$PI(3,5)P_2$ and NAADP: team players or lone warriors? – new insights into TPC activation modes

Dawid Jaślan[1], Irene Flavia Ferro[1], Veronika Kudrina[1], Yu Yuan[2], Sandip Patel[2], and Christian Grimm[1,*]

[1]Walther Straub Institute of Pharmacology and Toxicology, Faculty of Medicine, Ludwig-Maximilians-University, Munich, Germany.

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

***** Correspondence: christian.grimm@med.uni-muenchen.de

Abstract: NAADP (nicotinic acid adenine dinucleotide phosphate) is a second messenger, releasing Ca^{2+} from acidic calcium stores such as endosomes and lysosomes. $PI(3,5)P_2$ (phosphatidylinositol 3,5-bisphosphate) is a phospho-inositide, residing on endolysosomal membranes and likewise releasing Ca^{2+} from endosomes and lysosomes. Both compounds have been shown to activate endolysosomal two-pore channels (TPCs) in mammalian cells. However, their effects on ion permeability as demonstrated specifically for TPC2 differ. While $PI(3,5)P_2$ elicits predominantly Na^+-selective currents, NAADP increases the Ca^{2+} permeability of the channel. What happens when both compounds are applied simultaneously was unclear until recently.

Keywords: TPC1, TPC2, NAADP, $PI(3,5)P_2$, lysosome, endosome

1. TPCs: an introduction

Two pore channels (TPCs) belong to the superfamily of voltage-gated ion channels (VGIC) sharing with their relatives, similarities in basic transmembrane and overall channel structures. TPCs probably originated from a gene-duplication event of single Shaker-like domains typical of bacterial Na_v channels, K_v, TRP, and CatSper, which in turn underwent another round of gene duplication to form channels with four Shaker-like domains such as Ca_v or Na_v (20–30% sequence identity with particular domains) (Fig.1) [1–5]. They are therefore considered key evolutionary intermediates [3].

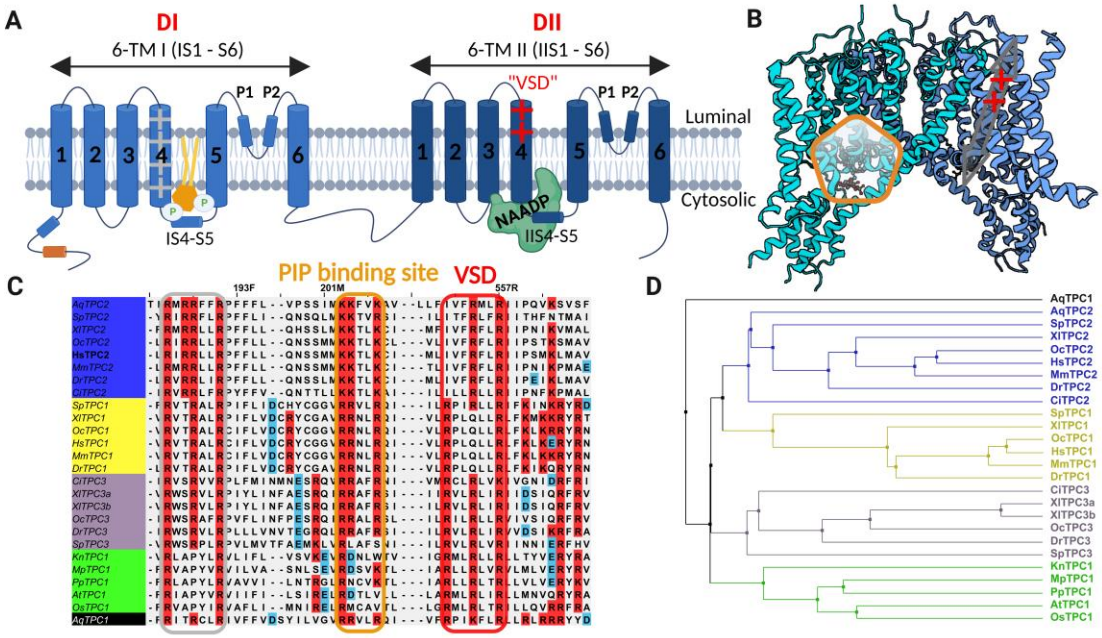

Fig.1 **Structure and evolution of TPCs.** (A) Illustrative 2D structure of TPCs (TPC2 used as example) depicting Shaker-like domains (DI and DII) spanning through the lipid membrane each consisting of six transmembrane (TM) segments (IS1–S6 and IIS1–S6). Depicted are: voltage sensing domains (VSD) – degenerated IS4, i.e. lacking key features of a canonical voltage sensor (gray crosses) [6–10] and cryptic IIS4, i.e. preserving some key features of a canonical voltage sensor such as formation of a 3_{10} helix in part of IIS4 and the presence of the conserved gating charge transfer center (red crosses visualize positive charges; arginines) [9–12], ion-conducting pore forming loops (P1 and P2) between segments S5 and S6, $PI(3,5)P_2$ binding site near IS4-S5 and proposed

location of NAADP binding proteins interacting with TPCs (green spot) (B) 3D visualization of TPC topology (hTPC2 used as example; PDB accession number 6NQ0) with marked bound $PI(3,5)P_2$ and cryptic VSD. (C) Sequence alignment domains ($PI(3,5)P_2$ binding site and VSD2) in plant and animal TPCs (sequences taken from available databases (*Amphimedon queenslandica (Aq),* XP_019852734.1, XP_019856673.1; *Strongylocentrotus purpuratus (Sp), NP_001138446.2,* NP_001138448.1, NP_001138449.1; *Xenopus laevis (Xl),* XP_018120624.1, XP_018116215.1, XP_018117727.1, XP_018112419.1; *Oryctolagus cuniculus (Oc), UTN00728.1, NP_001137406.1, UTN00729.1; Mus musculus (Mm), NP_665852.1, XP_006508676.1; Homo sapiens (Hs), Q9ULQ1, Q8NHX9*; *Danio rerio (Dr), A0JMD4, C4IXV6, A2BHL7; Ciona intestinalis (Ci), XP_004226033.2, XP_002122201.1*; *Klebsormidium nitens (Kn), A0A1Y1ICK0; Marchantia polymorpha (Mp), A0A176W9B8*; *Physcomitrium patens (Pp), Q05KM6*; *Arabidopsis thaliana (At), Q94KI8*; *Oryza sativa (Os), Q5QM84*) were aligned and analyzed using MAFFT). Positively and negatively charged amino acids are marked with red and blue color, respectively. Areas responsible for $PI(3,5)P_2$ binding and voltage sensing in the different TPC paralogues and orthologues from the same and different species are marked by frames. (D) TPC phylogenetic tree, visualized by cladogram generated based on average distance using percent sequence identity (Jalview v.2.11.2.4). Layout created with BioRender.com

TPC genes are rather common throughout evolution and together with mucolipins (TRPMLs/MCOLNs) represent families of Ca^{2+}-permeable channels that localize to acidic organelles. While TPCs are expressed in endolysosomal vesicles in animals, they are found in vacuoles in plants [13–17,5]. TPCs are present throughout animal and plant lineages but not in fungi, whereas TRPMLs diversified greatly in animals, being to some extent present in fungi and green algae but absent from land plants. These two channel families have evolved independently, with the number of mucolipins steadily rising from 1 to 3-5 members during evolution while TPCs had reached a maximum of 6-7 in Apusozoa and sponges with only 2 remaining members in human, some primates and rodents, e.g. mouse while most other mammals still have 3

members [16,18]. In most species both endolysosomal channel families coexist [2,17,5,19].

In this review, we will discuss recent findings on TPC2 and its endogenous activators NAADP (nicotinic acid adenine dinucleotide phosphate) and $PI(3,5)P_2$ (phosphatidylinositol 3,5-bisphosphate). NAADP is a Ca^{2+} mobilizing second messenger, which was originally postulated, after local Ca^{2+} release, to initiate Ca^{2+}-induced Ca^{2+} release through inositol 1,4,5-trisphosphate receptors (IP_3Rs) and ryanodine receptors (RyRs) in the endoplasmic reticulum (ER), giving rise to more global Ca^{2+} signals [20]. Ten years later, NAADP was demonstrated to mediate Ca^{2+} release from lysosomes via TPCs [10], a finding that was challenged shortly after by two other groups, claiming that not NAADP but $PI(3,5)P_2$, an endogenous phosphoinositide found predominantly on endolysosomal membranes, activates TPCs to release Na^+ not Ca^{2+} [21,22]. A further decade on, as a result of high-throughput screenings novel lipophilic small molecule agonists of TPC2 (TPC2-A1-N and TPC2-A1-P), mimicking NAADP and $PI(3,5)P_2$, respectively, were discovered, revealing that TPCs may not only be changing their ion selectivity in a ligand-dependent manner (more Na^+ with $PI(3,5)P_2$ and more Ca^{2+} with NAADP) [23] but also that co-application of both ligands further increases Ca^{2+} but not Na^+ flux [24].

2. TPC diversity – multiple stimuli converging

Ion channel activities heavily depend on the microenvironment provided by their host membranes (lipid bilayer composition, membrane potential and interacting membrane proteins) and the surrounding liquid phase (extracellular, cytosolic, or luminal ion content and soluble interacting proteins). The interactions between the channels and their environment are key for a comprehensive understanding of their function and regulation [25]. TPC activation has been the subject of extensive study, which revealed regulation by e.g., Ca^{2+}, voltage, pH, phosphatidylinositol phosphates (PIPs) and nicotinic acid adenine dinucleotide phosphate (NAADP) (Fig. 2) [26,15,14,27,28,21,29–31,8,32–36].

In animals, TPC-mediated cation fluxes are elicited by both $PI(3,5)P_2$ and NAADP, while in plants TPCs are insensitive to $PI(3,5)P_2$ and NAADP [37]. Other important differences exist between different species. Thus, differences in pH sensitivity of TPC2 activity in response to $PI(3,5)P_2$ were demonstrated between rabbit and human variants. While human TPC2 is largely independent in its activity from luminal pH, rabbit TPC2 activity decreases rapidly from pH 6.0 to pH 7.2 (luminal pH), but remains largely unchanged between pH 4.6 and pH 6.0 (luminal pH) [21,38]. In contrast, rabbit TPC3 activity increases with increasing luminal pH, similar to rabbit TPC1. This might be attributed to differences in subcellular localization, with TPC2 being predominantly found in highly acidic lysosomes, while TPC1 and TPC3 are also found in less acidic endosomes [38,39]. In line with this, TPC1 was found to be activated , in addition to $PI(3,5)P_2$, by the $PI(3,5)P_2$ precursor PI3P (phosphatidylinositol 3-phosphate) which is predominantly found on endocytic membranes, , while TPC2 is activated only by

$PI(3,5)P_2$ [38]. Another example highlighting differences in phosphoinositide sensitivity is *Xenopus tropicalis* TPC3, which is activated by $PI(3,4)P_2$ and $PI(3,5)P_2$ [40], while zebrafish TPC3 is insensitive to these PIPs [29,41]. Regarding NAADP action, chicken and rat TPC3 may conduct Ca^{2+} ions in response to NAADP [42], whereas conflicting reports about the NAADP sensitivity of invertebrate TPC3 exist [43,44].

NAADP sensitivity and activation of TPCs, as mentioned above have long been a matter of debate with speculations over possible indirect activation mechanisms via accessory proteins [45]. Indeed, NAADP activation of TPCs and also RyRs gained some momentum recently with the discovery of several NAADP binding proteins, likely explaining why NAADP effects on TPCs were seen less consistently, especially in endolysosomal patch-clamp experiments (i.e., endolysosomes isolated and separated from the cytosol) than direct activation by $PI(3,5)P_2$ [46]. Two independent groups have described Jupiter microtubule-associated homolog 2 protein (JPT2, also called HNL1) as NAADP binding protein [47,48], activating RyRs and TPC1 but not TPC2 (Fig.2; for review see also: Krogsaeter et al., 2021) [49]. Two other proteins have been suggested to bind NAADP: the Sm-like protein Lsm12 [50,46,51] and aspartate dehydrogenase domain-containing protein (ASPDH) [52]. In the latter work, interaction of NAADP with the two previous putative NAADP receptors, JPT2 and Lsm12 could reportedly not be confirmed, while Zhang et al. (2021) showed evidence of TPC2 being activated by NAADP after Lsm12 binding. It remains enigmatic at this point, why so many different NAADP-binding proteins would be

necessary and whether they indeed are all mediators of NAADP effects on TPCs or whether, perhaps different NAADP binding proteins are necessary to target different channels (RyRs vs. TPCs; Fig.2).

3. NAADP and PI(3,5)P_2 – independent or interdependent?

TPCs are highly unusual in changing their selectivity upon ligand binding. This has recently been demonstrated in the context of the discovery of the first lipophilic TPC2 agonists [23]. It was found that the identified agonists resulted in predominant Na^+ permeability (TPC2-A1-P) or a Na^+ and Ca^{2+}-permeable state (TPC2-A1-N). The two compounds were named TPC2-A1-P and TPC2-A1-N to reflect their functional similarity to PI(3,5)P_2 and NAADP as the former ones essentially mimic the effects of the latter ones despite being structurally different. For TPC2-A1-P it was demonstrated that the K204A mutation in TPC2 (the mutation is located within the PI(3,5)P_2 binding pocket) results in reduced activity, leaving TPC2-A1-N activity unaffected [23]. A binding site for TPC2-A1-N has not been discovered so far (Fig.1A,B). While stimulation with TPC2-A1-N evokes a readily recordable $TPC2^{GCaMP}$-mediated Ca^{2+} response in intact cells, TPC2-A1-P induces only a minor one, in line with endolysosomal patch-clamp evidence demonstrating larger Na^+ currents with TPC2-A1-P and higher Ca^{2+} permeability with TPC2-A1-N [23,24]. Surprisingly, co-application of the two agonists evoked a markedly potentiated Ca^{2+} response compared to TPC2-A1-N or TPC2-A1-P alone [24]. Indeed, this was confirmed by both endo-lysosomal and whole-cell patch-clamp recordings under bi-ionic conditions using Ca^{2+} in the pipette

solution and Na^+ in the bath solution. TPC2-A1-N and TPC2-A1-P when co-applied or sequentially applied induced larger inward (into the cytosol from the lysosome) Ca^{2+} currents compared to the compounds applied alone. In marked contrast, the outward Na^+ currents were unchanged. Similar results were obtained when NAADP and $PI(3,5)P_2$ were co-applied [24]. TPC2 therefore selectively alters its Ca^{2+} permeability upon co-stimulation.

In response to the application of NAADP/TPC2-A1-N, TPC2 responds with a current characterized by a less negative reversal potential (~-10 mV) and a higher P_{Ca}/P_{Na} value (0.6) compared to the current elicited by $PI(3,5)P_2$/TPC2-A1-P (reversal potential of about -60 to -70 mV and P_{Ca}/P_{Na} of 0.04). The combination of the agonists, on the other hand, shows an intermediate value for the reversal potential of -30 to -40 mV, which corresponds to a P_{Ca}/P_{Na} value of 0.2-0.3. Furthermore, by changing the application order of the synthetic and endogenous agonists, a “dominant effect” of TPC2-A1-N on TPC2 ion selectivity was demonstrated, as the subsequent application of TPC2-A1-P resulted in an increase of the Ca^{2+} current but did not affect the reversal potential. Thus, TPC2 activation by the combination of TPC2-A1-N and TPC2-A1-P seems to affect Ca^{2+} permeability independently from ion selectivity [24]. This could be due to a selective increase in Ca^{2+} conductance of the channel by the agonist combination.

Wang and Zhu (2022) corroborated these data recently and concluded that TPCs exhibit different modes of activation when stimulated by NAADP or $PI(3,5)P_2$, respectively. Further, they showed that co-application of NAADP and $PI(3,5)P_2$

synergistically activates TPC2 and proposed that $PI(3,5)P_2$ may be required for NAADP signaling [53]. These data are reminiscent of early studies showing that manipulation of $PI(3,5)P_2$ synthesis regulates NAADP-evoked Ca^{2+} signals in intact cells [31]. By contrast, experiments with vacuolin, which has an inhibitory effect on PIKfyve revealed that NAADP-AM activity is largely unaffected by $PI(3,5)P_2$ depletion, albeit incubation time with vacuolin was fairly short in that case [54].

4. Cytosolic Ca^{2+}: a question of life and death?

Proper control of cytosolic Ca^{2+} levels e.g., in neurons is crucial for their development and function [55]. If not carefully controlled, spatially and temporally within cells, Ca^{2+} can cause severe cell dysfunctions and even cell death [56,57]. Ca^{2+} is also a prominent regulator of processes as diverse as gene transcription, cell motility, autophagy, proliferation, neuronal development, or cell growth [58]. By contrast, Ca^{2+} release from the ER and subsequent Ca^{2+} entry via plasma membrane (PM) Ca^{2+} channels and uptake by mitochondria can trigger apoptotic signals. So far, there is convincing evidence that endolysosomal cation channels, i.e., TRPMLs and TPCs play crucial roles in autophagy [59–67] In neurodegenerative diseases (ND) such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease or ALS (amyotrophic lateral sclerosis), intracellular protein inclusions or extracellular protein aggregates are common features and impairment in autophagy steps can cause or exacerbate the

accumulation of protein aggregates and ultimately lead to cell death. Promoting TRPML/TPC dependent autophagy and lysosomal exocytosis has consequently been postulated to ameliorate ND and neurodegenerative lysosomal storage disease (LSD) phenotypes [68–72,66], albeit for ND some works claim the opposite (discussed extensively in [67,73]). Regarding TPC2, beneficial effects on LSD phenotypes have been shown so far indeed only for TPC2-A1-P ($PI(3,5)P_2$ mode of activation). NAADP-like TPC2 activation may have a different outcome, which could be explained by the synergistic effect discussed above between NAADP and $PI(3,5)P_2$ leading to more Ca^{2+} release with the eventual possibility of triggering a global Ca^{2+} signal. That sustained high cytosolic Ca^{2+} can negatively impact LSDs has been indeed shown before, e.g., for Gaucher disease neurons [74] or in a mouse model of Sandhoff disease [75], emphasizing once again the necessary fine balance between too much and too little Ca^{2+} , i.e. taking into account the spatial and temporal factor.

5. Final remarks and conclusions

The results by Gerndt et al. (2020) and Yuan et al. (2022) suggest that activation of TPC2 with TPC2-A1-P or $PI(3,5)P_2$ result only in very small, essentially local Ca^{2+} signals, which may be sufficient for e.g., triggering lysosomal exocytosis or endolysosomal fusion events or stimulating autophagy. By contrast, the production of NAADP as a consequence of upstream signalling would likely act on top of $PI(3,5)P_2$ as a complete lack of $PI(3,5)P_2$ in the endolysosomal membrane would be an unlikely scenario (the phenotype of a complete depletion

of $PI(3,5)P_2$ is lethal in the mouse model) [76]. Thus, NAADP addition would likely either enhance $PI(3,5)P_2$ mediated effects or result in globalized Ca^{2+} signalling, perhaps by enhancing interaction between lysosomes and ER [77]. As a consequence of the synergism, the Ca^{2+} released from TPC2 might lead to Ca^{2+} induced Ca^{2+} release by IP_3Rs and RyRs, expressed on the ER membrane [77–80] as claimed previously [20]. The release of Ca^{2+} from the ER in turn triggers Ca^{2+} influx from the extracellular space via PM Ca^{2+} channels [81–83].

In addition, lysosomal Ca^{2+} release has also been shown to promote Ca^{2+} transfer to mitochondria via the lysosomal Ca^{2+} channel TRPML1, which is defective in the lysosomal storage disorder mucolipidosis type IV (MLIV; caused by TRPML1 mutations), adding to the MLIV pathophysiology. Whether such a crosstalk also exists between TPC-mediated Ca^{2+} release and mitochondria remain to be investigated [84].

In sum, we suggest that by lysosomal motility upon $PI(3,5)P_2$/NAADP co-application [23,24], ER-lysosome contacts may be facilitated and prolonged. Local Ca^{2+} signals from the lysosome may then propagate into a global Ca^{2+} response by stimulating Ca^{2+} release from the ER and subsequent Ca^{2+} influx across the PM. Local or global Ca^{2+} signals mediated through TPCs would therefore depend on the relative levels of $PI(3,5)P_2$ and NAADP, the presence of regulatory and auxiliary proteins such as NAADP-binding proteins and additional interacting proteins controlling TPC2 activity, e.g. mammalian target of rapamycin (mTOR) or Rab7, and the number and duration of contacts between ER and lysosomes [22,85]. TPC2 thus emerges as a channel tightly regulated by multiple

parameters, in a time- and space-dependent manner (Fig.2), which depending on the mode of activation might differentially affect physiological and pathophysiological states.

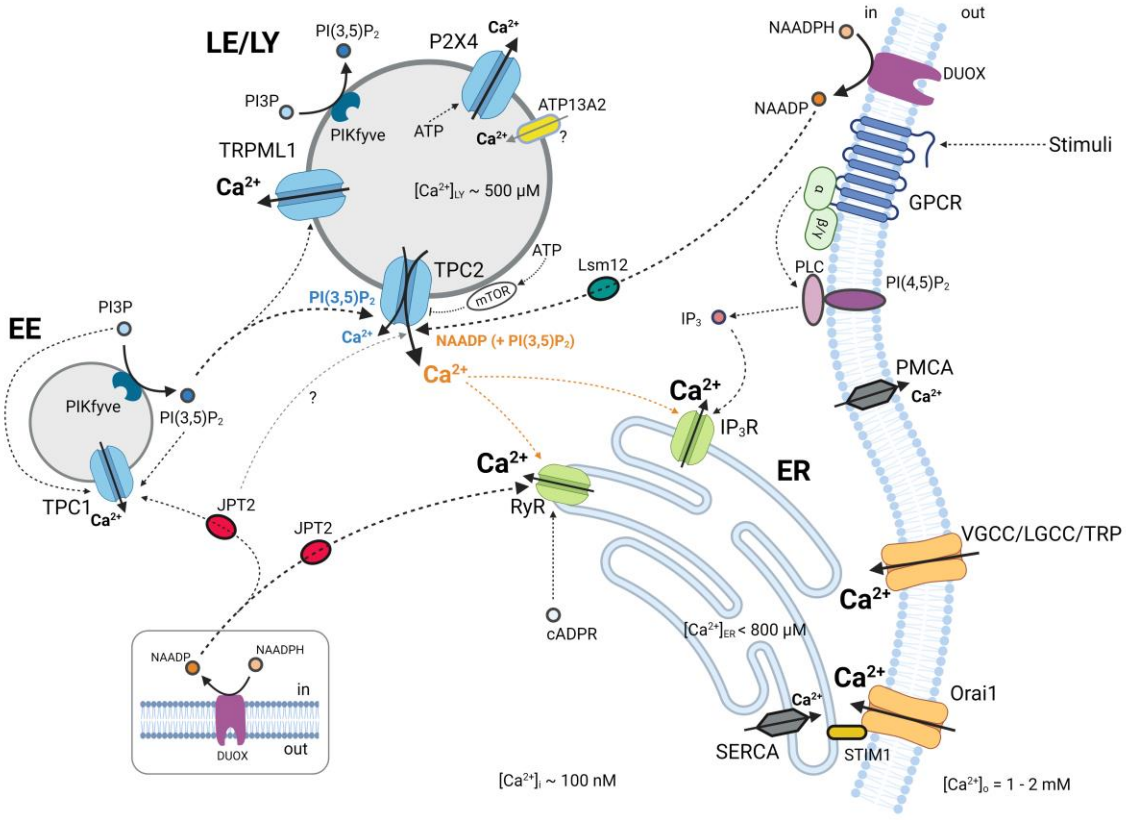

Fig.2 **Intracellular Ca^{2+} signaling – an update.** (A) Ca^{2+} signals are generated either from Ca^{2+} entering across the plasma membrane (through voltage- or ligand-gated Ca^{2+} channels (VGCC or LGCC), store-operated Orai channels and TRP channels) or Ca^{2+} release from intracellular Ca^{2+} stores (ER, lysosomes (LY), early and late endosomes (EE and LE)). The intracellular Ca^{2+} release is mediated by resident Ca^{2+} channels, such as IP_3Rs, RyRs TPCs and P2X4, that open in response to the Ca^{2+} messengers (IP_3, cyclic ADP ribose (cADPR) and NAADP) and ATP. High levels of ATP enable mTOR to inhibit TPC2. NAADP may be produced via DUOX (challenging the hitherto prevailing, albeit debated view that it may be produced by CD38 [86–94]; a further postulated alternative would be SARM1) and binds to accessory proteins: Lsm12 to act on TPC2; and JPT2 to act on TPC1 as well as RyRs. $PI(3,5)P_2$ is produced by PIKfyve and activates TPCs and TRPMLs. The co-application of NAADP and $PI(3,5)P_2$ leads to a strong Ca^{2+} release by TPC2, which might induce Ca^{2+} induced Ca^{2+} release by IP_3R and RyRs, further stimulating Ca^{2+} influx across the PM by Orai. Sarcoendoplasmic reticulum Ca^{2+} ATPase (SERCA) and stromal interaction molecule (STIM) contribute to the Ca^{2+} homeostasis in the ER. Plasma

membrane Ca^{2+} ATPase (PMCA) modulates Ca^{2+} levels in the cytosol. ATP13A2 was claimed to transport Ca^{2+} to lysosomes. Note: organelles are not to scale [95–98,47,48,50,99,24,100]. Layout created with BioRender.com.

Acknowledgements

This work was supported, in part, by funding of the German Research Foundation DFG (SFB/TRR152 project P04, GR-4315/4-1, GR-4315/2-1, SFB1328 project A21 to C.G.), the Biotechnology and Biological Sciences Research Council (BB/T015853/1 and BB/W01551X/1) and by the NCL Stiftung, Hamburg, Germany.

References

[1] J. Payandeh, T. Scheuer, N. Zheng, W.A. Catterall, The crystal structure of a voltage-gated sodium channel, Nature. 475 (2011) 353–358. https://doi.org/10.1038/nature10238.

[2] T. Rahman, X. Cai, G.C. Brailoiu, M.E. Abood, E. Brailoiu, S. Patel, Two-pore channels provide insight into the evolution of voltage-gated Ca2+ and Na+ channels, Sci. Signal. 7 (2014) ra109. https://doi.org/10.1126/scisignal.2005450.

[3] S. Patel, X. Cai, Evolution of acidic Ca^{2+} stores and their resident Ca^{2+}-permeable channels, Cell Calcium. 57 (2015) 222–230. https://doi.org/10.1016/j.ceca.2014.12.005.

[4] R. Hedrich, T.D. Mueller, D. Becker, I. Marten, Structure and Function of TPC1 Vacuole SV Channel Gains Shape, Mol. Plant. 11 (2018) 764–775. https://doi.org/10.1016/j.molp.2018.03.017.

[5] D. Jaślan, J. Böck, E. Krogsaeter, C. Grimm, Evolutionary Aspects of TRPMLs and TPCs, Int. J. Mol. Sci. 21 (2020). https://doi.org/10.3390/ijms21114181.

[6] J. Guo, W. Zeng, Q. Chen, C. Lee, L. Chen, Y. Yang, C. Cang, D. Ren, Y. Jiang, Structure of the voltage-gated two-pore channel TPC1 from Arabidopsis thaliana, Nature. 531 (2016) 196–201. https://doi.org/10.1038/nature16446.

[7] A.F. Kintzer, R.M. Stroud, Structure, inhibition and regulation of two-pore channel TPC1 from Arabidopsis thaliana, Nature. 531 (2016) 258–262. https://doi.org/10.1038/nature17194.

[8] D. Jaślan, T.D. Mueller, D. Becker, J. Schultz, T.A. Cuin, I. Marten, I. Dreyer, G. Schönknecht, R. Hedrich, Gating of the two-pore cation channel AtTPC1 in the plant vacuole is based on a single voltage-sensing domain, Plant Biol. 18 (2016) 750–760. https://doi.org/10.1111/plb.12478.
[9] J. She, J. Guo, Q. Chen, W. Zeng, Y. Jiang, X. Bai, Structural insights into the voltage and phospholipid activation of the mammalian TPC1 channel, Nature. 556 (2018) 130–134. https://doi.org/10.1038/nature26139.
[10] J. She, W. Zeng, J. Guo, Q. Chen, X. Bai, Y. Jiang, Structural mechanisms of phospholipid activation of the human TPC2 channel, ELife. 8 (2019) e45222. https://doi.org/10.7554/eLife.45222.
[11] X. Zhang, W. Chen, P. Li, R. Calvo, N. Southall, X. Hu, M. Bryant-Genevier, X. Feng, Q. Geng, C. Gao, M. Yang, K. Tang, M. Ferrer, J.J. Marugan, H. Xu, Agonist-specific voltage-dependent gating of lysosomal two-pore Na+ channels, ELife. 8 (2019). https://doi.org/10.7554/eLife.51423.
[12] T. Shimomura, K. Hirazawa, Y. Kubo, Conformational rearrangements in 2nd voltage sensor domain switch PIP2- and voltage-gating modes in two-pore channels, (2022) 2022.06.14.494918. https://doi.org/10.1101/2022.06.14.494918.
[13] E. Peiter, F.J.M. Maathuis, L.N. Mills, H. Knight, J. Pelloux, A.M. Hetherington, D. Sanders, The vacuolar Ca2+-activated channel TPC1 regulates germination and stomatal movement, Nature. 434 (2005) 404–408. https://doi.org/10.1038/nature03381.
[14] P.J. Calcraft, M. Ruas, Z. Pan, X. Cheng, A. Arredouani, X. Hao, J. Tang, K. Rietdorf, L. Teboul, K.-T. Chuang, P. Lin, R. Xiao, C. Wang, Y. Zhu, Y. Lin, C.N. Wyatt, J. Parrington, J. Ma, A.M. Evans, A. Galione, M.X. Zhu, NAADP mobilizes calcium from acidic organelles through two-pore channels, Nature. 459 (2009) 596–600. https://doi.org/10.1038/nature08030.
[15] E. Brailoiu, D. Churamani, X. Cai, M.G. Schrlau, G.C. Brailoiu, X. Gao, R. Hooper, M.J. Boulware, N.J. Dun, J.S. Marchant, S. Patel, Essential requirement for two-pore channel 1 in NAADP-mediated calcium signaling, J. Cell Biol. 186 (2009) 201–209. https://doi.org/10.1083/jcb.200904073.
[16] X. Cai, S. Patel, Degeneration of an intracellular ion channel in the primate lineage by relaxation of selective constraints, Mol. Biol. Evol. 27 (2010) 2352–2359. https://doi.org/10.1093/molbev/msq122.
[17] G. Peng, X. Shi, T. Kadowaki, Evolution of TRP channels inferred by their classification in diverse animal species, Mol. Phylogenet. Evol. 84 (2015) 145–157. https://doi.org/10.1016/j.ympev.2014.06.016.
[18] H. Xu, D. Ren, Lysosomal physiology, Annu. Rev. Physiol. 77 (2015) 57–80. https://doi.org/10.1146/annurev-physiol-021014-071649.
[19] N.J. Himmel, D.N. Cox, Transient receptor potential channels: current perspectives on evolution, structure, function and nomenclature, Proc. R. Soc. B Biol. Sci. 287 (2020) 20201309. https://doi.org/10.1098/rspb.2020.1309.
[20] J.M. Cancela, G.C. Churchill, A. Galione, Coordination of agonist-induced Ca2+-signalling patterns by NAADP in pancreatic acinar cells, Nature. 398 (1999) 74–76. https://doi.org/10.1038/18032.

[21] X. Wang, X. Zhang, X.-P. Dong, M. Samie, X. Li, X. Cheng, A. Goschka, D. Shen, Y. Zhou, J. Harlow, M.X. Zhu, D.E. Clapham, D. Ren, H. Xu, TPC proteins are phosphoinositide- activated sodium-selective ion channels in endosomes and lysosomes, Cell. 151 (2012) 372–383. https://doi.org/10.1016/j.cell.2012.08.036.
[22] C. Cang, Y. Zhou, B. Navarro, Y.-J. Seo, K. Aranda, L. Shi, S. Battaglia-Hsu, I. Nissim, D.E. Clapham, D. Ren, mTOR regulates lysosomal ATP-sensitive two-pore Na(+) channels to adapt to metabolic state, Cell. 152 (2013) 778–790. https://doi.org/10.1016/j.cell.2013.01.023.
[23] S. Gerndt, C.-C. Chen, Y.-K. Chao, Y. Yuan, S. Burgstaller, A. Scotto Rosato, E. Krogsaeter, N. Urban, K. Jacob, O.N.P. Nguyen, M.T. Miller, M. Keller, A.M. Vollmar, T. Gudermann, S. Zierler, J. Schredelseker, M. Schaefer, M. Biel, R. Malli, C. Wahl-Schott, F. Bracher, S. Patel, C. Grimm, Agonist-mediated switching of ion selectivity in TPC2 differentially promotes lysosomal function, ELife. 9 (2020). https://doi.org/10.7554/eLife.54712.
[24] Y. Yuan, D. Jaślan, T. Rahman, S.R. Bolsover, V. Arige, L.E. Wagner, C. Abrahamian, R. Tang, M. Keller, J. Hartmann, A.S. Rosato, E.-M. Weiden, F. Bracher, D.I. Yule, C. Grimm, S. Patel, Segregated cation flux by TPC2 biases Ca2+ signaling through lysosomes, Nat. Commun. 13 (2022) 4481. https://doi.org/10.1038/s41467-022-31959-0.
[25] I. Levental, E. Lyman, Regulation of membrane protein structure and function by their lipid nano-environment, Nat. Rev. Mol. Cell Biol. (2022) 1–16. https://doi.org/10.1038/s41580-022-00524-4.
[26] D. Beyhl, S. Hörtensteiner, E. Martinoia, E.E. Farmer, J. Fromm, I. Marten, R. Hedrich, The fou2 mutation in the major vacuolar cation channel TPC1 confers tolerance to inhibitory luminal calcium, Plant J. Cell Mol. Biol. 58 (2009) 715–723. https://doi.org/10.1111/j.1365-313X.2009.03820.x.
[27] X. Zong, M. Schieder, H. Cuny, S. Fenske, C. Gruner, K. Rötzer, O. Griesbeck, H. Harz, M. Biel, C. Wahl-Schott, The two-pore channel TPCN2 mediates NAADP-dependent Ca2+-release from lysosomal stores, Pflugers Arch. 458 (2009) 891–899. https://doi.org/10.1007/s00424-009-0690-y.
[28] B. Dadacz-Narloch, D. Beyhl, C. Larisch, E.J. López-Sanjurjo, R. Reski, K. Kuchitsu, T.D. Müller, D. Becker, G. Schönknecht, R. Hedrich, A novel calcium binding site in the slow vacuolar cation channel TPC1 senses luminal calcium levels, Plant Cell. 23 (2011) 2696–2707. https://doi.org/10.1105/tpc.111.086751.
[29] C. Cang, K. Aranda, D. Ren, A non-inactivating high-voltage-activated two-pore Na^+ channel that supports ultra-long action potentials and membrane bistability, Nat. Commun. 5 (2014) 5015. https://doi.org/10.1038/ncomms6015.
[30] C. Cang, B. Bekele, D. Ren, The voltage-gated sodium channel TPC1 confers endolysosomal excitability, Nat. Chem. Biol. 10 (2014) 463–469. https://doi.org/10.1038/nchembio.1522.
[31] A. Jha, M. Ahuja, S. Patel, E. Brailoiu, S. Muallem, Convergent regulation of the lysosomal two-pore channel-2 by Mg2+, NAADP, PI(3,5)P2 and multiple

protein kinases, EMBO J. 33 (2014) 501–511. https://doi.org/10.1002/embj.201387035.
[32] L. Lagostena, M. Festa, M. Pusch, A. Carpaneto, The human two-pore channel 1 is modulated by cytosolic and luminal calcium, Sci. Rep. 7 (2017) 1–11. https://doi.org/10.1038/srep43900.
[33] S.A. Kirsch, A. Kugemann, A. Carpaneto, R.A. Böckmann, P. Dietrich, Phosphatidylinositol-3,5-bisphosphate lipid-binding-induced activation of the human two-pore channel 2, Cell. Mol. Life Sci. CMLS. 75 (2018) 3803–3815. https://doi.org/10.1007/s00018-018-2829-5.
[34] K. Hirazawa, M. Tateyama, Y. Kubo, T. Shimomura, Phosphoinositide regulates dynamic movement of the S4 voltage sensor in the 2nd repeat in Two-pore channel 3, J. Biol. Chem. 0 (2021). https://doi.org/10.1016/j.jbc.2021.101425.
[35] S. Patel, Y. Yuan, C.-C. Chen, D. Jaślan, G. Gunaratne, C. Grimm, T. Rahman, J.S. Marchant, Electrophysiology of Endolysosomal Two-Pore Channels: A Current Account, Cells. 11 (2022) 2368. https://doi.org/10.3390/cells11152368.
[36] M. Festa, V. Minicozzi, A. Boccaccio, L. Lagostena, A. Gradogna, T. Qi, A. Costa, N. Larisch, S. Hamamoto, E. Pedrazzini, S. Milenkovic, J. Scholz-Starke, M. Ceccarelli, A. Vitale, P. Dietrich, N. Uozumi, F. Gambale, A. Carpaneto, Current Methods to Unravel the Functional Properties of Lysosomal Ion Channels and Transporters, Cells. 11 (2022) 921. https://doi.org/10.3390/cells11060921.
[37] A. Boccaccio, J. Scholz-Starke, S. Hamamoto, N. Larisch, M. Festa, P.V.K. Gutla, A. Costa, P. Dietrich, N. Uozumi, A. Carpaneto, The phosphoinositide $PI(3,5)P_2$ mediates activation of mammalian but not plant TPC proteins: functional expression of endolysosomal channels in yeast and plant cells, Cell. Mol. Life Sci. CMLS. 71 (2014) 4275–4283. https://doi.org/10.1007/s00018-014-1623-2.
[38] X. Feng, J. Xiong, W. Cai, J.-B. Tian, M.X. Zhu, The Three Two-Pore Channel Subtypes from Rabbit Exhibit Distinct Sensitivity to Phosphoinositides, Voltage, and Extracytosolic pH, Cells. 11 (2022) 2006. https://doi.org/10.3390/cells11132006.
[39] J.S. Marchant, S. Patel, Two-pore channels at the intersection of endolysosomal membrane traffic, Biochem. Soc. Trans. 43 (2015) 434–441. https://doi.org/10.1042/BST20140303.
[40] T. Shimomura, Y. Kubo, Phosphoinositides modulate the voltage dependence of two-pore channel 3, J. Gen. Physiol. 151 (2019) 986–1006. https://doi.org/10.1085/jgp.201812285.
[41] M.S. Dickinson, A. Myasnikov, J. Eriksen, N. Poweleit, R.M. Stroud, Resting state structure of the hyperdepolarization activated two-pore channel 3, Proc. Natl. Acad. Sci. U. S. A. 117 (2020) 1988–1993. https://doi.org/10.1073/pnas.1915144117.
[42] O.A. Ogunbayo, Y. Zhu, B. Shen, E. Agbani, J. Li, J. Ma, M.X. Zhu, A.M. Evans, Organelle-specific Subunit Interactions of the Vertebrate Two-pore

Channel Family, J. Biol. Chem. 290 (2015) 1086–1095. https://doi.org/10.1074/jbc.M114.610493.
[43] E. Brailoiu, R. Hooper, X. Cai, G.C. Brailoiu, M.V. Keebler, N.J. Dun, J.S. Marchant, S. Patel, An Ancestral Deuterostome Family of Two-pore Channels Mediates Nicotinic Acid Adenine Dinucleotide Phosphate-dependent Calcium Release from Acidic Organelles, J. Biol. Chem. 285 (2010) 2897–2901. https://doi.org/10.1074/jbc.C109.081943.
[44] M. Ruas, K. Rietdorf, A. Arredouani, L.C. Davis, E. Lloyd-Evans, H. Koegel, T.M. Funnell, A.J. Morgan, J.A. Ward, K. Watanabe, X. Cheng, G.C. Churchill, M.X. Zhu, F.M. Platt, G.M. Wessel, J. Parrington, A. Galione, Purified TPC isoforms form NAADP receptors with distinct roles for Ca(2+) signaling and endolysosomal trafficking, Curr. Biol. CB. 20 (2010) 703–709. https://doi.org/10.1016/j.cub.2010.02.049.
[45] J.S. Marchant, Y. Lin-Moshier, T.F. Walseth, S. Patel, The Molecular Basis for Ca2+ Signalling by NAADP: Two-Pore Channels in a Complex?, Messenger Los Angel. Calif Print. 1 (2012) 63–76. https://doi.org/10.1166/msr.2012.1003.
[46] J.S. Marchant, G.S. Gunaratne, X. Cai, J.T. Slama, S. Patel, NAADP-binding proteins find their identity, Trends Biochem. Sci. 47 (2022) 235–249. https://doi.org/10.1016/j.tibs.2021.10.008.
[47] G.S. Gunaratne, E. Brailoiu, S. He, E.M. Unterwald, S. Patel, J.T. Slama, T.F. Walseth, J.S. Marchant, Essential requirement for JPT2 in NAADP-evoked Ca2+ signaling, Sci. Signal. 14 (2021). https://doi.org/10.1126/scisignal.abd5605.
[48] H.G. Roggenkamp, I. Khansahib, L.C.H. C, Y. Zhang, D. Lodygin, A. Krüger, F. Gu, F. Möckl, A. Löhndorf, V. Wolters, D. Woike, A. Rosche, A. Bauche, D. Schetelig, R. Werner, H. Schlüter, A.V. Failla, C. Meier, R. Fliegert, T.F. Walseth, A. Flügel, B.-P. Diercks, A.H. Guse, HN1L/JPT2: A signaling protein that connects NAADP generation to Ca2+ microdomain formation, Sci. Signal. 14 (2021). https://doi.org/10.1126/scisignal.abd5647.
[49] E. Krogsaeter, R. Tang, C. Grimm, JPT2: The missing link between intracellular Ca2+ release channels and NAADP?, Cell Calcium. 97 (2021) 102405. https://doi.org/10.1016/j.ceca.2021.102405.
[50] J. Zhang, X. Guan, K. Shah, J. Yan, Lsm12 is an NAADP receptor and a two-pore channel regulatory protein required for calcium mobilization from acidic organelles, Nat. Commun. 12 (2021) 4739. https://doi.org/10.1038/s41467-021-24735-z.
[51] K.R. Shah, X. Guan, J. Yan, Diversity of two-pore channels and the accessory NAADP receptors in intracellular Ca2+ signaling, Cell Calcium. (2022) 102594. https://doi.org/10.1016/j.ceca.2022.102594.
[52] X. He, Y. Kang, L. Chen, Identification of ASPDH as a novel NAADP-binding protein, Biochem. Biophys. Res. Commun. 621 (2022) 168–175. https://doi.org/10.1016/j.bbrc.2022.06.100.
[53] Q. Wang, M.X. Zhu, NAADP-Dependent TPC Current, Handb. Exp. Pharmacol. (2022). https://doi.org/10.1007/164_2022_606.

[54] M. Ruas, L.C. Davis, C.-C. Chen, A.J. Morgan, K.-T. Chuang, T.F. Walseth, C. Grimm, C. Garnham, T. Powell, N. Platt, F.M. Platt, M. Biel, C. Wahl-Schott, J. Parrington, A. Galione, Expression of Ca2+-permeable two-pore channels rescues NAADP signalling in TPC-deficient cells, EMBO J. 34 (2015) 1743–1758. https://doi.org/10.15252/embj.201490009.
[55] M.J. Berridge, M.D. Bootman, H.L. Roderick, Calcium signalling: dynamics, homeostasis and remodelling, Nat. Rev. Mol. Cell Biol. 4 (2003) 517–529. https://doi.org/10.1038/nrm1155.
[56] E. Lloyd-Evans, F.M. Platt, Lysosomal Ca(2+) homeostasis: role in pathogenesis of lysosomal storage diseases, Cell Calcium. 50 (2011) 200–205. https://doi.org/10.1016/j.ceca.2011.03.010.
[57] E. Carafoli, J. Krebs, Why Calcium? How Calcium Became the Best Communicator, J. Biol. Chem. 291 (2016) 20849–20857. https://doi.org/10.1074/jbc.R116.735894.
[58] P. Sukumaran, V. Nascimento Da Conceicao, Y. Sun, N. Ahamad, L.R. Saraiva, S. Selvaraj, B.B. Singh, Calcium Signaling Regulates Autophagy and Apoptosis, Cells. 10 (2021) 2125. https://doi.org/10.3390/cells10082125.
[59] D.L. Medina, A. Ballabio, Lysosomal calcium regulates autophagy, Autophagy. 11 (2015) 970–971. https://doi.org/10.1080/15548627.2015.1047130.
[60] V. García-Rúa, S. Feijóo-Bandín, D. Rodríguez-Penas, A. Mosquera-Leal, E. Abu-Assi, A. Beiras, L. María Seoane, P. Lear, J. Parrington, M. Portolés, E. Roselló-Lletí, M. Rivera, O. Gualillo, V. Parra, J.A. Hill, B. Rothermel, J.R. González-Juanatey, F. Lago, Endolysosomal two-pore channels regulate autophagy in cardiomyocytes, J. Physiol. 594 (2016) 3061–3077. https://doi.org/10.1113/JP271332.
[61] W. Sun, J. Yue, TPC2 mediates autophagy progression and extracellular vesicle secretion in cancer cells, Exp. Cell Res. 370 (2018) 478–489. https://doi.org/10.1016/j.yexcr.2018.07.013.
[62] A. Scotto Rosato, S. Montefusco, C. Soldati, S. Di Paola, A. Capuozzo, J. Monfregola, E. Polishchuk, A. Amabile, C. Grimm, A. Lombardo, M.A. De Matteis, A. Ballabio, D.L. Medina, TRPML1 links lysosomal calcium to autophagosome biogenesis through the activation of the CaMKKβ/VPS34 pathway, Nat. Commun. 10 (2019) 5630. https://doi.org/10.1038/s41467-019-13572-w.
[63] D.L. Medina, Lysosomal calcium and autophagy, in: Int. Rev. Cell Mol. Biol., Academic Press, 2021. https://doi.org/10.1016/bs.ircmb.2021.03.002.
[64] J. Qi, Y. Xing, Y. Liu, M.-M. Wang, X. Wei, Z. Sui, L. Ding, Y. Zhang, C. Lu, Y.-H. Fei, N. Liu, R. Chen, M. Wu, L. Wang, Z. Zhong, T. Wang, Y. Liu, Y. Wang, J. Liu, H. Xu, F. Guo, W. Wang, MCOLN1/TRPML1 finely controls oncogenic autophagy in cancer by mediating zinc influx, Autophagy. 17 (2021) 4401–4422. https://doi.org/10.1080/15548627.2021.1917132.
[65] P. Rühl, A.S. Rosato, N. Urban, S. Gerndt, R. Tang, C. Abrahamian, C. Leser, J. Sheng, A. Jha, G. Vollmer, M. Schaefer, F. Bracher, C. Grimm, Estradiol analogs attenuate autophagy, cell migration and invasion by direct

and selective inhibition of TRPML1, independent of estrogen receptors, Sci. Rep. 11 (2021) 8313. https://doi.org/10.1038/s41598-021-87817-4.
[66] A. Scotto Rosato, E.K. Krogsaeter, D. Jaślan, C. Abrahamian, S. Montefusco, C. Soldati, B. Spix, M.T. Pizzo, G. Grieco, J. Böck, A. Wyatt, D. Wünkhaus, M. Passon, M. Stieglitz, M. Keller, G. Hermey, S. Markmann, D. Gruber-Schoffnegger, S. Cotman, L. Johannes, D. Crusius, U. Boehm, C. Wahl-Schott, M. Biel, F. Bracher, E. De Leonibus, E. Polishchuk, D.L. Medina, D. Paquet, C. Grimm, TPC2 rescues lysosomal storage in mucolipidosis type IV, Niemann–Pick type C1, and Batten disease, EMBO Mol. Med. 14 (2022) e15377. https://doi.org/10.15252/emmm.202115377.
[67] S. Prat Castro, V. Kudrina, D. Jaślan, J. Böck, A. Scotto Rosato, C. Grimm, Neurodegenerative Lysosomal Storage Disorders: TPC2 Comes to the Rescue!, Cells. 11 (2022) 2807. https://doi.org/10.3390/cells11182807.
[68] D. Shen, X. Wang, X. Li, X. Zhang, Z. Yao, S. Dibble, X. Dong, T. Yu, A.P. Lieberman, H.D. Showalter, H. Xu, Lipid storage disorders block lysosomal trafficking by inhibiting a TRP channel and lysosomal calcium release, Nat. Commun. 3 (2012) 731. https://doi.org/10.1038/ncomms1735.
[69] P. Rivero-Ríos, P. Gómez-Suaga, E. Fdez, S. Hilfiker, Upstream deregulation of calcium signaling in Parkinson's disease, Front. Mol. Neurosci. 7 (2014) 53. https://doi.org/10.3389/fnmol.2014.00053.
[70] P. Rivero-Ríos, B. Fernández, J. Madero-Pérez, M.R. Lozano, S. Hilfiker, Two-Pore Channels and Parkinson's Disease: Where's the Link?, Messenger Los Angel. Calif Print. 5 (2016) 67–75. https://doi.org/10.1166/msr.2016.1051.
[71] E. Seranova, K.J. Connolly, M. Zatyka, T.R. Rosenstock, T. Barrett, R.I. Tuxworth, S. Sarkar, Dysregulation of autophagy as a common mechanism in lysosomal storage diseases, Essays Biochem. 61 (2017) 733–749. https://doi.org/10.1042/EBC20170055.
[72] E. Lloyd-Evans, H. Waller-Evans, Lysosomal Ca2+ Homeostasis and Signaling in Health and Disease, Cold Spring Harb. Perspect. Biol. (2019) a035311. https://doi.org/10.1101/cshperspect.a035311.
[73] E. Krogsaeter, A.S. Rosato, C. Grimm, TRPMLs and TPCs: targets for lysosomal storage and neurodegenerative disease therapy?, Cell Calcium. (2022) 102553. https://doi.org/10.1016/j.ceca.2022.102553.
[74] E. Korkotian, A. Schwarz, D. Pelled, G. Schwarzmann, M. Segal, A.H. Futerman, Elevation of Intracellular Glucosylceramide Levels Results in an Increase in Endoplasmic Reticulum Density and in Functional Calcium Stores in Cultured Neurons *, J. Biol. Chem. 274 (1999) 21673–21678. https://doi.org/10.1074/jbc.274.31.21673.
[75] D. Pelled, E. Lloyd-Evans, C. Riebeling, M. Jeyakumar, F.M. Platt, A.H. Futerman, Inhibition of calcium uptake via the sarco/endoplasmic reticulum Ca2+-ATPase in a mouse model of Sandhoff disease and prevention by treatment with N-butyldeoxynojirimycin, J. Biol. Chem. 278 (2003) 29496–29501. https://doi.org/10.1074/jbc.M302964200.
[76] O.C. Ikonomov, D. Sbrissa, K. Delvecchio, Y. Xie, J.-P. Jin, D. Rappolee, A. Shisheva, The phosphoinositide kinase PIKfyve is vital in early embryonic

development: preimplantation lethality of PIKfyve-/- embryos but normality of PIKfyve+/- mice, J. Biol. Chem. 286 (2011) 13404–13413. https://doi.org/10.1074/jbc.M111.222364.
[77] B.S. Kilpatrick, E.R. Eden, L.N. Hockey, E. Yates, C.E. Futter, S. Patel, An Endosomal NAADP-Sensitive Two-Pore Ca2+ Channel Regulates ER-Endosome Membrane Contact Sites to Control Growth Factor Signaling, Cell Rep. 18 (2017) 1636–1645. https://doi.org/10.1016/j.celrep.2017.01.052.
[78] A. Galione, G.C. Churchill, Cyclic ADP ribose as a calcium-mobilizing messenger, Sci. STKE Signal Transduct. Knowl. Environ. 2000 (2000) pe1. https://doi.org/10.1126/stke.2000.41.pe1.
[79] M. Iwai, T. Michikawa, I. Bosanac, M. Ikura, K. Mikoshiba, Molecular basis of the isoform-specific ligand-binding affinity of inositol 1,4,5-trisphosphate receptors, J. Biol. Chem. 282 (2007) 12755–12764. https://doi.org/10.1074/jbc.M609833200.
[80] Q. Zheng, Y. Chen, D. Chen, H. Zhao, Y. Feng, Q. Meng, Y. Zhao, H. Zhang, Calcium transients on the ER surface trigger liquid-liquid phase separation of FIP200 to specify autophagosome initiation sites, Cell. 0 (2022). https://doi.org/10.1016/j.cell.2022.09.001.
[81] M. Prakriya, S. Feske, Y. Gwack, S. Srikanth, A. Rao, P.G. Hogan, Orai1 is an essential pore subunit of the CRAC channel, Nature. 443 (2006) 230–233. https://doi.org/10.1038/nature05122.
[82] J.T. Smyth, W.I. DeHaven, B.F. Jones, J.C. Mercer, M. Trebak, G. Vazquez, J.W. Putney, Emerging perspectives in store-operated Ca2+ entry: Roles of Orai, Stim and TRP, Biochim. Biophys. Acta BBA - Mol. Cell Res. 1763 (2006) 1147–1160. https://doi.org/10.1016/j.bbamcr.2006.08.050.
[83] A.V. Yeromin, S.L. Zhang, W. Jiang, Y. Yu, O. Safrina, M.D. Cahalan, Molecular identification of the CRAC channel by altered ion selectivity in a mutant of Orai, Nature. 443 (2006) 226–229. https://doi.org/10.1038/nature05108.
[84] W. Peng, Y. Wong, D. Krainc, Mitochondria-lysosome contacts regulate mitochondrial Ca 2+ dynamics via lysosomal TRPML1, Proc. Natl. Acad. Sci. 117 (2020) 202003236. https://doi.org/10.1073/pnas.2003236117.
[85] B. Fernández, E. Fdez, P. Gómez-Suaga, F. Gil, I. Molina-Villalba, I. Ferrer, S. Patel, G.C. Churchill, S. Hilfiker, Iron overload causes endolysosomal deficits modulated by NAADP-regulated 2-pore channels and RAB7A, Autophagy. 12 (2016) 1487–1506. https://doi.org/10.1080/15548627.2016.1190072.
[86] O.H. Petersen, Is CD38 involved in Ca2+ signalling elicited by activation of T cell receptors?, Cell Calcium. 101 (2022) 102524. https://doi.org/10.1016/j.ceca.2021.102524.
[87] C. Fang, T. Li, Y. Li, G.J. Xu, Q.W. Deng, Y.J. Chen, Y.N. Hou, H.C. Lee, Y.J. Zhao, CD38 produces nicotinic acid adenosine dinucleotide phosphate in the lysosome, J. Biol. Chem. 293 (2018) 8151–8160. https://doi.org/10.1074/jbc.RA118.002113.
[88] W.K. Lin, E.L. Bolton, W.A. Cortopassi, Y. Wang, F. O'Brien, M. Maciejewska, M.P. Jacobson, C. Garnham, M. Ruas, J. Parrington, M. Lei,

R. Sitsapesan, A. Galione, D.A. Terrar, Synthesis of the Ca2+-mobilizing messengers NAADP and cADPR by intracellular CD38 enzyme in the mouse heart: Role in β-adrenoceptor signaling, J. Biol. Chem. 292 (2017) 13243–13257. https://doi.org/10.1074/jbc.M117.789347.

[89] F. Schmid, S. Bruhn, K. Weber, H.-W. Mittrücker, A.H. Guse, CD38: a NAADP degrading enzyme, FEBS Lett. 585 (2011) 3544–3548. https://doi.org/10.1016/j.febslet.2011.10.017.

[90] F. Cosker, N. Cheviron, M. Yamasaki, A. Menteyne, F.E. Lund, M.-J. Moutin, A. Galione, J.-M. Cancela, The ecto-enzyme CD38 is a nicotinic acid adenine dinucleotide phosphate (NAADP) synthase that couples receptor activation to Ca2+ mobilization from lysosomes in pancreatic acinar cells, J. Biol. Chem. 285 (2010) 38251–38259. https://doi.org/10.1074/jbc.M110.125864.

[91] P. Palade, The hunt for an alternate way to generate NAADP. Focus on “NAADP as a second messenger: neither CD38 nor base-exchange reaction are necessary for in vivo generation of NAADP in myometrial cells,” Am. J. Physiol. Cell Physiol. 292 (2007) C4-7. https://doi.org/10.1152/ajpcell.00390.2006.

[92] S. Soares, M. Thompson, T. White, A. Isbell, M. Yamasaki, Y. Prakash, F.E. Lund, A. Galione, E.N. Chini, NAADP as a second messenger: neither CD38 nor base-exchange reaction are necessary for in vivo generation of NAADP in myometrial cells, Am. J. Physiol. Cell Physiol. 292 (2007) C227-239. https://doi.org/10.1152/ajpcell.00638.2005.

[93] R. Graeff, Q. Liu, I.A. Kriksunov, Q. Hao, H.C. Lee, Acidic residues at the active sites of CD38 and ADP-ribosyl cyclase determine nicotinic acid adenine dinucleotide phosphate (NAADP) synthesis and hydrolysis activities, J. Biol. Chem. 281 (2006) 28951–28957. https://doi.org/10.1074/jbc.M604370200.

[94] H.C. Lee, Y.J. Zhao, Resolving the topological enigma in Ca2+ signaling by cyclic ADP-ribose and NAADP, J. Biol. Chem. 294 (2019) 19831–19843. https://doi.org/10.1074/jbc.REV119.009635.

[95] P. Huang, Y. Zou, X.Z. Zhong, Q. Cao, K. Zhao, M.X. Zhu, R. Murrell-Lagnado, X.-P. Dong, P2X4 forms functional ATP-activated cation channels on lysosomal membranes regulated by luminal pH, J. Biol. Chem. 289 (2014) 17658–17667. https://doi.org/10.1074/jbc.M114.552158.

[96] N. Narayanaswamy, K. Chakraborty, A. Saminathan, E. Zeichner, K. Leung, J. Devany, Y. Krishnan, A pH-correctable, DNA-based fluorescent reporter for organellar calcium, Nat. Methods. 16 (2019) 95–102. https://doi.org/10.1038/s41592-018-0232-7.

[97] K. Rahate, L.K. Bhatt, K.S. Prabhavalkar, SERCA stimulation: A potential approach in therapeutics, Chem. Biol. Drug Des. 95 (2020) 5–15. https://doi.org/10.1111/cbdd.13620.

[98] P.S.-W. Yeung, M. Yamashita, M. Prakriya, Molecular basis of allosteric Orai1 channel activation by STIM1, J. Physiol. 598 (2020) 1707–1723. https://doi.org/10.1113/JP276550.

[99] A.H. Guse, NAADP Signaling: New Kids on the Block, Cells. 11 (2022) 1054. https://doi.org/10.3390/cells11061054.
[100] P. Rivero-Ríos, L.S. Weisman, Roles of PIKfyve in multiple cellular pathways, Curr. Opin. Cell Biol. 76 (2022) 102086. https://doi.org/10.1016/j.ceb.2022.102086.