findings in *Drosophila* upon knockout of its single mucolipin homologue (Wong et al., 2012) and in some TRPML1-deficicent mammalian cells (Cao et al., 2015b) but not others (Soyombo et al., 2006).

Finally, recent work by Lee et al. show that lysosomal Ca^{2+} levels are reduced in cells lacking the Alzheimer disease-linked gene, Presenilin 1 (*PSEN1*) (Lee et al., 2015). These findings are consistent with earlier findings in *PSEN1* and *PSEN2* double knockout cells (Coen et al., 2012). Interestingly, endogenous Ca^{2+} responses to a synthetic TRPML agonist were paradoxically enhanced upon PSEN1 knockout, pointing to a model whereby the hyperactivation of TRPML1 lowers steady state lysosomal Ca^{2+} levels (Lee et al., 2015). In accord, reduced lysosomal Ca^{2+} and the associated elevation in cytosolic Ca^{2+} were reversed by knockdown of TRPML1. Interestingly, treatment of PSEN1-deficient cells with an NAADP antagonist was also effective in resetting Ca^{2+} homeostasis but knockdown of TPC2 was not. These data suggest complex interplay between TRPML and NAADP signalling possibly involving TPC1. Normalising Ca^{2+} levels however failed to reverse proteolytic and autophagic defects in PSEN1-deficient cells. Rather the associated changes in lysosomal pH upon PSEN knockout (albeit disputed) appeared to be more functionally relevant (Lee et al., 2015).

In sum, TRPML1 has been implicated in a number of neurodegenerative diseases with evidence for both a gain and loss of function in activity associated with complex effects on lysosomal Ca^{2+} content.

TPC2 AND NEURODEGENERATION

Like, TRPML1, TPC2 has also been linked to neurodegeneration. Reviews in this issue by both Hilfiker and colleagues (Rivero-Rios et al., 2016), and Kilpatrick (2016) discuss defective lysosomal Ca^{2+} signalling in Parkinson disease. Initial overexpression studies of the Parkinson disease-linked protein LRRK2 identified autophagic defects (Gomez-Suaga et al., 2012), adding to what is now a body of literature implicating endo-lysosomal dysfunction in the disease (Abeliovich and Gitler, 2016). Importantly, these defects were recapitulated upon NAADP treatment and reversed by chemically antagonising NAADP action or by overexpressing a dominant-negative TPC2 construct (Gomez-Suaga et al., 2012).

Subsequent work by Hockey et al. identified endo-lysosomal morphology defects in Parkinson disease patient fibroblasts carrying the G2019S mutation in LRRK2 (Hockey et al., 2015). Again, these defects were reversed by NAADP antagonism including a novel analogue better suited for *in vivo* studies. Chemical or molecular inhibition of TPCs, local Ca^{2+} fluxes, $PI(3,5)P_2$ signalling, and the TPC-interactor Rab7 (Lin-Moshier et al., 2014) all reversed endo-lysosomal morphology defects, further highlighting this axis as a potential therapeutic target (Hockey et al., 2015). Like in PSEN1-deficent cells, these data point to a gain of function in lysosomal Ca^{2+} signalling. In accord, NAADP-evoked Ca^{2+} signals were enhanced upon mutation of LRRK2. Steady state lysosomal Ca^{2+} levels were not measured in *LRRK2*-linked Parkinson disease. However, as further discussed by Kilpatrick (2016), lysosomal Ca^{2+} levels were reduced in *GBA1*-linked Parkinson disease (Kilpatrick et al., 2016a). This form of the disease is due to mutations in glucocerebrosidase, a lysosomal enzyme, and is highly relevant because recessive mutations in *GBA1* cause Gaucher disease, another lysosomal storage disorder.

Rare lysosomal storage disorders and more common neurodegenerative disease thus seem to be intimately linked through defects in lysosomal Ca^{2+}.

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A ROLE FOR OTHER LYSOSOMAL CHANNELS IN NEURODEGENERATION?

Whereas TRPMLs and TPCs localise predominantly to the endo-lysosomal system, other Ca^{2+}-permeable channels traditionally thought of as plasma membrane proteins are also found within lysosomes. These include TRPM2 (Lange et al., 2009), P2X4 (Qureshi et al., 2007) and more recently the voltage-gated Ca^{2+} channel, Cav2.1 (Tian et al., 2015) and TRPA1 (Shang et al., 2016). This raises the possibility that these channels might also (de) regulate lysosomal Ca^{2+} signalling. Indeed, autophagic defects in neurons from the *leaner* mouse have been ascribed to lysosomal Cav2.1 (Tian et al., 2015) which might link defective lysosomal Ca^{2+} signalling to neurodegenerative diseases associated with Cav2.1 mutation such as episodic ataxia 2. By the same logic, perhaps lysosomal P2X4 and TRPA1 contribute to neuropathic pain which is often associated with neurodegeneration.

Although not a Ca^{2+} channel, the big-conductance Ca^{2+}-activated K^+ (BK) channel, Slo1 also localises to lysosomes, interacts with TRPML1 and is thought to provide a counter current to sustain Ca^{2+} release (Cao et al., 2015b). Notably, overexpression or chemical activation of Slo1 reverses storage phenotypes in patient fibroblasts from several lysosomal storage disorders including NPC and MLIV (Cao et al., 2015b; Zhong et al., 2016a).

The number of lysosomal ion channels potentially relevant for neurodegeneration is steadily growing.

LYSOSOMAL Ca^{2+}-PERMEABLE CHANNELS AND ENDO-LYSOSOMAL TRAFFICKING

Ca^{2+}-regulates endo-lysosome fusion and lysosome reformation necessary for endo-lysosomal trafficking (Pryor et al., 2000). Thus, the identification of an endo-lysosomal

Ca^{2+} permeable channel (TRPML1) immediately suggested a mechanism to explain aberrant lysosome morphology and the mis-trafficking of lipids characteristic upon loss of channel function (in MLIV) (Pryor et al., 2006). However, pinpointing the exact subcellular 'lesion' is challenging due to the difficulties in assaying these dynamic processes in live cells and the interconnected and heterogeneous nature of the endocytic system.

In the case of TPC2, it is clear that gain-of function, be it pathological (manifest in Parkinson disease) (Hockey et al., 2015) or experimental (upon TPC2 overexpression) (Lin-Moshier et al., 2014), enlarges lysosomes. This points to a fusogenic role for TPC2 within the endo-lysosomal system, as discussed in the review by Hilficker (Rivero-Rios et al., 2016). Indeed, TPCs associate with the fusogenic machinery (Grimm et al., 2014; Lin-Moshier et al., 2014; Marchant and Patel, 2015). Similar roles for P2X4 in endo-lysosome fusion (Cao et al., 2015a) and Cav2.1 in endo-lysosome/autophagosome fusion (Tian et al., 2015) have also been advanced. In the case of TRPML1 however, it is loss of function that consistently results in lysosome enlargement. Might this result due to a block in fission. In accord, fission is altered in FIG4-deficient cells in a TRPML-dependent manner (Zou et al., 2015). But potential fusogenic roles for TRPML1 in the context of endo-lysosome/amphisome fusion in *Drosophila* (Wong et al., 2012) and lysosomal exocytosis in mammalian cells (Samie et al., 2013) should not be ignored.

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In sum, lysosomal channel dysfunction is associated with endo-lysosomal trafficking defects but the mechanistic details are still hazy.

SCOPE

Growing evidence links dysregulated lysosomal Ca^{2+} signalling to neurodegeneration. Currently available small molecule activators and inhibitors, together with molecular manipulations, have been used with promising effect to reverse cellular phenotypes and identify the relevant target channels. But mechanistically, potentiation or inhibition of target channels does not always intuitively correlate with steady-state levels of lysosomal Ca^{2+}. This underscores the need for rigorous analyses of lysosomal Ca^{2+} signals and better methods to do so. Indeed, flux of other ions such as Fe^{2+} through TRPML1 (Dong et al., 2008) and likely TPCs too (Fernandez et al., 2016) might also be functionally relevant. Whilst, there is no doubt that channel dysfunction is manifest in vesicular trafficking defects, further work is required to more precisely delineate the affected processes. Finally, considering potential roles for lysosomal ion channels in regulating non-vesicular traffic may also be of merit given physical contact of endo-lysosomes with other organelles (Kilpatrick et al., 2013) and the regulation of such contact by stored Ca^{2+} (Kilpatrick et al., 2017). These considerations will no doubt advance the ultimate aim of developing novel mechanism-based therapeutics for tackling neurodegeneration in our ever-aging population.

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