



# Neurophysiological functions and pharmacological tools of acidic and non-acidic Ca<sup>2+</sup> stores

Lora L Martucci, José-Manuel Cancela

## ► To cite this version:

Lora L Martucci, José-Manuel Cancela. Neurophysiological functions and pharmacological tools of acidic and non-acidic Ca<sup>2+</sup> stores. *Cell Calcium*, 2022, 104, pp.102582. 10.1016/j.ceca.2022.102582 . hal-03875116

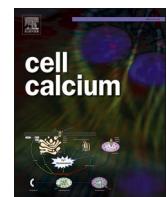
HAL Id: hal-03875116

<https://hal.science/hal-03875116>

Submitted on 28 Nov 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



## Neurophysiological functions and pharmacological tools of acidic and non-acidic $\text{Ca}^{2+}$ stores

Lora L. Martucci <sup>a,\*</sup>, José-Manuel Cancela <sup>b,\*</sup>

<sup>a</sup> Department of Pharmacology, University of Oxford, Mansfield Road, Oxford, OX1 3QT, UK.

<sup>b</sup> Neuroscience Paris-Saclay Institute (Neuro-PSI), UMR 9197, CNRS - University Paris-Sud, Campus CEA, 151 Rte de la Rotonde, 91400 Saclay, France.



### ABSTRACT

$\text{Ca}^{2+}$  signalling is of prime importance in controlling numerous cell functions in the brain. Endolysosomes are acidic organelles currently emerging as important  $\text{Ca}^{2+}$  stores in astrocytes, microglia, endothelial cells, and neurons. In neurons, these acidic  $\text{Ca}^{2+}$  stores are found in axons, soma, dendrites, and axon endings and could provide local sources of  $\text{Ca}^{2+}$  to control synaptic transmission, neuronal plasticity, and autophagy to name a few. This review will address how acidic  $\text{Ca}^{2+}$  stores are recruited in response to cell stimulation. We will focus on the role of the endolysosomal two-pore channels (TPCs) and their physiological agonist nicotinic acid adenine dinucleotide phosphate (NAADP) and how they interact with cyclic ADP-ribose and ryanodine receptors from the endoplasmic reticulum. Finally, this review will describe new pharmacological tools and animal mutant models now available to explore acidic  $\text{Ca}^{2+}$  stores as key elements in brain function and dysfunction.

### Abbreviations

TPC	Two-pore channel
NAADP	Nicotinic acid adenine dinucleotide phosphate
NAAD	Nicotinic acid adenine dinucleotide
NAD <sup>+</sup>	Nicotinamide adenine dinucleotide
NADP <sup>+</sup>	Nicotinamide adenine dinucleotide phosphate
CADPR	cyclic ADP-Ribose
RyR	Ryanodine receptor
CICR	$\text{Ca}^{2+}$ -induced $\text{Ca}^{2+}$ release
GPCR	G-protein coupled receptor
S/ER	(sarco-)endoplasmic reticulum
VGC	Voltage-gated channel
CNS	Central nervous system

In the central nervous system (CNS), the  $\text{Ca}^{2+}$  ion occupies a place of primary importance.  $\text{Ca}^{2+}$  is involved in numerous functions such as in neurotransmitter and neuropeptide release, signal transduction, neuronal excitability, synaptic plasticity, gene transcription, cell metabolism and cerebral blood flow to cite a few (for review, [1–5]). Such essential roles highlight the need for a better understanding of specific  $\text{Ca}^{2+}$  signalling pathways, channels and receptors involved in these disparate processes. Cytosolic  $\text{Ca}^{2+}$  changes occur following  $\text{Ca}^{2+}$  influx from the extracellular space via the opening of plasma membrane channels and through the release of  $\text{Ca}^{2+}$  from intracellular stores such as the (sarco-)endoplasmic reticulum (S/ER) and endolysosomes. In this review, we will focus on the recruitment of intracellular acidic  $\text{Ca}^{2+}$

stores in brain cells and not discuss the pathways for extracellular  $\text{Ca}^{2+}$  entry that have been well described elsewhere (for review, [3,6]). Although considerable advances have been made to understand the  $\text{Ca}^{2+}$  signalling pathways in neurons, many questions remain to be answered, in particular concerning the role of intracellular  $\text{Ca}^{2+}$  stores such as the acidic stores and how they often interact with other organelles to control so many cellular processes.

### 1. A brief history of intracellular $\text{Ca}^{2+}$ signalling

Intracellular  $\text{Ca}^{2+}$  stores came to the fore since the 1960s when researchers discovered that the S/ER was replete with  $\text{Ca}^{2+}$  [7–11]. In skeletal and cardiac muscles, it was then shown that ryanodine, a plant alkaloid, inhibits a “ $\text{Ca}^{2+}$  channel located on the sarcoplasmic reticulum” [12–14] later named as the ryanodine receptor (RyR). RyRs were then eventually purified by two teams and identified as the main  $\text{Ca}^{2+}$  release channel of the SR [15–19]. In parallel, the  $\text{Ca}^{2+}$  mobilizing messenger inositol-1, 4, 5-trisphosphate ( $\text{IP}_3$ ) targeting the ER store was discovered [20,21] and its receptor ( $\text{IP}_3\text{R}$ ) was then purified from rat cerebellum [22–24].

These two  $\text{Ca}^{2+}$  channels of the S/ER became widely accepted as the principal channels controlling the intracellular  $\text{Ca}^{2+}$  stores and have been well-characterized (for review, [25,26]). Still, additional  $\text{Ca}^{2+}$ -releasing molecules were discovered during the 1980s. In a seminal study, Hon-Cheung Lee and colleagues showed that two pyridine nucleotides evoked  $\text{Ca}^{2+}$  release by  $\text{IP}_3$ -independent mechanisms in

\* Corresponding authors.

E-mail addresses: [lora.martucci@new.ox.ac.uk](mailto:lora.martucci@new.ox.ac.uk) (L.L. Martucci), [jose-manuel.cancela@universite-paris-saclay.fr](mailto:jose-manuel.cancela@universite-paris-saclay.fr) (J.-M. Cancela).

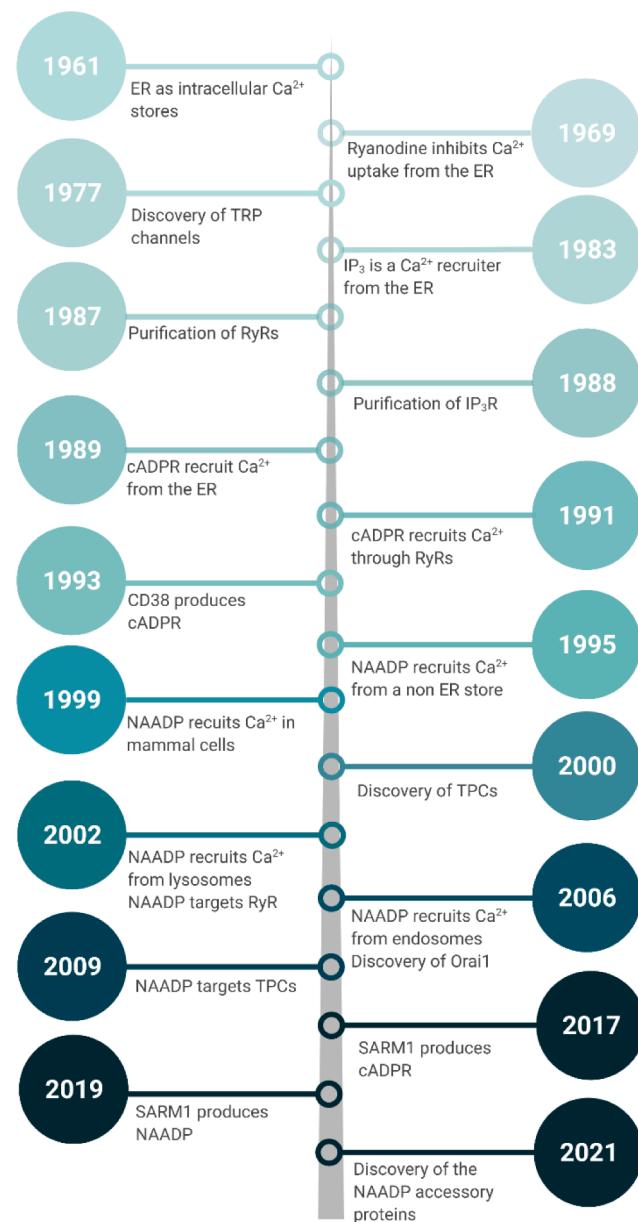
*Lytechinus pictus* (sea urchin) microsomes [27]. They discovered that the addition of NADP<sup>+</sup> (nicotinamide adenine dinucleotide phosphate) triggered rapid Ca<sup>2+</sup> release and that NAD<sup>+</sup> (nicotinamide adenine dinucleotide) was metabolized by an unknown enzyme to form an active Ca<sup>2+</sup>-releasing messenger, later identified by x-ray crystallography as a novel cyclic nucleotide, namely cyclic ADP-ribose (cADPR) [27–29]. Soon after, the principal target channel of cADPR was established as being the well-known RyR [30]. In mammals, one of the enzymes producing cADPR was then identified by Hon-Cheung Lee's team as being the ubiquitous CD38 molecule [31–33]. A few years later, Lee and Aarhus demonstrated that, as they already suspected in their first publication, NADP<sup>+</sup> was not the molecule releasing Ca<sup>2+</sup> from intracellular stores but it was instead NAADP (nicotinic acid adenine dinucleotide phosphate) [34] present as a contaminant in commercial NADP<sup>+</sup> [27, 35]. Indeed, they showed that NAADP triggered Ca<sup>2+</sup> release from a separate store from the ER [35,36]. *In vitro*, NAADP could be synthesized by *L. pictus* and *Aplysia* ADP-ribosyl cyclase [37,38] and the mammalian CD38 [38]. Importantly, NAADP and cADPR both act at lower concentrations than IP<sub>3</sub> to release Ca<sup>2+</sup> [35,39]. The first experiments were conducted in *L. pictus* and *Aplysia californica* and soon thereafter researchers demonstrated the Ca<sup>2+</sup> releasing property of NAADP in various invertebrate models such as in *Phallusia mammillata* (ascidia) oocytes [40], *Chaetopterus pergamentaceus* (parchment worm) eggs [41] and *Asterina pectinifera* (starfish) oocytes [42]. In mammals, it was known that NAADP was effectively synthesized by mammalian cells [34, 36,43] but the first studies failed to detect any cytosolic Ca<sup>2+</sup> elevation by directly injecting NAADP into mammalian intact cells [44,45]. In 1999, Cancela *et al.*, finally demonstrated that NAADP evoked Ca<sup>2+</sup> release in mouse pancreatic acinar cells [46]. They proposed that the primary released Ca<sup>2+</sup> from the unidentified store/receptor could be amplified by further Ca<sup>2+</sup> release from the ER through the recruitment of both RyR and IP<sub>3</sub>R by a mechanism called Ca<sup>2+</sup>-induced Ca<sup>2+</sup> release (CICR). They also obtained the first evidence for a second messenger role of NAADP in hormone signalling [46]. These studies were the starting point for hunting for the NAADP target and the 21st-century studies have been full of astonishing accomplishments about NAADP signalling as depicted in Fig. 1.

NAADP releases Ca<sup>2+</sup> in various cell types from plants to mammals [46–53] but the subcellular compartment from which this Ca<sup>2+</sup> is released was debated for some time. For instance, it has been proposed that NAADP was directly targeting the ER Ca<sup>2+</sup> stores and in particular RyR1 and 2 [53–59]. Understanding of NAADP's mechanism of action reached a higher level when it was discovered that the stores from which NAADP triggers Ca<sup>2+</sup> release were lysosomal-related organelles [60]. What a surprise to discover that NAADP targets lysosomes, a completely ignored Ca<sup>2+</sup> store compared to the well-recognised ER! A few years later, it was also shown that endosomes, which are acidic organelles related to lysosomes were also a source of Ca<sup>2+</sup> mobilized by NAADP [61]. From 1999 to 2009, multiple NAADP molecular targets were proposed including RyR1 [54,55], TRPM2 ([62] but see [63]) and TRPML1 ([64] but see [65]), and a newly discovered protein called Two-Pore Channel, TPC [66–68]. So far, RyR1 and TPCs are the most widely accepted targets for NAADP. In support of this view, two accessory proteins have been recently identified; the Jupiter microtubule-associated homolog 2 (JPT2) [69,70] that allows NAADP to act on TPC1 and RyR1 [70]; and Lsm12 (Like-sm protein) that links NAADP to both TPC1 and TPC2 [71].

## 2. Nucleotide-producing enzymes

### 2.1. CD38

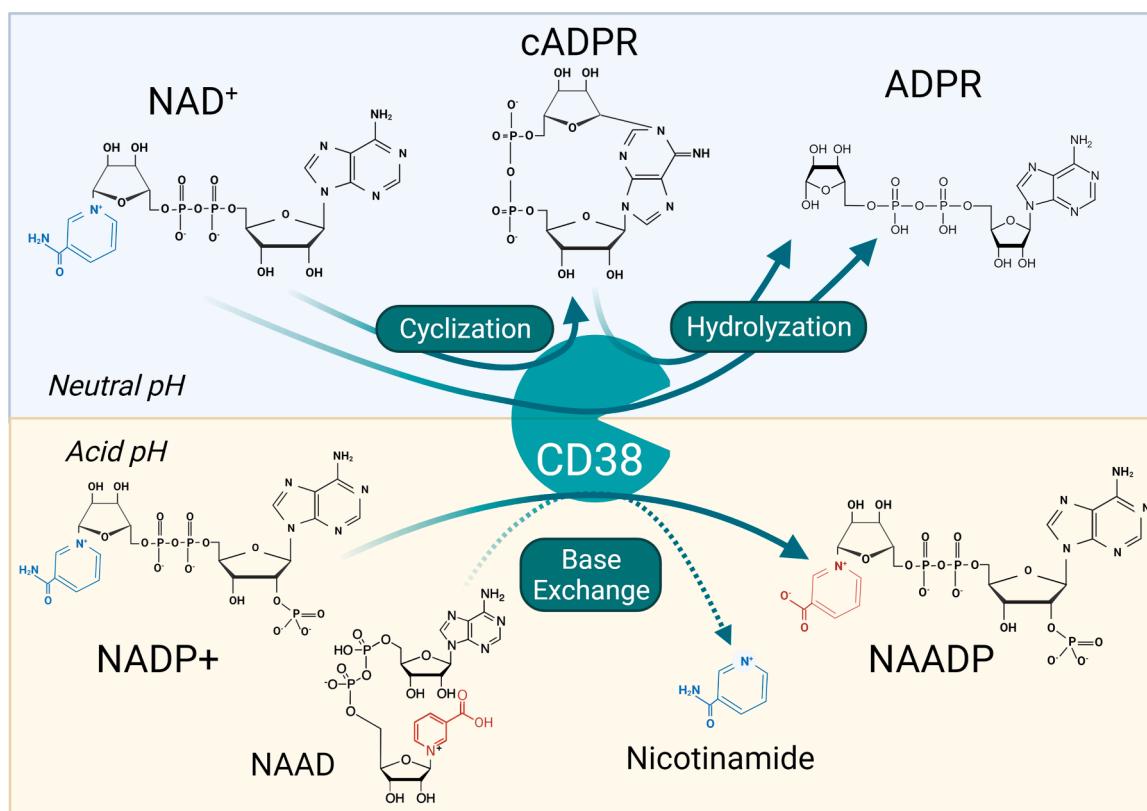
During the 1980s, a large-scale project aiming to identify human surface molecules of the immune system was undertaken. These molecules were designated as "CD" for "Cluster of Differentiation" followed by a number incremented by each new molecule discovered. This led to



**Fig. 1. Chronology of the main discoveries about intracellular Ca<sup>2+</sup> signalling.** The timeline begins at the top thin line in 1961 and run until 2021 at the bottom.

the discovery of CD38, identified as a marker of T lymphocyte activation [72–74].

CD38 is a transmembrane enzyme composed of a single chain of ~45 kDa [74,75] that has been described *in vitro* for its ability to produce cADPR from NAD<sup>+</sup> [31,76,77]. Strikingly, CD38 catalyses many different enzymatic reactions and the three most studied are described in Fig. 2: the cyclization of NAD<sup>+</sup> into cADPR, the hydrolyzation of NAD<sup>+</sup> into ADPR and, the base-exchange reaction to produce NAADP [31,35, 37,38,76,78–82]. As illustrated in Fig. 2, the production of NAADP *in vitro* is optimal in acidic conditions in contrast to cADPR production that preferentially occurs at neutral pH. For many years, it was proposed that the base-exchange reaction for the NAADP synthesis occurs by exchanging the co-substrate nicotinic acid with the nicotinamide group of NADP<sup>+</sup> (nicotinic adenine dinucleotide phosphate) [38,83]. Intriguingly, no study so far has shown that endogenous nicotinic acid levels can change in response to cell stimulation and recently, Kim's group proposed that the base rather comes from the nicotinic acid adenine



**Fig. 2. Drawing showing that CD38 is a multifunctional enzyme.** The cyclase and hydrolase reaction occur preferentially at neutral pH (top) and the base-exchange (bottom) reaction occurs under acidic conditions. Of note, until very recently the candidate substrate for the base exchange reaction was nicotinic acid. Now, a new report has proposed that NAAD is the nicotinic acid donor [84]. Abbreviations: NAD<sup>+</sup>, nicotinamide adenine dinucleotide; cADPR, cyclic adenosine diphosphate ribose; ADPR, adenosine diphosphate ribose; NADP<sup>+</sup>, nicotinamide adenine dinucleotide phosphate; NAAD, nicotinic acid adenine dinucleotide; NAADP, nicotinic acid adenine dinucleotide phosphate.

dinucleotide (NAAD) which accumulates in the acidic endolysosomal lumen [84].

Structurally, CD38 is predicted to be a type-II transmembrane protein with its catalytic site exposed to the extracellular space [31,74, 85–87]. Under such an orientation, the endocytosed CD38 has its catalytic site within the vesicular lumen (Fig. 3), providing the acidic environment required for NAADP synthesis [81,82,84,88]. CD38 has also a type-III orientation coexpressed with the type-II [89], exposing the catalytic site in the cytosol where it could have direct access to its intracellular substrate NAD<sup>+</sup> to produce cADPR under neutral pH [52, 90,91].

CD38 has virtually ubiquitous expression but a few number of studies have looked at its role in the brain [93,94]. Brain expression of CD38 has been demonstrated in mice [95], rats [96,97], and humans [98], and its expression has been shown in neurons [96,98], astrocytes [96,99–102], and microglia [102–104]. In the brain, as for the periphery, CD38 appears highly involved in inflammation processes [100,102–107].

## 2.2. Other nucleotide-producing enzymes

If CD38 is now widely accepted as a cADPR- and NAADP-synthesizing enzyme, several studies have shown that other enzymes may also synthesize cADPR and/or NAADP. It appears that the mammalian CD38 shares 68% homology with the *Aplysia* cyclase, the first ADP-ribosyl cyclase identified from *A. californica*. The enzyme shares with CD38 its ability to produce cADPR [31,77,108–111] and NAADP through the base-exchange reaction [38,112]. In other invertebrates, an ADP-ribosyl cyclase has also been purified from *L. pictus* [113] and *Schistosoma mansoni* (trematode) [114]. In mammal neural cells, a CD38-independent ADP-ribosyl cyclase activity was also

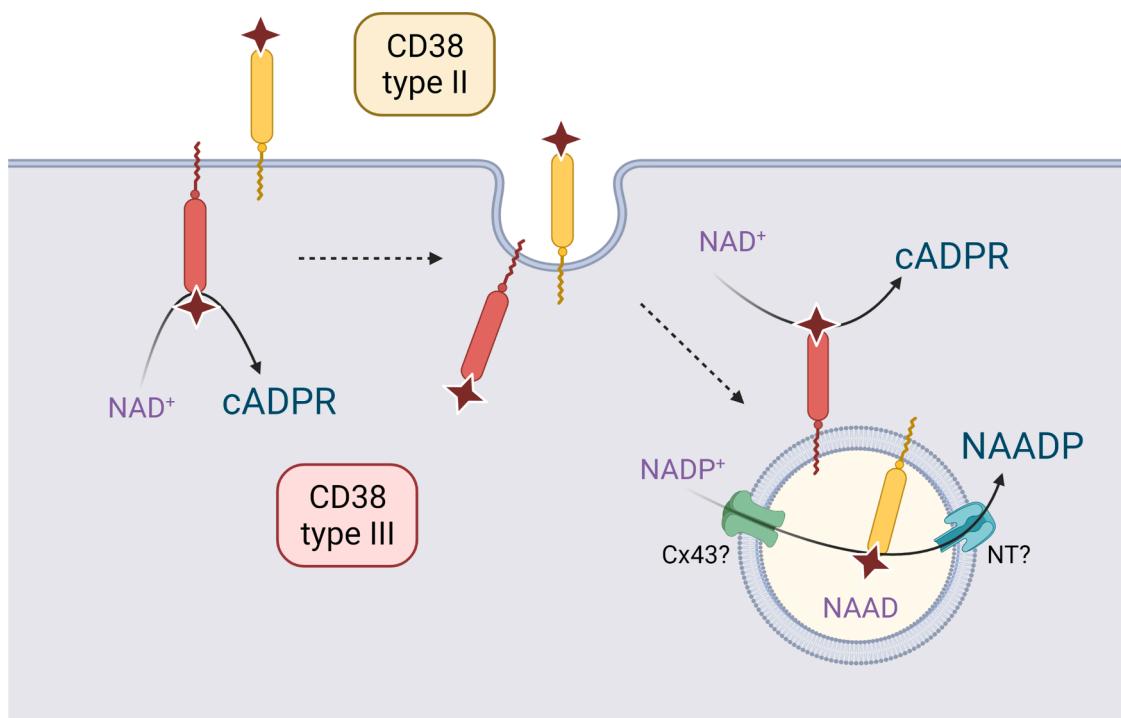
detected [95] which efficiently produced cADPR despite a low basal activity [115]. Since the discovery of the *A.californica* cyclase, other ADP-ribosyl cyclases have been identified in many species, including marine invertebrates, amphibians, birds, and zebrafish [116–118].

Another enzyme called CD157 (or BST-1 for bone marrow stromal cell antigen 1) also shares high homology with CD38 as it results from a duplication of the ancestor gene located on chromosome 4 in humans [119,120]. CD157 exhibits both the cyclase and hydrolase activity but not the base-exchange activity and appears to be several hundred-fold less efficient than CD38 at producing cADPR [121–126]. CD157 is highly expressed in the brain throughout the neonatal period and its expression notably decreases in adulthood [127–129].

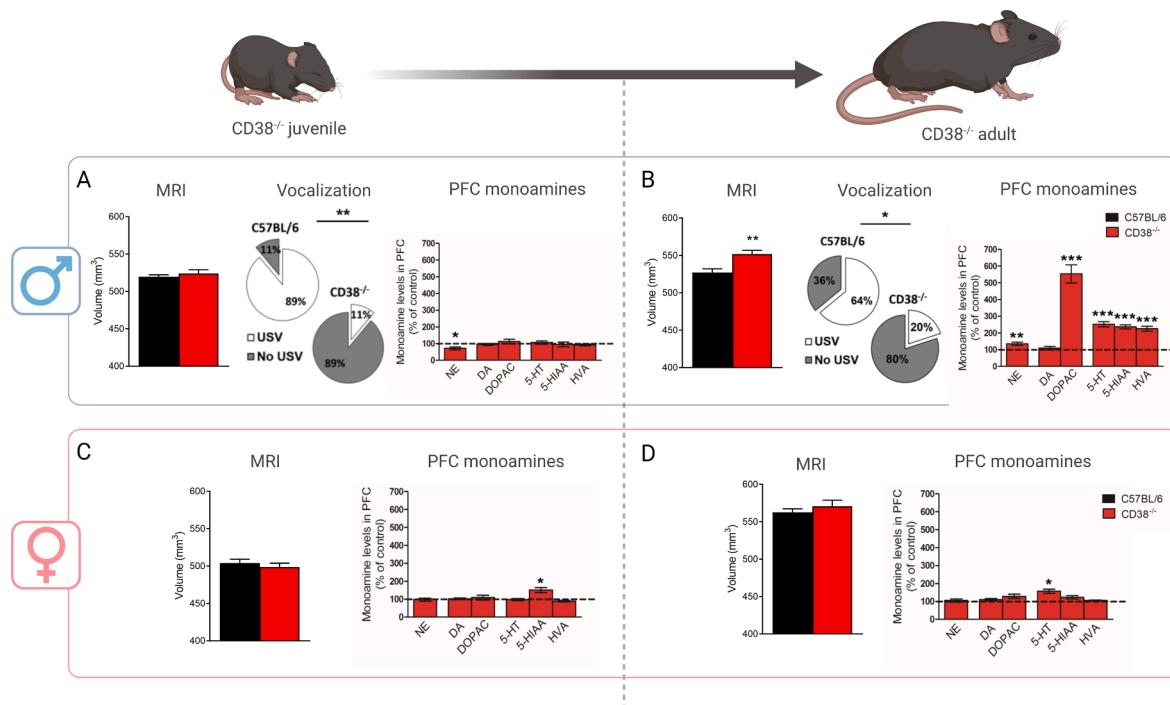
The enzyme SARM1 has been identified and shown to use NAD<sup>+</sup> as a substrate to produce ADPR and cADPR [130–132] and strikingly, could also produce NAADP from NADP<sup>+</sup> [133]. SARM1 is highly expressed in neurons and, so far, has been mostly studied in pathological conditions where deletion of SARM1 has proven to be beneficial for neuron survival [134,135]. Additionally, in lymphocytes T-cells, it has recently been proposed that the enzyme DUOX could also produce NAADP [136]. It is now of importance to better characterize these nucleotides producing enzymes, their regulation, and their cell-specific expression.

## 3. The cADPR-RyR signalling pathway

The messenger cADPR is known to release Ca<sup>2+</sup> from the ER by activating RyRs [30,49,137]. cADPR production in the brain occurs following the activation of G-protein coupled receptors (GPCR) such as the glutamatergic metabotropic receptor (mGluR) and the oxytocinergic receptor (OTR) [106,138].



**Fig. 3. Scheme showing the co-expression of type II and type III CD38.** The star-shaped symbol represents the catalytic site of the CD38 enzyme. Type II (in yellow) is internalized to provide the acidic conditions to produce NAADP [81,88]. Connexin 43 (Cx43) has been proposed to transport NAD<sup>+</sup>/NADP<sup>+</sup> into the endosomes [84,92]. The co-substrate NAAD is present in the acidic lumen of the endolysosomes [84]. In this model, the product NAADP is released into the cytosol by an unidentified nucleotidic transporter (NT).



**Fig. 4. Gender- and age-specific effect of CD38 deletion on brain function.** The left panel depicts results obtained in juvenile mice while the right panels depict results from adult mice. (B) Magnetic Resonance Imaging (MRI) reveals that adult male mice exhibit a macrocephaly compared with male juvenile (A) and female mice (C, D). During a free social interaction, ultrasonic vocalizations (USV) were recorded, in CD38<sup>-/-</sup> male mice (A, B) that emitted significantly fewer USVs compared with WT mice (A, B). The monoamine content of the prefrontal cortex (PFC) was measured and appears dramatically altered in adult male mice (B) compared with the limited changes observed in juvenile mice (A, C) and adult females (D). Abbreviations: NE, norepinephrine; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; 5-HT, serotonin; 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid. (from [93]).

### 3.1. Neurons

As early as 1998, it was demonstrated that presynaptic injection of cADPR into neurons of the buccal ganglion of *A. californica* induces a presynaptic  $\text{Ca}^{2+}$  elevation that modulates acetylcholine release [139, 140]. In addition to its role in neurotransmitter release, cADPR also stimulates secretion of neuropeptides such as oxytocin and adrenocorticotropin [141,142]. Using acute brain slice preparation, it has been shown that cADPR participates in both rat hippocampal neuronal long-term depression (LTD) induction [143], and the regulation of the neuronal firing activity of the rat dorsolateral geniculate nucleus [144]. Interestingly, a recent study has also shown a cADPR-dependent activation of TRPM2 that led to stellar neuron depolarisation and increased firing rate [145]. Finally, it appears that the cADPR pathway can form a positive feedback loop since it is also recruited during neuron depolarization through the opening of L-Type  $\text{Ca}^{2+}$  channels as proposed in *A. californica* buccal ganglion neurons [146]. In contrast, in rats, an inverse relationship was observed between cADPR brain levels and spatial learning ability assessed in the Morris water maze [147]. This effect could be related to the role of cADPR in LTD [143,148] that is known to modulate learning ability (for review, [149]). cADPR has also been shown to be involved in the glutamatergic regulation of the circadian clock [150] and in the regulation of social behaviours by modulating the release of the prosocial neurohormone oxytocin [138, 142]. Finally, it has been proposed that CD38, through cADPR production, regulates neural proliferation and differentiation during development [151,152] and modulates the dendritic organization in hippocampal neurons [153].

In line with the role of CD38 in development [107,151–153] and the report of CD38 single nucleotide polymorphisms (SNPs) found in autistic patients [154], we recently demonstrated that CD38 deletion in mice led to neurodevelopmental alterations such as macrocephaly observed by magnetic resonance imaging (Fig. 4, [93]). Knowing that CD38 is involved in neural differentiation and microglial activation [103,104, 107,152,155], we postulated that CD38 deletion may lead to impaired processes such as pruning or neuronal apoptosis. Interestingly, these features are found in autistic patients who typically exhibit a higher number of neurons [156] or spine density that could be due to pruning deficits [157–159] as well as modification in the size of brain structures [160–165]. We also described a progressive phenotype since the macrocephaly was not present in juvenile CD38<sup>−/−</sup> mice (Fig. 4). The first behavioural alterations observed were fewer vocalizations during an interaction in juvenile male CD38<sup>−/−</sup> mice, preceding the appearance of a more severe phenotype in adult male mice (Fig. 4, [93]). The adult phenotype is characterized by impaired social interactions and aggressiveness [93] as well as defects in maternal behaviour, social memory [142] and learning and spatial memory [166]. It has been proposed that such behavioural alterations are due to the lack of the prosocial hormone oxytocin in these mice [93,142] but we further demonstrated that CD38 deletion also led to dramatic changes in monoamine levels in the prefrontal cortex (Fig. 4, [93]) which is a key structure for regulating social behaviours. The prefrontal cortex is regulated by both oxytocin and monoamine neurotransmitters such as 5-HT, dopamine and norepinephrine that modulate behavioural flexibility [167–172] as well as anxiety and aggressiveness [173–176]. Thus, the lack of oxytocin from the CD38<sup>−/−</sup> mice is not the sole neuromodulator that account for the behavioural alterations observed in these mice. We also demonstrated a role for CD38 in regulating the excitation/inhibition balance and the long-term potentiation (LTP) in the prefrontal cortex [93].

### 3.2. Glial cells

Astrocytes also have ADP ribosyl cyclase activity and highly express CD38 [107,177]. In these cells, the addition of cADPR induces a cytosolic  $\text{Ca}^{2+}$  elevation that leads to the release of glutamate and GABA [99, 106]. It has also been shown that CD38, through its ability to produce

cADPR, regulates oligodendrocyte development [107]. Importantly, the role of cADPR in astrocytes has also been investigated in pathological contexts. In response to transient neuroinflammation, astrocytes are recruited and proliferate, to release numerous inflammatory components in concert with microglia, the immune cells of the CNS [178–183]. These astrocyte and microglial activations could then lead to neurotoxicity and neurodegeneration [184–186]. The microglial activation has been shown to depend on both CD38 and cADPR [103,187] and the so-called “activated microglia” can enter the cell death program, a process also relying on CD38 and cADPR upregulation induced by lipopolysaccharides and interferon-γ [103,187,188]. In activated astrocytes, CD38 is upregulated by interleukins and TNFα [100] and the resulting  $\text{Ca}^{2+}$  signalling generated is dependent on cADPR [189]. Similarly, it has been reported that the increase in the cytosolic  $\text{Ca}^{2+}$  concentration observed under hypoxia conditions in cultured astrocytes, is dependent on cADPR-evoked  $\text{Ca}^{2+}$  release from RyRs [190]. Finally, studies have recently demonstrated an intriguing role for CD38 and cADPR in enabling the transfer of functional mitochondria from astrocytes to neurons and back [191–193]. Such mitochondrial transfer has been suggested to be part of a protective mechanism promoting neuronal survival after a transient focal cerebral ischaemia [191].

## 4. NAADP-TPC signaling pathways molecule

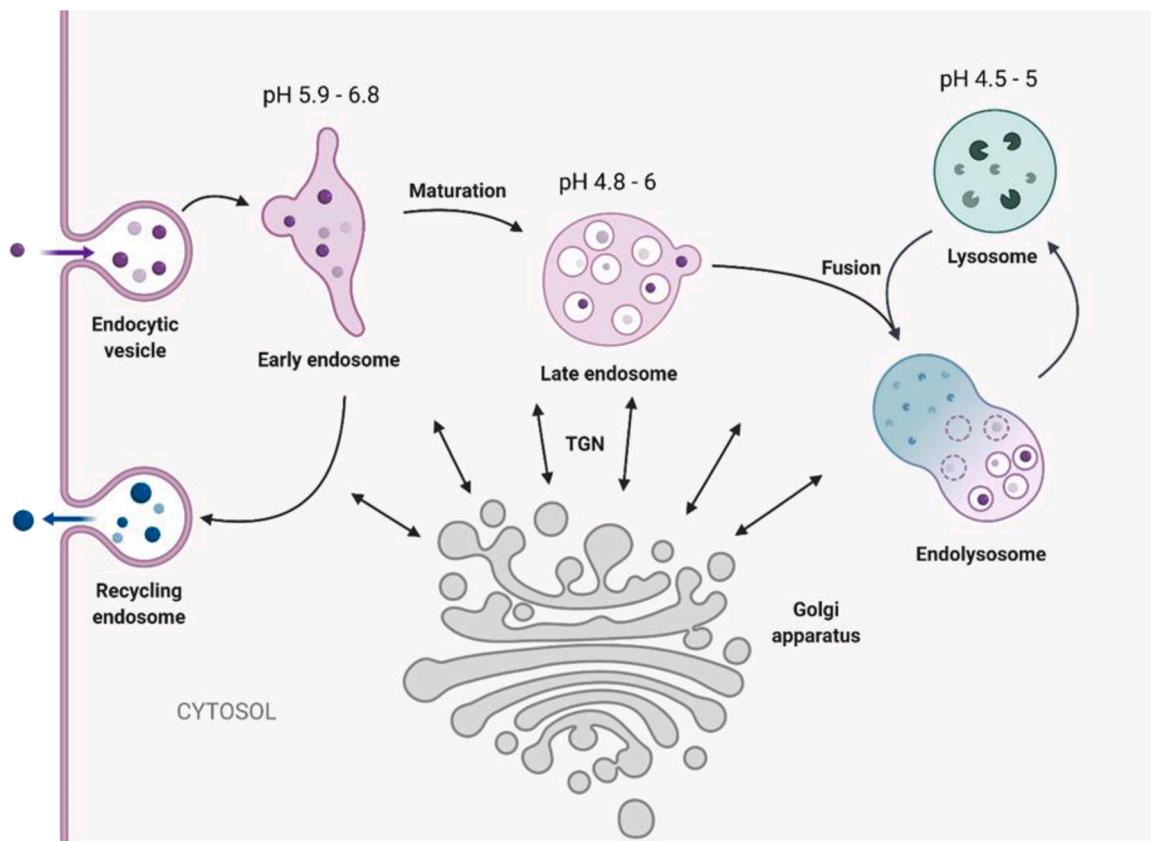
NAADP differs from cADPR by its ability to release  $\text{Ca}^{2+}$  not only from the ER but also from endosomes, lysosomes and other acidic organelles [46,53,60,61,194–199]. Notably, NAADP is now essentially described to mobilize  $\text{Ca}^{2+}$  through the opening of the endolysosomal TPCs, but it may also release  $\text{Ca}^{2+}$  from the ER and/or the nucleus by activating RyR and IP<sub>3</sub>R (for review [49,53,200,201]). Of note, NAADP does not bind directly to TPCs or RyR, but it needs an accessory protein that has been sought for many years [202–207]. NAADP requires JPT2 to bind to TPC1 and RyR1 [69,70] and it requires Lsm12 to bind to TPC1 and TPC2 [71]. So far, the physiological role of these two binding proteins in the brain is poorly understood.

### 4.1. Lysosomal $\text{Ca}^{2+}$ and organelle interactions

Since their discovery by de Duve [208], lysosomes have been viewed as degradative organelles containing proteases and other enzymes. And of course, this is true. Yet, it is quite reductive as we will see here. Lysosomes have long been known to be in every cell type of the brain such as neurons, astrocytes, or microglia [209–212]. In neurons, lysosomes are localized in axons [213–215], dendrites [216–218] and in the soma [213,219,220]. These strategic locations sustain the lysosomal-dependent cellular functions as described thereafter. The last years have seen a growing interest in lysosomal  $\text{Ca}^{2+}$  signalling especially in the brain where lysosomal dysfunctions are linked with numerous psychiatric and neurological diseases [221–228]. For instance, it has been shown that the endolysosomal LRRK2 kinase mutation involved in a familial form of Parkinson disease leads to TPC2 overactivation and lysosomal morphological defect [228,229]. Another example of lysosomal disease is the mucolipidosis IV associated with a mutation in the lysosomal TRPML channels that leads to severe psychomotor deficiency [230–233].

Endosomes are organelles formed both by the *trans*-Golgi budding and endocytosis of the plasma membrane (Fig. 5). They can mature to sort recycling proteins [234] and eventually fuse with the lysosome (Fig. 5) to degrade their non-recycling endocytic content [235,236]. Both endosomes and lysosomes (here called endolysosomes) are acidic organelles (pH 4.8–6 and 4.5–5 respectively) that acidify due to the presence of an H<sup>+</sup>-ATPase pump on their membrane [237,238].

Lysosomes are complex organelles containing a large variety of enzymes, ion channels and transporters and ions ( $\text{H}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ) that sustain various intracellular signalling functions [238,240]. The lysosomal luminal  $\text{Ca}^{2+}$  concentration is high (~500 μM) and comparable



**Fig. 5. Schematic drawing of endolysosomal traffic and maturation.** Early endosomes are formed by endocytosis of the plasma membrane or by budding from the Golgi apparatus. Endosomes could either be recycled to the plasma membrane or mature into late endosomes that aim to fuse with lysosomes. Abbreviations: TGN, Trans Golgi network (Adapted from [239]).

with the ER  $\text{Ca}^{2+}$  content [225,241–244]. However, the  $\text{Ca}^{2+}$  refilling mechanisms that maintain such luminal concentration remain to be identified. Luminal  $\text{Ca}^{2+}$  is regulated in lysosomes, either through an ion transporter or an ion exchanger. Indeed, CAX, a  $\text{Ca}^{2+}/\text{H}^+$  exchanger that uses the high  $\text{H}^+$  gradient to counter transport  $\text{Ca}^{2+}$  in acidic organelles has been identified in yeast and plant cells [245] and some animal cells of lower vertebrates such as *Xenopus* neural crest cells [246]. It has also been shown that lysosomes express the S/ER  $\text{Ca}^{2+}$ -ATPase 3 (SERCA3) but, until now, this has only been observed in human platelets [247, 248]. Additionally,  $\text{Ca}^{2+}$  refilling of lysosomes may also require interaction with various cell compartments. Notably, some studies suggest that lysosomes require the ER  $\text{Ca}^{2+}$  store to refill. For example, studies have shown that lysosomes sequester the  $\text{Ca}^{2+}$  released by the IP<sub>3</sub>R opening which requires an intact ER  $\text{Ca}^{2+}$  pool [223,249–253] and recently, it has been proposed that the  $\text{Ca}^{2+}$  sensor STIM1 (stromal interaction molecule) regulates lysosomal-ER coupling in cortical neurons [223,254]. Lysosomes form contact sites with other organelles by close apposition ( $\sim 30$  nm) and it has been reported that 50% of early endosome and 95% of lysosomes are in contact with the ER [255–258]. However, these values are not set in stone as lysosomes are highly mobile in the cell [259–263]. These studies demonstrate that lysosomes may interact with the ER, either to reuptake  $\text{Ca}^{2+}$  or to fulfil more complex functions. Remarkably, physical [258,264] and functional contacts between lysosomes and mitochondria have also been described and notably a  $\text{Ca}^{2+}$  flux exchange has been shown between these two organelles [265]. These interactions appear to be crucial, for instance, for regulating energy metabolism [266–268]. Disruption in mitochondrial-lysosomal interactions may also be involved in diseases such as Niemann-Pick disease [269] or Parkinson's disease [270–272]. Finally, contact sites between lysosomes and the plasma membrane have also been described [273] and seem important in membrane repair

processes [274–278] and for regulation of spine morphology in neurons [217]. Additionally, it has been proposed that lysosomal  $\text{Ca}^{2+}$  facilitates  $\text{Ca}^{2+}$  influx through the opening of several plasma membrane channels such as N-type  $\text{Ca}^{2+}$  channels in the hippocampus [279] and Orai1 in various cell lines [280–283].

How lysosomal  $\text{Ca}^{2+}$  is mobilized is currently an active field of research and numerous channels and enzymes have been identified and described elsewhere [284]. Most studies aiming to understand the role of TPCs were conducted in peripheral cells of mice and zebrafish, such as in smooth muscle myocytes [285], ventricular myocardium [286], superficial slow muscle cells in the trunk of zebrafish [287,288], T-cell [289], embryonic stem cells [290] or platelets [291] to cite a few (for review,[201,292]). It was only in 2018 that the first study on TPCs was conducted in neurons [293]. The next section will describe some aspects of the lysosomal channel TPC, its structure and properties, what we know about the cellular roles of NAADP and TPCs, and which lessons could be drawn for brain studies.

#### 4.2. TPC structure & biochemical properties

Three isoforms of TPCs have been characterized: TPC1, TPC2, and TPC3 (*Tpcn* for gene name) and exhibit different distribution patterns based on a dileucine motif at their N-terminal end [294]. TPC1 and TPC3 are mainly expressed on endosomes (recycling endosome, early endosome, and late endosome) while TPC2 is preferentially expressed on late endosomal- and lysosomal membranes [66–68,200,295]. The gene encoding TPC3 (*Tpcn3*) is absent or incomplete (pseudogene) in mice, rats, primates, and humans [296]. The two genes *Tpcn1* and *Tpcn2* are encoded on distinct chromosomes: in the region 12q24.13 for human *Tpcn1* and 11q13.3 for human *Tpcn2*.

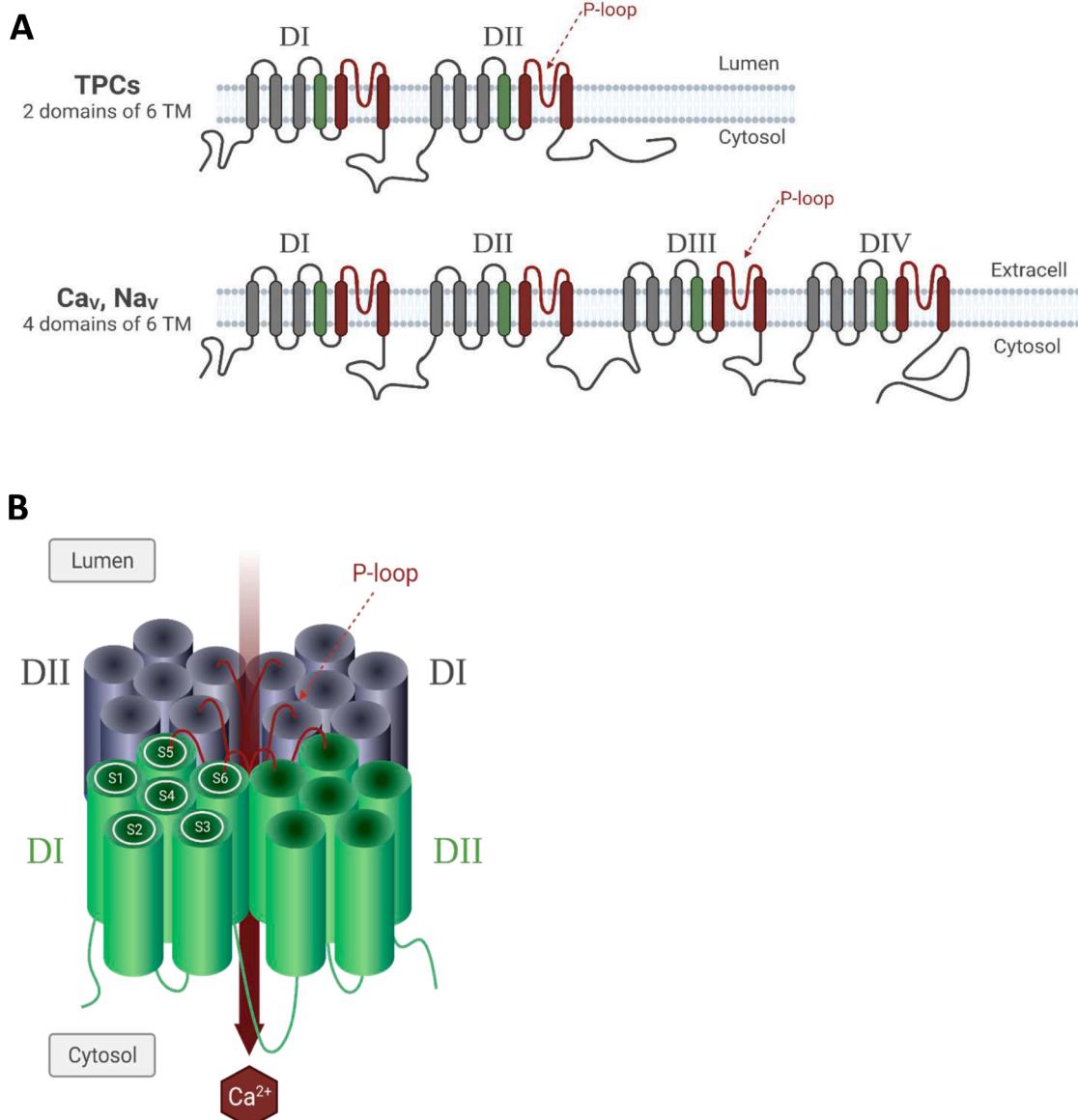
TPCs are ancient ion channels found in very different species from

plants to mammals and have been proposed to have a common ancestor with  $\text{Ca}^{2+}$  and  $\text{Na}^+$  channels [297–301]. Like voltage-gated cation channels ( $\text{Ca}^{2+}$  and  $\text{Na}^+$  VGCS), TPCs are composed of six transmembrane segments forming a domain. But, instead of being assembled as four domains like VGCS, only two domains are linked in TPCs (Fig. 6) [297]. The name “two-pore” channel comes from their structure. In each domain, between the transmembrane segment 5 and 6, there is a “P-loop” (Fig. 6) that could also be called a “pore domain” even if a single p-loop is not sufficient to form the ion-permeant pore in a membrane. To form such a pore, two subunits of TPCs need to assemble as a dimer leading to a four-domain structure (Fig. 6). In accordance with the similarity with  $\text{Ca}^{2+}$  and  $\text{Na}^+$  VGCS, TPCs are also voltage-sensitive [300,302]. This voltage sensitivity is provided by the transmembrane segments 4 and 10 but is not required for channel opening [303]. TPC1 and TPC3 are particularly sensitive to the voltage which may modulate the affinity for NAADP but, surprisingly, TPC2 appears to be mostly

voltage-insensitive [304,305]. Of note, TPCs are nonselective cation channels for which the ion preference conductance have been long debated [268,302,304,306–310]. If the ion selectivity of TPC1 and TPC2 may vary depending on experimental conditions, nowadays, it is quite well accepted that TPC1 is rather  $\text{H}^+$  selective ( $\text{H}^+ >> \text{K}^+ > \text{Na}^+ > \text{Ca}^{2+}$ ) whereas TPC2 is rather  $\text{Ca}^{2+}$  and  $\text{Na}^+$  selective [50,305,307,308, 310–313]. Discrepancies about the ion selectivity of TPC2 (for review [314]) lasted for a decade and can now be explained by a peculiarity of TPCs. They can be activated by two different agonists, namely PI(3, 5)P<sub>2</sub> and NAADP that respectively leads to  $\text{Na}^+$ - or  $\text{Ca}^{2+}$ -current activation [310]. This interesting property will be further described in the following section about pharmacological tools.

#### 4.3. Pharmacological tools

To target the NAADP pathway, diverse strategies are available. We



**Fig. 6. TPCs and voltage-gated cation channels structures.** A) High structural similarity between voltage-sensitive ion channels since TPCs are composed of 2 domains (DI and DII) containing 6 transmembrane segments (TM) and  $\text{Ca}^{2+}$ - and  $\text{Na}^+$  voltage-gated channels are formed by 4 domains of 6-TM. The 4th segment (in green) is charged and confers the ionic selectivity. Between the 5th and 6th segments (in red), the P-loops form the pore of the channel. B) 3-dimensional structure of TPCs assembled in dimer (one in green and the other in grey). Such dimer forms the functional 4-domain channel. In dark red, the p-loops between each transmembrane segments 5 and 6 form the pore of the channel.

could either target the receptor (i.e., the channel), the producing enzyme or the  $\text{Ca}^{2+}$  stores recruited. Interestingly, activation of GPCR by diverse agonists such as cholecystokinin [81,315], histamine [316], interleukin 8 [82], thrombin [317],  $\beta$ -adrenergic stimulation [318], and metabotropic glutamatergic receptors (mGluR) [198,293,319] induces NAADP production. Besides measuring the changes in endogenous levels of NAADP following cell activation by extracellular hormones or neurotransmitters, the role of NAADP in agonist-evoked  $\text{Ca}^{2+}$  response has been also investigated. These investigations took advantage of the biphasic property of NAADP which releases  $\text{Ca}^{2+}$  at low nanomolar range concentrations (5–100 nM) whereas, at a high micromolar range (10–100  $\mu\text{M}$ ), NAADP shows a self-desensitization property [46,47,194,293]. More recently various studies used Ned-19, a permeant NAADP antagonist, in addition to NAADP [293,320–325]. Most of the reports also concomitantly used pharmacological tools to disrupt the lysosomal  $\text{Ca}^{2+}$  store either with the lysosomotropic agent, GPN (glycyl-L-phenylalanine-beta-naphthylamide) that disrupts the lysosome or with the  $\text{H}^{+}$ -ATPase inhibitor, bafilomycin A1 [60,61,81,194,293,318,321,324–328] (Fig. 7). Alternatively, researchers have also used mutant mice such as CD38<sup>−/−</sup> [93,94] or TPC1/2<sup>−/−</sup> mice [293,329] as well as mutant zebrafish [330,331] for studying the role of this pathway in neural cells.

However, NAADP has been shown to target not only TPCs but also RyR and therefore to further investigate the role of the NAADP/TPC pathway, selective agonists and antagonists of TPCs are crucially needed. Many years before the discovery of TPCs as being an NAADP target, Genazzani *et al.* discovered that a high concentration of L-type  $\text{Ca}^{2+}$  blockers completely abolishes NAADP-evoked  $\text{Ca}^{2+}$  release, thus suggesting that the NAADP sensitive  $\text{Ca}^{2+}$ -channel could be related to L-type  $\text{Ca}^{2+}$  channels [332]. The discovery of TPCs' structure has proven that the presumption of Genazzani *et al.*, was correct (see "TPC structure and biochemical properties"). The structural homology between TPCs and voltage-gated channels (Fig. 6) is the basis of their common sensitivity to VGCs blockers as summarized in Table 1. Recent years have seen the description of a growing number of various blockers targeting TPCs, such as tricyclic antidepressants, anaesthetics or dihydropyridines (Table 1). Due to their poor selectivity, such molecules should be used with caution to study TPCs' functions. However, it is of crucial

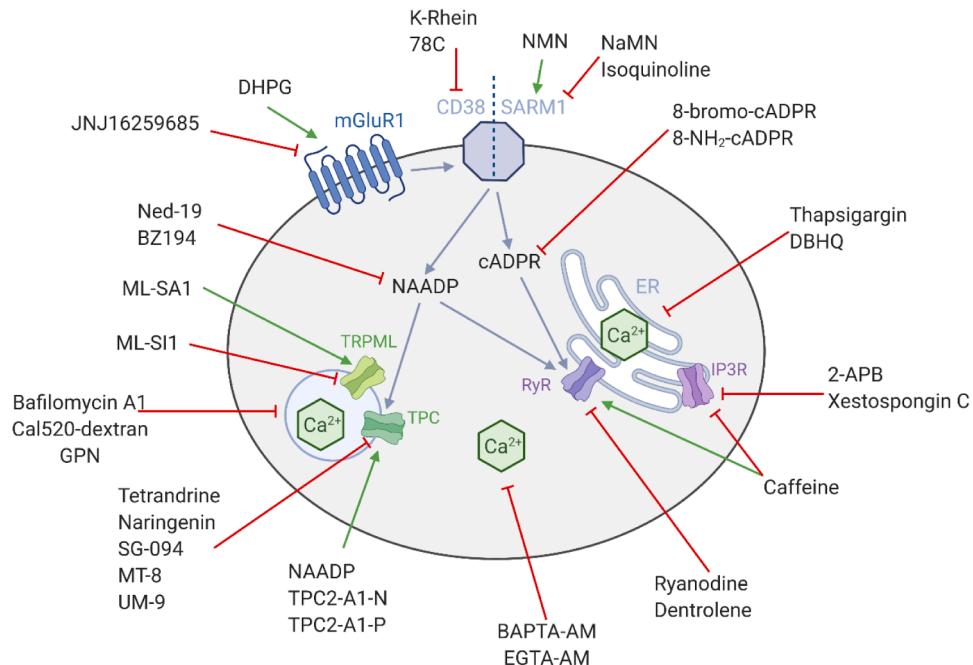
importance that studies using these drugs for other purposes consider the possibility of off-target effects on TPCs to fully interpret the data. To facilitate TPC research, selective pharmacological tools need to be developed. In this respect, a recent study has described new promising inhibitors that preferentially target TPC2 such as SG-094 [333,334] that could be a highly valuable addition to the mostly commonly used non-selective TPC inhibitors such as tetrandrine [335] and naringenin [336]. Not only is it important to block TPCs, but it is also important to selectively activate TPCs to elucidate their functions, and lately, Gerndt *et al.* successfully identified two TPC2 agonists: TPC2-A1-N and TPC2-A1-P [310]. In the meantime, the study revealed that TPC2-A1-N and TPC2-A1-P likely bind to different sites on TPC2 and control the ion selectivity of this channel. The authors demonstrated that TPC2-A1-N mimicking NAADP favoured the  $\text{Ca}^{2+}$  conductance by inducing  $\text{Ca}^{2+}$  release from endolysosomes whereas TPC2-A1-P mimicking PI(3, 5)P<sub>2</sub> preferentially activates the  $\text{Na}^{+}$  conductance of TPC2 [310]. These TPC2 agonists (Fig. 7) were identified very recently and should greatly facilitate the study of TPCs in the field for the coming years [310].

#### 4.4. Lysosome and TPC, the local $\text{Ca}^{2+}$ signal trigger

Using various pharmacological tools and genetic deletion of TPCs, several studies have begun to unravel the cellular functions of the TPCs. As previously mentioned in the "Lysosomal  $\text{Ca}^{2+}$ " section, lysosomes often couple to the ER to generate a  $\text{Ca}^{2+}$  signal in response to physiological agonists. During lysosome-ER coupling, the ER  $\text{Ca}^{2+}$  is released by CICR following a primary lysosomal  $\text{Ca}^{2+}$  release called a trigger [49, 50,370] as illustrated in Fig. 8.

Of note, similarly to IP<sub>3</sub>R and RyR, TPCs could be directly activated by  $\text{Ca}^{2+}$  [302–304,312,372]. Thus, NAADP may be a modulator of a positive  $\text{Ca}^{2+}$  feedback loop by activating both TPCs and RyR (Fig. 9), a mechanism relying on  $\text{Ca}^{2+}$  microdomains. Indeed, several studies have shown that NAADP-evoked  $\text{Ca}^{2+}$  signalling occurred at "discrete trigger areas" [46,60,196,256,257,373–377,417]. The role of TPCs in these  $\text{Ca}^{2+}$  microdomains has been subsequently demonstrated [66,256,370] and these microdomains represent a trigger for CICR to induce a larger  $\text{Ca}^{2+}$  response from the ER [51, 66,378,379].

The interaction between lysosomal TPCs and the ER controls



**Fig. 7. Pharmacology of TPC signalling pathway and affiliated pathways.** Red lines represent an inhibitory effect. Green arrows represent agonistic effect. Abbreviations and references are in Table 1.

**Table 1**  
Pharmacological components of the intracellular  $\text{Ca}^{2+}$  signalling components.

Target	Component	Action	Notes	Ref
mGluR1	DHPG ((S)-3,5-Dihydroxyphenylglycine)	+		[337]
	JNJ16259685	-		[338]
CD38	IL-8 (interleukin-8)	+		[339]
	ATRA ( <i>all-trans</i> retinoic acid)	+	Active metabolite of vitamin A - Induce CD38 expression	[340, 341]
SARM1	K-Rhein	-		[342]
	78C	-		[343]
cADPR	NAD <sup>+</sup>	-	Substrate and self-inhibitory binding site of SARM1.	[344]
	NMN (nicotinamide mononucleotide)	+		[345, 346]
ER	CZ-48	+	NMN mimetic.	[133]
	NaMN (Nicotinic acid mononucleotide)	-		[347]
ER	Isoquinoline	-		[348]
	8-bromo-cADPR	-	Membrane permeant.	[349]
ER	8-NH <sub>2</sub> -cADPR	-	Membrane non-permeant.	[349, 350]
	Thapsigargin	-	Inhibit SERCA pump leading to $\text{Ca}^{2+}$ leak and ultimately to empty the ER store.	[351]
IP <sub>3</sub> R	DBHQ (2,5-Di(tert-butyl)-1,4-benzohydroquinone)	-	Inhibit SERCA pump leading to $\text{Ca}^{2+}$ leak and ultimately to empty the ER store.	[352]
	Cyclopiazonic acid	-	Inhibit SERCA pump pump leading to $\text{Ca}^{2+}$ leak and ultimately to empty the ER store.	[353, 354]
RyR	2-APB (2-aminoethoxydiphenyl borate)	-	Inhibit TRP channels too.	[355]
	Xestospongin C	-		[356]
RyR	Caffeine	-		[357]
	Caffeine	+		[358]
Free $\text{Ca}^{2+}$	Ryanodine	-		[12]
	Dantrolene	-		[359]
NAADP	BAPTA	-	Fast chelator	[360, 361]
	EGTA	-	Slow chelator	[362, 363]
NAADP	Ned-19	-		[320]
	BZ194	-	Inhibit NAADP action on RyR1	[59]
TRPML	NAADP	-	Self-inhibition at high concentration (10–100 $\mu\text{M}$ )	[46]
	ML-SA1	+		[364]
Lysosome	ML-SI1	-		[365]
	Bafilomycin A1	-	Inhibitor of the H <sup>+</sup> -ATPase leading to a leak in lysosomal $\text{Ca}^{2+}$	[366]
Cal-520-dextran	GPN (Glycyl-L-phenylalanine 2-naphthylamide)	-	Ca <sup>2+</sup> chelator of the lysosomal lumen Causes osmotic change leading to the rupture of the	[367]

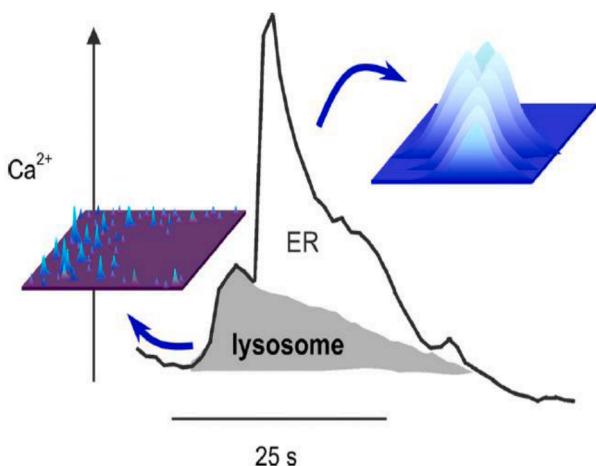
**Table 1 (continued)**

Target	Component	Action	Notes	Ref
TPC1 & TPC2	Tetrandrine	-	lysosomal membrane Clinically used as anti-inflammatory and anti-fibrogenic. Also used to block the entry of the Ebola virus in the cell	[335]
SG-005		-	Derived from tetrandrine – As potent as tetrandrine to inhibit TPC2. Inhibit TRPML1 and TPC1 too.	[334]
NAADP		+	Preferentially trigger $\text{Ca}^{2+}$ release under 5–100nM	[66–68]
PI(3, 5)P2		+	Preferentially conducts $\text{Na}^+$ current	[308]
TPC2	TPC2-A1-N	+	Drives $\text{Ca}^{2+}$ current	[310]
	TPC2-A1-P	+	Drives $\text{Na}^+$ current	[310]
	Riluzole	+	Clinically used to treat amyotrophic lateral sclerosis	[305]
Naringenin		-	Derived from tetrandrine – More potent than tetrandrine - No considerable inhibitory effect on TRPML1	[336]
SG-094		-	O-methylated isoflavone extract from <i>Dalbergia parviflora</i> (Akar Laka). Suggested anti-cancer effect	[334]
Duartin (UM-09)		-	Tri-O-methylated isoflavan extract from <i>Kaempferia parviflora</i> (Thai ginseng).	[333]
		-	Suggested anti-cancer effect	
Raloxifene		-	Selective estrogen receptor modulators	[369]
Clomiphene		-	Selective estrogen receptor modulators. Only partially blocks NAADP $\text{Ca}^{2+}$ response	[369]
Fluphenazine		-	Dopamine receptor antagonist	[369]
Pimozide		-	Dopamine receptor antagonist	[369]
Tricyclic antidepressant (amitriptyline, clomipramine, chlorpromazine, desipramine, imipramine, nortriptyline, trifluoperazine)		+	Clinically used as an antidepressant. Believed to act on neurotransmitter transporters or voltage-gated $\text{Na}^+$ channels	[305]
TPC1		-	Clinically used as an antidepressant.	[305]

(continued on next page)

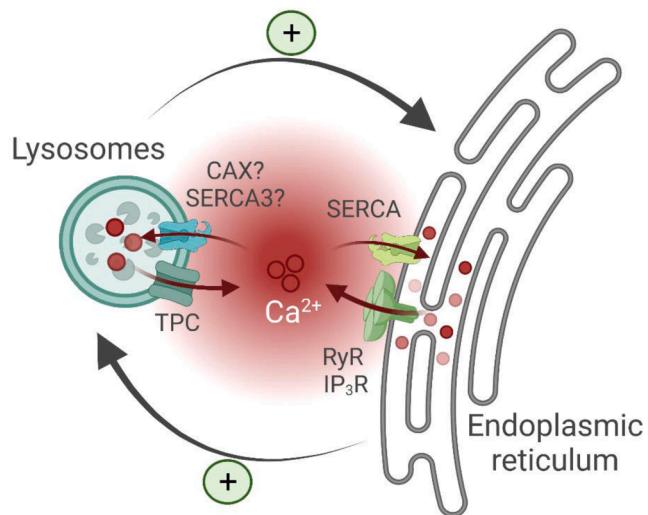
**Table 1 (continued)**

Target	Component	Action	Notes	Ref
	Tricyclic antidepressant (clomipramine, chlorpromazine)		Believed to act on neurotransmitter transporters or voltage-gated $\text{Na}^+$ channels	
Ca <sub>1</sub> & TPC	Dihydropyridines (Felodipine, Amlodipine, Isradipine, <b>Nicardipine</b> , Nifedipine, Nimodipine, Nitrendipine, Oxodipine)	-	Clinically used against hypertension	[300, 332]
	BayK 8644	+	Once used to treat angina	[332]
	Bephratel	-	Clinically used to treat high blood pressure, angina and tachycardia	[300, 332]
Cav & TPC	Verapamil	-	Clinically used to treat high blood pressure, angina and tachycardia	[300, 332]
	Diltiazem	-	An alkaloid that simultaneously opens voltage dependant $\text{Na}^+$ channels, blocks $\text{Na}^+$ channel activation and induces $\text{Ca}^{2+}$ influx	[300]
Nav & TPC	Veratridine	-	Commonly used as local anaesthetics	[300]
	Amide (benzocaine, bupivacaine, dibucaine, etidocaine, lidocaine, mepivacaine, prilocaine, procaine, tetracaine, trimecaine)	-		



**Fig. 8. Diagram showing the local lysosomal  $\text{Ca}^{2+}$  amplified by the ER into a global  $\text{Ca}^{2+}$  signal. The primary  $\text{Ca}^{2+}$  release from lysosomes (in grey) triggers a subsequent release of  $\text{Ca}^{2+}$  from the ER (from [371]).**

secretion events such as the hormonal pancreatic release [66,380], cytotoxic T lymphocyte granule exocytosis [289] and mast cell histamine release [381]. The lysosomal TPC-ER interactions are also important regulators of endolysosomal trafficking, maturation, and fusion events [295,382–384] and have also been described to regulate smooth muscle contraction and  $\beta$ -adrenergic modulation of cardiomyocyte contractility [323,376] and in endothelial-colony forming cells [385].



**Fig. 9. Representation of endolysosomal traffic and interactions with the ER.** Endolysosomes closely interact with RyR and IP<sub>3</sub>R where  $\text{Ca}^{2+}$  release from TPCs triggers  $\text{Ca}^{2+}$  mobilization from the ER. Such lysosome-ER interaction is also required to replenish the  $\text{Ca}^{2+}$  stores. The  $\text{Ca}^{2+}/\text{H}^+$  exchanger (CAX) that pumps the  $\text{Ca}^{2+}$  back into the lysosomal lumen has not been clearly identified yet in mammals. Similarly, the lysosomal SERCA3 pump has been only observed in human platelets.

#### 4.5. Neuronal roles

Limited information exists about the role of NAADP and TPCs in the brain. An important study has described NAADP binding sites in rat whole brain regions, suggesting a prominent role of NAADP in the nervous system [386]. It is well known that mammalian neurons express both CD38 and SARM1, two enzymes that likely produce NAADP in neurons [27,38,133], and the endogenous cellular content of NAADP can be modulated by various physiological agonists such as glutamate [198,293,387]. Because glutamate is one of the most abundant neurotransmitters in the brain, the role of mGluR activation in NAADP production [198,387] has been further investigated and it appears that mGluR1 preferentially triggers the synthesis of NAADP in hippocampal neurons of mice [293]. In peripheral organs, hormones shown to stimulate NAADP synthesis include cholecystokinin [81] and oxytocin [388], two hormones showing receptors in the brain. For example, in the rat uterus, the binding of oxytocin to its receptor (OTR) induces an increase in endogenous NAADP levels and releases lysosomal  $\text{Ca}^{2+}$  to induce myometrial contraction [388]. Interestingly, OTR is widely expressed in the brain, but whether oxytocin induces NAADP production in the central nervous system has not yet been investigated. In the hypothalamus and pituitary gland, it has been suggested that OTR activation recruits CD38 and increases cADPR synthesis [138]. Interestingly, in these hypothalamic neurons, a positive autocrine feedback loop has been proposed in which cADPR produced in response to OTR activation is involved in additional oxytocin release from oxytocinergic neurons [138,142]. Intriguingly, exogenous addition of NAADP does not stimulate oxytocin secretion by itself in permeabilized neurons [142] whereas in other cell systems such as in the pancreas, NAADP and cADPR combine to control hormone and enzyme secretion [194,373,389]. So far, whether OTR signalling requires NAADP synthesis and lysosomal  $\text{Ca}^{2+}$  in hypothalamic neurons remain to be investigated.

Regarding NAADP action in neurons, several studies have injected NAADP and showed that in *A. californica* neurons [140] and neuromuscular junctions in frogs [390,391], NAADP induces cytosolic  $\text{Ca}^{2+}$  elevation and controls the secretion of acetylcholine. To sustain this neurotransmitter release, it was proposed that NAADP triggers  $\text{Ca}^{2+}$

from an unidentified store interacting with the ER [49,140,390,391]. The presynaptic effect of NAADP could be due to the presence of both ER and lysosomes in presynaptic terminals [392]. At a post-synaptic level, lysosomes are also present and could be exocytosed to release cathepsin and activate metalloprotease 9 (MMP9) which regulates structural plasticity of the dendritic spines in hippocampal neurons [217]. In this study, the authors demonstrated that the  $\text{Ca}^{2+}$  response evoked by back-propagating action potentials not only requires extracellular  $\text{Ca}^{2+}$  influx but also involves the lysosomal  $\text{Ca}^{2+}$  stores and NAADP [217]. These results suggest a role for lysosomes and NAADP signalling in long-term plasticity [217]. Exogenous addition of NAADP-containing liposomes have been shown to depolarize medullary neurons [67] and recently, a study proposed that TPCs play a key role in neuronal depolarization [293]. The authors recorded hippocampal neurons and showed that NAADP intracellular injection evoked depolarization of hippocampal neurons. Using a pharmacological approach, they showed that NAADP recruits both lysosomes and ER to generate this depolarizing effect. Importantly, the study elucidated the long-sought mechanism of mGluR1-induced neuronal depolarization. Indeed, they demonstrated that inhibition of NAADP signalling with either NAADP inhibitors or lysosomal disruptors abolished the mGluR1-induced cell depolarization [293]. The authors further proposed that the mGluR1-induced depolarization is mediated through the sequential activation of TPC2 and RyRs [293]. The  $\text{Ca}^{2+}$  released then inhibits the  $\text{Ca}^{2+}$ -sensitive SK channels in the plasma membrane, probably by activating the  $\text{Ca}^{2+}$ -dependent protein phosphatase 2A [293] that forms a macromolecular complex with SK channels [393,394]. The authors proposed that this mechanism might help to understand how mGluR1 can produce both synaptic potentiation and synaptic depression.

In addition to the effects of NAADP on adult neurons, CD38 is also greatly expressed at early developmental stages [95] suggesting a potential role for NAADP in neuronal development. Indeed, the addition of NAADP-containing liposomes induces neuronal differentiation in PC12 cell lines [395] and neurite outgrowth in cultures of rat cortical neurons [195]. Furthermore, using both exogenous cell-permeant NAADP-AM, and TPC2<sup>-/-</sup> mice, a study has shown that the neuronal differentiation of mouse embryonic stem cells occurs through TPC2 [290]. Recently, *in vivo* evidence has been reported for a neurodevelopmental role of NAADP and TPCs in the CNS development. Indeed, in zebrafishes, TPC2 are required for  $\text{Ca}^{2+}$  transients frequency involved in normal spinal circuitry maturation and in particular in the regulation of primary motor neuron innervation of the skeletal musculature by regulating the establishment of synchronized activity once innervation has taken place [330,331] (for review [292]).

#### 4.6. Glial roles

In glial cells, a few studies are available relating to the role of NAADP and TPCs. It has been reported that CD38 [96,99–102,326], lysosomes [209,210] and TPCs are present [324] in astrocytes. With regard to NAADP, it appears that intracellular NAADP mobilizes  $\text{Ca}^{2+}$  from lysosomes in astrocytes [324,326,327] whereas extracellular addition of NAADP can mobilize  $\text{Ca}^{2+}$  in rat astrocytes through activation of plasma membrane purinergic P2Y receptors [326,396]. On the other hand, it has been proposed that the astrocytic endogenous NAADP level is regulated by purinergic receptors activated by ATP as well as endothelin-1 [327]. This NAADP releases  $\text{Ca}^{2+}$  from “lysosome-related  $\text{Ca}^{2+}$  stores” [327], raising the potential of a role for TPCs such as demonstrated by Pereira *et al.* in astrocytic autophagy [324,387]. The authors demonstrated that intracellular microinjection of NAADP in cultured astrocytes evoked the release of lysosomal  $\text{Ca}^{2+}$  that subsequently stimulated autophagic vacuole formation. Using either over-expression of TPC2 or a dead-pore mutated TPC2, they further demonstrated that the NAADP-induced  $\text{Ca}^{2+}$  response relies on TPC2 [324]. The role of TPCs in autophagy has been also shown in peripheral cells [397–399] and cultured cells [400,401]. Overall, it has been

proposed that TPCs could be an ATP-sensor [268] and are inhibited by both ATP, and mTOR, an autophagic regulator [202,268,398,399]. Interestingly, mTOR is tethered to lysosomal membranes [402–404] and could inhibit both the PI(3, 5)P<sub>2</sub>-Na<sup>+</sup> [268] and the NAADP- $\text{Ca}^{2+}$  currents of TPCs [399]. The role of TPCs in autophagy in astrocytes and neurons is poorly understood and requires further study.

#### 4.7. Endothelial roles

Regional brain blood supply matches local metabolic demand and requires local vasodilation in active region [405–407]. These processes depend on interactions between endothelial cells and neurons. Endothelial cells have lysosomes [408] and their role in agonist-evoked  $\text{Ca}^{2+}$  signalling has been well-studied. One of the first study was published by Brailoiu's group which demonstrated that in endothelial cells, NAADP evokes  $\text{Ca}^{2+}$  release from lysosomes and also stimulates nitric oxide (NO) production to control blood pressure [409]. Filippini's group in a seminal study has demonstrated the role of NAADP and TPC2 in VEGF2-evoked  $\text{Ca}^{2+}$  release, NO production and neoangiogenesis [321]. Regarding brain endothelial cells, it has been shown that glutamate is one of the signalling molecules that acts on N-methyl-D-aspartate receptors (NMDARs) and mGluR located at the surface of endothelial cells [406,410]. Glutamate triggers the production of NO in a  $\text{Ca}^{2+}$ -dependent manner and NO eventually acts as a vasodilator agent. However, by which mechanism glutamate activation led to intracellular  $\text{Ca}^{2+}$  signals is poorly understood. Using various pharmacological tools in human and rodent brain microvascular endothelial cell lines, recent studies have proposed that glutamate, recruits IP<sub>3</sub> and NAADP signalling pathways as well as the lysosomal  $\text{Ca}^{2+}$  stores to evoke  $\text{Ca}^{2+}$  release and NO production [411–413]. Similarly, NAADP and lysosomal  $\text{Ca}^{2+}$  are recruited by acetylcholine and histamine to stimulate endothelial NO production [410,414]. At this point, it would be valuable to now explore the role of TPCs in brain microvascular endothelial cells as well as to identify the enzyme that may produce NAADP in response to physiological stimulation.

#### 5. Unanswered questions

Lysosomes have emerged in the last decade as an important hub between metabolism and  $\text{Ca}^{2+}$  signalling. Indeed, lysosomes have been mostly studied in regard to their degradative property and their involvement in numerous diseases link to cell degeneration. Most recently studies of  $\text{Ca}^{2+}$  signalling have demonstrated that lysosomes and the related acidic organelles are important sources of intracellular  $\text{Ca}^{2+}$  involved in cell proliferation, autophagy and secretion to name a few. Questioning how the lysosomal  $\text{Ca}^{2+}$  could be mobilized, researchers have discovered numerous endolysosomal  $\text{Ca}^{2+}$  channels, such as TRPML, TPCs and P2X4, for instance. How these channels are recruited and interact to control so many  $\text{Ca}^{2+}$ -dependent processes remain to be further investigated.

Only a limited number of studies have investigated the role of NAADP and the endolysosomal TPCs in the brain. NAADP-dependent lysosomal  $\text{Ca}^{2+}$  signalling has been described as modulating neurotransmitter release, neuronal differentiation, neuronal plasticity and astrogliial autophagy. However, whether NAADP recruiting TPCs is a general mechanism remains to be shown since in the periphery NAADP has multiple targets that are also expressed in the brain. Additionally, NAADP acts on RyR and two accessory proteins have been discovered that link either to TPCs (Lsm12, [71]) or couple RyR and TPC1 (JPT2, [69]). Additionally, several enzymes can produce NAADP such as CD38 [27,38] and SARM1 [133] but so far, no report exists describing a neuronal function linking either CD38 or SARM1 to TPC activity. For their part, TPCs could also be recruited independently of NAADP. Undeniably, evidence exists for higher complexity. Indeed, it has been reported that TPCs could also be recruited by either change in the cytosolic  $\text{Ca}^{2+}$  concentration [252,303,312,415] or by small molecules such as P

(3,5)IP<sub>2</sub> [308]. Neurons, astrocytes and endothelial cells integrate exceptional amounts of extracellular stimuli and generate adapted cellular responses. These adaptive responses greatly rely on intracellular machinery. In the brain, we know that mGluR1 activation recruits TPCs [293] but many other RCPGs may also have this property. Although some evidence exists that CD38 and mGluR signalling are linked, a demonstration that CD38 activation leads to NAADP-activated TPC signalling remains to be performed. It is early days and our knowledge about the intracellular pathways recruiting TPCs is at a nascent stage. Most of the studies have so far shown that lysosomal Ca<sup>2+</sup> and TPCs act by interacting with the ER and whether a cellular response will be modulated by pure lysosomal Ca<sup>2+</sup> signal remains to be shown (see “Lysosome and TPCs, the local Ca<sup>2+</sup> signal trigger”).

A precise characterization of endolysosomal Ca<sup>2+</sup> signalling is now crucial in the CNS. This leads us to the last point. The last decade has seen the development of numerous pharmacological tools that makes it possible to interfere with lysosomes, TPCs and the Ca<sup>2+</sup>-releasing messenger synthetizing enzymes CD38 and SARM1 (see “Pharmacological tools”). These pharmacological approaches have made it possible to outline the *in vitro* role of the lysosomal Ca<sup>2+</sup> and TPCs in secretion and autophagy for instance. It is important to note that mouse, pig, and zebrafish mutants are now available which make *in vivo* study possible and thus firmly establish the importance of lysosomal Ca<sup>2+</sup> signalling in brain functions. So far, the CD38<sup>-/-</sup> mouse have been the most studied model revealing the importance of CD38 in brain development, inflammation, plasticity and social behaviour (for review, [94,105]). The SARM1<sup>-/-</sup> mouse has been mostly studied in neuronal degeneration and whether SARM1 and CD38 are complementary or have a selective role in brain functions remained to be discovered. Finally, TPC mutant mice have been barely studied in the context of brain function, revealing so far, a role in plasticity and learning [293,329] and using TPC mutant zebrafish revealed their role in the regulation of primary motor neuron innervation of the skeletal musculature [330]. Recently, TPC mutant pigs have been developed that would permit to investigate higher brain function [416].

Future discoveries will rely on investigating the lysosomal Ca<sup>2+</sup> signalling in animal mutant models for studying brain function and dysfunction. This approach has been already valuable for CD38 which has been associated with a familial form of autism [154]. Finally, looking at polymorphisms of TPC and other endolysosomal proteins in humans would be a very promising avenue to understand the role of such proteins in normal brain function and also in pathological brain such as in social behaviour deficits and neurodegenerative diseases.

## Acknowledgement

LLM research is funded by Oxford University. JMC research is funded by the CNRS. Images were created using biorender.com.

## References

- [1] M.J. Berridge, Neuronal calcium signaling, *Neuron* 21 (1998) 13–26, [https://doi.org/10.1016/S0896-6273\(00\)80510-3](https://doi.org/10.1016/S0896-6273(00)80510-3).
- [2] Z. Padamsey, W.J. Foster, N.J. Emptage, Intracellular Ca<sup>2+</sup> Release and Synaptic Plasticity: A Tale of Many Stores, *Neurosci. Rev. J. Bringing Neurobiol. Neurol. Psychiatry.* 25 (2019) 208–226, <https://doi.org/10.1177/107385418785334>.
- [3] C. Grienberger, X. Chen, A. Konnerth, Dendritit function *in vivo*, *Trends Neurosci.* 38 (2015) 45–54, <https://doi.org/10.1016/j.tins.2014.11.002>.
- [4] T.A. Longden, D.C. Hill-Eubanks, M.T. Nelson, Ion channel networks in the control of cerebral blood flow, *J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab.* 36 (2016) 492–512, <https://doi.org/10.1177/0271678X15616138>.
- [5] G. Guerra, A. Lucariello, A. Perna, L. Botta, A. De Luca, F. Moccia, The Role of Endothelial Ca<sup>2+</sup> Signaling in Neurovascular Coupling: A View from the Lumen, *Int. J. Mol. Sci.* 19 (2018), <https://doi.org/10.3390/ijms19040938>. E938.
- [6] B.A. Simms, G.W. Zamponi, Neuronal voltage-gated calcium channels: structure, function, and dysfunction, *Neuron* 82 (2014) 24–45, <https://doi.org/10.1016/j.neuron.2014.03.016>.
- [7] S. Ebashi, F. Lipmann, Adenosine triphosphate-linked concentration of calcium ions in a particulate fraction of rabbit muscle, *J. Cell Biol.* (1962), <https://doi.org/10.1083/JCB.14.3.389>.
- [8] W. Hasselbach, Relaxing factor and the relaxation of muscle, *Prog. Biophys. Mol. Biol.* 14 (1964), [https://doi.org/10.1016/S0079-6107\(64\)80006-7](https://doi.org/10.1016/S0079-6107(64)80006-7), 167-IN2.
- [9] A. Martonosi, R. Feretos, Sarcoplasmic reticulum I. The uptake of Ca++ by sarcoplasmic reticulum fragments, *J. Biol. Chem.* 239 (1964) 648–658.
- [10] L.L. Costantin, C. Franzini-Armstrong, R.J. Podolsky, Localization of calcium-accumulating structures in striated muscle fibers, *Science* 147 (1965) 158–160, <https://doi.org/10.1126/science.147.3654.158>.
- [11] F.J. Samaha, J. Gergely, Ca++ uptake and ATPase of human sarcoplasmic reticulum, *J. Clin. Invest.* 44 (1965) 1425–1431, <https://doi.org/10.1172/JCI105248>.
- [12] A.S. Fairhurst, D.J. Jenden, Effect of ryanodine on the calcium uptake system of skeletal muscle, *Proc. Natl. Acad. Sci. U. S. A.* 48 (1962) 807–813, <https://doi.org/10.1073/pnas.48.5.807>.
- [13] L.R. Jones, H.R. Besch, J.L. Sutko, J.T. Willerson, Ryanodine-induced stimulation of net Ca++ uptake by cardiac sarcoplasmic reticulum vesicles, *J. Pharmacol. Exp. Ther.* 209 (1979) 48–55.
- [14] J.L. Sutko, K. Ito, J.L. Kenyon, Ryanodine: a modifier of sarcoplasmic reticulum calcium release in striated muscle, *Fed. Proc.* 44 (1985) 2984–2988.
- [15] T. Imagawa, J.S. Smith, R. Coronado, K.P. Campbell, Purified ryanodine receptor from skeletal muscle sarcoplasmic reticulum is the Ca<sup>2+</sup>-permeable pore of the calcium release channel, *J. Biol. Chem.* 262 (1987) 16636–16643.
- [16] L. Hymel, H. Schindler, L. Inui, S. Fleischer, Reconstitution of purified cardiac muscle calcium release channel (ryanodine receptor) in planar bilayers, *Biochem. Biophys. Res. Commun.* 152 (1988) 308–314, [https://doi.org/10.1016/s0006-291x\(88\)80715-0](https://doi.org/10.1016/s0006-291x(88)80715-0).
- [17] F.A. Lai, K. Anderson, E. Rousseau, Q.Y. Liu, G. Meissner, Evidence for a Ca<sup>2+</sup> channel within the ryanodine receptor complex from cardiac sarcoplasmic reticulum, *Biochem. Biophys. Res. Commun.* 151 (1988) 441–449, [https://doi.org/10.1016/0006-291x\(88\)90613-4](https://doi.org/10.1016/0006-291x(88)90613-4).
- [18] J.S. Smith, T. Imagawa, J. Ma, M. Fill, K.P. Campbell, R. Coronado, Purified ryanodine receptor from rabbit skeletal muscle is the calcium-release channel of sarcoplasmic reticulum, *J. Gen. Physiol.* 92 (1988) 1–26, <https://doi.org/10.1085/jgp.92.1.1>.
- [19] D.P. Rardon, D.C. Cefali, R.D. Mitchell, S.M. Seiler, L.R. Jones, High molecular weight proteins purified from cardiac junctional sarcoplasmic reticulum vesicles are ryanodine-sensitive calcium channels, *Circ. Res.* 64 (1989) 779–789, <https://doi.org/10.1161/01.res.64.4.779>.
- [20] M.J. Berridge, Rapid accumulation of inositol trisphosphate reveals that agonists hydrolyse polyphosphoinositides instead of phosphatidylinositol, *Biochem. J.* 212 (1983) 849–858, <https://doi.org/10.1042/bj2120849>.
- [21] H. Streb, E. Bayerdörffer, W. Haase, R.F. Irvine, I. Schulz, Effect of inositol-1,4,5-trisphosphate on isolated subcellular fractions of rat pancreas, *J. Membr. Biol.* 81 (1984) 241–253, <https://doi.org/10.1007/BF01868717>.
- [22] S. Supattapone, P.F. Worley, J.M. Baraban, S.H. Snyder, Solubilization, purification, and characterization of an inositol trisphosphate receptor, *J. Biol. Chem.* 263 (1988) 1530–1534.
- [23] K. Mikoshiba, Role of IP<sub>3</sub> receptor signaling in cell functions and diseases, *Adv. Biol. Regul.* 57 (2015) 217–227, <https://doi.org/10.1016/j.jbior.2014.10.001>.
- [24] N. Maeda, M. Niinobe, K. Nakahira, K. Mikoshiba, Purification and characterization of P400 protein, a glycoprotein characteristic of Purkinje cell, from mouse cerebellum, *J. Neurochem.* 51 (1988) 1724–1730, <https://doi.org/10.1111/j.1471-4159.1988.tb01151.x>.
- [25] M.J. Berridge, Inositol trisphosphate and calcium signalling mechanisms, *Biochim. Biophys. Acta.* 1793 (2009) 933–940, <https://doi.org/10.1016/j.bbamer.2008.10.005>.
- [26] G. Santulli, D. Lewis, A. des Georges, A.R. Marks, J. Frank, Ryanodine Receptor Structure and Function in Health and Disease, *Subcell. Biochem.* 87 (2018) 329–352, [https://doi.org/10.1007/978-10-7757-9\\_11](https://doi.org/10.1007/978-10-7757-9_11).
- [27] D.L. Clapper, T.F. Walseth, P.J. Dargie, H.C. Lee, Pyridine nucleotide metabolites stimulate calcium release from sea urchin egg microsomes desensitized to inositol trisphosphate, *J. Biol. Chem.* 262 (1987) 9561–9568.
- [28] C.H. Lee, L.E. Hokin, Inositol 1,2-cyclic 4,5-trisphosphate is an order of magnitude less potent than inositol 1,4,5-trisphosphate in mobilizing intracellular stores of calcium in mouse pancreatic acinar cells, *Biochem. Biophys. Res. Commun.* 159 (1989) 561–565, [https://doi.org/10.1016/0006-291x\(89\)90030-2](https://doi.org/10.1016/0006-291x(89)90030-2).
- [29] H.C. Lee, R. Aarhus, R. Graeff, M.E. Gurnack, T.F. Walseth, Cyclic ADP ribose activation of the ryanodine receptor is mediated by calmodulin, *Nature* 370 (1994) 307–309, <https://doi.org/10.1038/370307a0>.
- [30] A. Galione, H.C. Lee, W.B. Busa, Ca(2+)-induced Ca<sup>2+</sup> release in sea urchin egg homogenates: modulation by cyclic ADP-ribose, *Science* 253 (1991) 1143–1146, <https://doi.org/10.1126/science.1909457>.
- [31] M. Howard, J.C. Grimaldi, J.F. Bazan, F.E. Lund, L. Santos-Argumedo, R. M. Parkhouse, T.F. Walseth, H.C. Lee, Formation and hydrolysis of cyclic ADP-ribose catalyzed by lymphocyte antigen CD38, *Science* 262 (1993) 1056–1059, <https://doi.org/10.1126/science.8235624>.
- [32] H.C. Lee, R. Aarhus, Wide distribution of an enzyme that catalyzes the hydrolysis of cyclic ADP-ribose, *Biochim. Biophys. Acta.* 1164 (1993) 68–74, [https://doi.org/10.1016/0167-4838\(93\)90113-6](https://doi.org/10.1016/0167-4838(93)90113-6).
- [33] E. Zocchi, L. Franco, L. Guida, U. Benatti, A. Bargellesi, F. Malavasi, H.C. Lee, A. De Flora, A single protein immunologically identified as CD38 displays NAD+-glycohydrolase, ADP-ribosyl cyclase and cyclic ADP-ribose hydrolase activities at

- the outer surface of human erythrocytes, *Biochem. Biophys. Res. Commun.* 196 (1993) 1459–1465, <https://doi.org/10.1006/bbrc.1993.2416>.
- [34] C. Bernofsky, Nicotinic acid adenine dinucleotide phosphate (NAADP+), *Methods Enzymol.* 66 (1980) 105–112, [https://doi.org/10.1016/0076-6879\(80\)66446-5](https://doi.org/10.1016/0076-6879(80)66446-5).
- [35] H.C. Lee, R. Aarhus, A derivative of NADP mobilizes calcium stores insensitive to inositol triphosphate and cyclic ADP-ribose, *J. Biol. Chem.* 270 (1995) 2152–2157, <https://doi.org/10.1074/jbc.270.5.2152>.
- [36] E.N. Chini, T.P. Dousa, Enzymatic synthesis and degradation of nicotinate adenine dinucleotide phosphate (NAADP), a Ca(2+)-releasing agonist, in rat tissues, *Biochem. Biophys. Res. Commun.* 209 (1995) 167–174, <https://doi.org/10.1006/bbrc.1995.1485>.
- [37] E.N. Chini, K.W. Beers, T.P. Dousa, Nicotinate adenine dinucleotide phosphate (NAADP) triggers a specific calcium release system in sea urchin eggs, *J. Biol. Chem.* 270 (1995) 3216–3223, <https://doi.org/10.1074/jbc.270.7.3216>.
- [38] R. Aarhus, R.M. Graeff, D.M. Dickey, T.F. Walseth, H.C. Lee, ADP-ribosyl cyclase and CD38 catalyze the synthesis of a calcium-mobilizing metabolite from NADP, *J. Biol. Chem.* 270 (1995) 30327–30333, <https://doi.org/10.1074/jbc.270.51.30327>.
- [39] P.J. Dargie, M.C. Agre, H.C. Lee, Comparison of Ca2+ mobilizing activities of cyclic ADP-ribose and inositol triphosphate, *Cell Regul* 1 (1990) 279–290, <https://doi.org/10.1091/mbc.1.3.279>.
- [40] M. Albrieux, H.C. Lee, M. Villaz, Calcium signaling by cyclic ADP-ribose, NAADP, and inositol triphosphate are involved in distinct functions in ascidian oocytes, *J. Biol. Chem.* 273 (1998) 14566–14574, <https://doi.org/10.1074/jbc.273.23.14566>.
- [41] T.W. Thomas, W.R. Eckberg, F. Dubé, A. Galiano, Mechanisms of calcium release and sequestration in eggs of *Chaetopterus pergamentaceus*, *Cell Calcium* 24 (1998) 285–292, [https://doi.org/10.1016/s0143-4160\(98\)90052-5](https://doi.org/10.1016/s0143-4160(98)90052-5).
- [42] L. Santella, K. Kyozuka, A.A. Genazzani, L. De Riso, E. Carafoli, Nicotinic acid adenine dinucleotide phosphate-induced Ca(2+)-release. Interactions among distinct Ca(2+) mobilizing mechanisms in starfish oocytes, *J. Biol. Chem.* 275 (2000) 8301–8306, <https://doi.org/10.1074/jbc.275.12.8301>.
- [43] C. Bernofsky, W.J. Gallagher, Liquid chromatography of pyridine nucleotides and associated compounds and isolation of several analogs of nicotinamide adenine dinucleotide phosphate, *Anal. Biochem.* 67 (1975) 611–624, [https://doi.org/10.1016/0003-2697\(75\)90336-x](https://doi.org/10.1016/0003-2697(75)90336-x).
- [44] Y. Tong, J. Zull, L. Yu, Functional expression and signaling properties of cloned human parathyroid hormone receptor in Xenopus oocytes. Evidence for a novel signaling pathway, *J. Biol. Chem.* 271 (1996) 8183–8191, <https://doi.org/10.1074/jbc.271.14.8183>.
- [45] K. Iizuka, A. Yoshii, K. Dobashi, T. Horie, M. Mori, T. Nakazawa, InsP<sub>3</sub>, but not novel Ca2+-releasers, contributes to agonist-initiated contraction in rabbit airway smooth muscle, *J. Physiol.* 511 (Pt 3) (1998) 915–933, <https://doi.org/10.1111/j.1469-7793.1998.915bg.x>.
- [46] J.M. Cancela, G.C. Churchill, A. Galiano, Coordination of agonist-induced Ca2+-signalling patterns by NAADP in pancreatic acinar cells, *Nature* 398 (1999) 74–76, <https://doi.org/10.1038/18032>.
- [47] I. Berg, B.V. Potter, G.W. Mayr, A.H. Guse, Nicotinic acid adenine dinucleotide phosphate (NAADP(+)) is an essential regulator of T-lymphocyte Ca(2+)-signaling, *J. Cell. Biol.* 150 (2000) 581–588, <https://doi.org/10.1083/jcb.150.3.581>.
- [48] S. Patel, G.C. Churchill, A. Galiano, Coordination of Ca2+ signalling by NAADP, *Trends Biochem. Sci.* 26 (2001) 482–489, [https://doi.org/10.1016/s0968-0004\(01\)01896-5](https://doi.org/10.1016/s0968-0004(01)01896-5).
- [49] S. Bezin, G. Charpentier, P. Fossier, J.-M. Cancela, The Ca2+-releasing messenger NAADP, a new player in the nervous system, *J. Physiol. Paris* 99 (2006) 111–118, <https://doi.org/10.1016/j.jphysparis.2005.12.007>.
- [50] A. Galiano, A primer of NAADP-mediated Ca(2+) signalling: From sea urchin eggs to mammalian cells, *Cell Calcium* 58 (2015) 27–47, <https://doi.org/10.1016/j.ceca.2014.09.010>.
- [51] C.J. Penny, B.S. Kilpatrick, E.R. Eden, S. Patel, Coupling acidic organelles with the ER through Ca<sup>2+</sup> microdomains at membrane contact sites, *Cell Calcium* 58 (2015) 387–396, <https://doi.org/10.1016/j.ceca.2015.03.006>.
- [52] 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>.
- [53] T.F. Walseth, A.H. Guse, NAADP: From Discovery to Mechanism, *Front. Immunol.* 12 (2021), 703326, <https://doi.org/10.3389/fimmu.2021.703326>.
- [54] A. Mojzisová, O. Krizanová, L. Záćiková, V. Komínková, K. Ondrias, Effect of nicotinic acid adenine dinucleotide phosphate on ryanodine calcium release channel in heart, *Pflugers Arch* 441 (2001) 674–677, <https://doi.org/10.1007/s004240000465>.
- [55] M. Hohenegger, J. Suková, R. Gscheidlinger, H. Drobny, A. Zidar, Nicotinic acid-adenine dinucleotide phosphate activates the skeletal muscle ryanodine receptor, *Biochem. J.* 367 (2002) 423–431, <https://doi.org/10.1042/BJ20020584>.
- [56] J.V. Gerasimenko, Y. Maruyama, K. Yano, N.J. Dolman, A.V. Tepikin, O. H. Petersen, O.V. Gerasimenko, NAADP mobilizes Ca2+ from a thapsigargin-sensitive store in the nuclear envelope by activating ryanodine receptors, *J. Cell Biol.* 163 (2003) 271–282, <https://doi.org/10.1083/jcb.200306134>.
- [57] M.F. Langhorst, N. Schwarzmüller, A.H. Guse, Ca2+ release via ryanodine receptors and Ca2+ entry: major mechanisms in NAADP-mediated Ca2+ signaling in T-lymphocytes, *Cell. Signal.* 16 (2004) 1283–1289, <https://doi.org/10.1016/j.cellsig.2004.03.013>.
- [58] I.M.A. Wolf, B.-P. Diercks, E. Gattkowsky, F. Czarniak, J. Kempinski, R. Werner, D. Schetelig, H.-W. Mittrucker, V. Schumacher, M. von Osten, D. Lodygin, A. Flügel, R. Fliegert, A.H. Guse, Frontrunners of T cell activation: Initial, localized Ca2+ signals mediated by NAADP and the type 1 ryanodine receptor, *Sci. Signal.* 8 (2015), <https://doi.org/10.1126/scisignal.aab0863> ra102.
- [59] W. Dammermann, B. Zhang, M. Nebel, C. Cordigliero, F. Odoardi, T. Kirchberger, N. Kawakami, J. Dowden, F. Schmid, K. Dormair, M. Hohenegger, A. Flügel, A. H. Guse, B.V.L. Potter, NAADP-mediated Ca2+ signaling via type 1 ryanodine receptor in T cells revealed by a synthetic NAADP antagonist, *Proc. Natl. Acad. Sci. U. S. A.* 106 (2009) 10678–10683, <https://doi.org/10.1073/pnas.0809997106>.
- [60] G.C. Churchill, Y. Okada, J.M. Thomas, A.A. Genazzani, S. Patel, A. Galiano, NAADP mobilizes Ca(2+) from reserve granules, lysosome-related organelles, in sea urchin eggs, *Cell* 111 (2002) 703–708, [https://doi.org/10.1016/s0092-8674\(02\)01082-6](https://doi.org/10.1016/s0092-8674(02)01082-6).
- [61] A. Menteyne, A. Burdakov, G. Charpentier, O.H. Petersen, J.-M. Cancela, Generation of specific Ca(2+) signals from Ca(2+) stores and endocytosis by differential coupling to messengers, *Curr. Biol.* 16 (2006) 1931–1937, <https://doi.org/10.1016/j.cub.2006.07.070>.
- [62] A. Beck, M. Kolisek, L.A. Bagley, A. Fleig, R. Penner, Nicotinic acid adenine dinucleotide phosphate and cyclic ADP-ribose regulate TRPM2 channels in T lymphocytes, *FASEB J.* Off. Publ. Fed. Am. Soc. Exp. Biol. 20 (2006) 962–964, <https://doi.org/10.1096/fj.05-5538fje>.
- [63] B. Tóth, I. Iordanov, L. Csányi, Ruling out pyridine dinucleotides as true TRPM2 channel activators reveals novel direct agonist ADP-ribose-2'-phosphate, *J. Gen. Physiol.* 145 (2015) 419–430, <https://doi.org/10.1085/jgp.201511377>.
- [64] F. Zhang, P.-L. Li, Reconstitution and Characterization of a Nicotinic Acid Adenine Dinucleotide Phosphate (NAADP)-sensitive Ca2+ Release Channel from Liver Lysosomes of Rats, *J. Biol. Chem.* 282 (2007) 25259–25269, <https://doi.org/10.1074/jbc.M701614200>.
- [65] S. Yamaguchi, A. Jha, Q. Li, A.A. Soyombo, G.D. Dickinson, D. Churamani, E. Brailoiu, S. Patel, S. Mualem, Transient Receptor Potential Mucolipin 1 (TRPML1) and Two-pore Channels Are Functionally Independent Organellar Ion Channels, *J. Biol. Chem.* 286 (2011) 22934–22942, <https://doi.org/10.1074/jbc.M110.210930>.
- [66] P.J. Calcraft, M. Ruas, Z. Pan, X. Cheng, A. Arredouani, X. Hao, J. Tang, K. Rieddorf, 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. Galiano, M.X. Zhu, NAADP mobilizes calcium from acidic organelles through two-pore channels, *Nature* 459 (2009) 596–600, <https://doi.org/10.1038/nature08030>.
- [67] 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>.
- [68] 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 Ca(2+)-release from lysosomal stores, *Pflugers Arch* 458 (2009) 891–899, <https://doi.org/10.1007/s00424-009-0690-y>.
- [69] G.S. Gunaratne, E. Brailoiu, S. He, S. Patel, J.T. Slama, T. Walseth, J.S. Marchant, Jupiter Microtubule Associated Homolog 2 is a Nicotinic Acid Adenine Dinucleotide Phosphate (NAADP) Binding Protein Required for NAADP-Evoked Intracellular Calcium Release, *Biophys. J.* 120 (2021), <https://doi.org/10.1016/j.bpj.2020.11.562>, 54a.
- [70] H.G. Roggenkamp, I. Khansahib, L.C. Hernandez C, Y. Zhang, D. Lodygin, A. Krüger, F. Gu, F. Möckl, A. Löhdorf, 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> eabd5647.
- [71] 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), <https://doi.org/10.1038/s41467-021-24735-z>, 4739.
- [72] E.L. Reinherz, L. Moretta, M. Roper, J.M. Breard, M.C. Mingari, M.D. Cooper, S. F. Schlossman, Human T lymphocyte subpopulations defined by Fc receptors and monoclonal antibodies. A comparison, *J. Exp. Med.* 151 (1980) 969–974, <https://doi.org/10.1084/jem.151.4.969>.
- [73] A.K. Bhan, E.L. Reinherz, S. Poppema, R.T. McCluskey, S.F. Schlossman, Location of T cell and major histocompatibility complex antigens in the human thymus, *J. Exp. Med.* 152 (1980) 771–782, <https://doi.org/10.1084/jem.152.4.771>.
- [74] D.G. Jackson, J.I. Bell, Isolation of a cDNA encoding the human CD38 (T10) molecule, a cell surface glycoprotein with an unusual discontinuous pattern of expression during lymphocyte differentiation, *J. Immunol. Baltim. Md* 1950 144 (1990) 2811–2815.
- [75] M. Alessio, S. Roggero, A. Funaro, L.B. De Monte, L. Peruzzi, M. Geuna, F. Malavasi, CD38 molecule: structural and biochemical analysis on human T lymphocytes, thymocytes, and plasma cells, *J. Immunol. Baltim. Md* 1950 145 (1990) 878–884.
- [76] S. Takasawa, A. Tohgo, N. Noguchi, T. Koguma, K. Nata, T. Sugimoto, H. Yonekura, H. Okamoto, Synthesis and hydrolysis of cyclic ADP-ribose by human leukocyte antigen CD38 and inhibition of the hydrolysis by ATP, *J. Biol. Chem.* 268 (1993) 26052–26054.
- [77] D.J. States, T.F. Walseth, H.C. Lee, Similarities in amino acid sequences of *Aplysia* ADP-ribosyl cyclase and human lymphocyte antigen CD38, *Trends Biochem. Sci.* 17 (1992) 495, [https://doi.org/10.1016/0968-0004\(92\)90337-9](https://doi.org/10.1016/0968-0004(92)90337-9).
- [78] H. Kim, E.L. Jacobson, M.K. Jacobson, Position of cyclization in cyclic ADP-ribose, *Biochem. Biophys. Res. Commun.* 194 (1993) 1143–1147, <https://doi.org/10.1006/bbrc.1993.1941>.

- [79] H. Muller-Steffner, M. Muzard, N. Oppenheimer, F. Schuber, Mechanistic implications of cyclic ADP-ribose hydrolysis and methanolysis catalyzed by calf spleen NAD<sup>+</sup>-glycohydrolase, *Biochem. Biophys. Res. Commun.* 204 (1994) 1279–1285, <https://doi.org/10.1006/bbrc.1994.2601>.
- [80] E. Zocchi, L. Franco, L. Guida, L. Calder, A. De Flora, Self-aggregation of purified and membrane-bound erythrocyte CD38 induces extensive decrease of its ADP-ribosyl cyclase activity, *FEBS Lett* 359 (1995) 35–40, [https://doi.org/10.1016/0014-5793\(95\)0005-t](https://doi.org/10.1016/0014-5793(95)0005-t).
- [81] 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 Ca<sup>2+</sup> mobilization from lysosomes in pancreatic acinar cells, *J. Biol. Chem.* 285 (2010) 38251–38259, <https://doi.org/10.1074/jbc.M110.125864>.
- [82] S.-Y. Rah, M. Mushtaq, T.-S. Nam, S.H. Kim, U.-H. Kim, Generation of cyclic ADP-ribose and nicotinic acid adenine dinucleotide phosphate by CD38 for Ca<sup>2+</sup> signaling in interleukin-8-treated lymphokine-activated killer cells, *J. Biol. Chem.* 285 (2010) 21877–21887, <https://doi.org/10.1074/jbc.M109.066290>.
- [83] 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>.
- [84] T.-S. Nam, D.-R. Park, S.-Y. Rah, T.-G. Woo, H.T. Chung, C. Brenner, U.-H. Kim, Interleukin-8 drives CD38 to form NAADP from NADP<sup>+</sup> and NAAD in the endolysosomes to mobilize Ca<sup>2+</sup> and effect cell migration, *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* 34 (2020) 12565–12576, <https://doi.org/10.1096/fj.202001249R>.
- [85] E. Zocchi, C. Usai, L. Guida, L. Franco, S. Bruzzone, M. Passalacqua, A. De Flora, Ligand-induced internalization of CD38 results in intracellular Ca<sup>2+</sup> mobilization: role of NAD<sup>+</sup> transport across cell membranes, *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* 13 (1999) 273–283, <https://doi.org/10.1096/fasebj.13.2.273>.
- [86] L. Yalcinteppe, S. Ercelen, S. Adin-Cinar, S. Badur, D. Tiryaki, E. Bermek, Hemin-dependent induction and internalization of CD38 in K562 cells, *J. Cell. Biochem.* 90 (2003) 379–386, <https://doi.org/10.1002/jcb.10637>.
- [87] S.-Y. Rah, K.-H. Park, T.-S. Nam, S.-J. Kim, H. Kim, M.-J. Im, U.-H. Kim, Association of CD38 with nonmuscle myosin heavy chain IIA and Lck is essential for the internalization and activation of CD38, *J. Biol. Chem.* 282 (2007) 5653–5660, <https://doi.org/10.1074/jbc.M609478200>.
- [88] 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>.
- [89] Y.J. Zhao, C.M.C. Lam, H.C. Lee, The membrane-bound enzyme CD38 exists in two opposing orientations, *Sci. Signal.* 5 (2012), <https://doi.org/10.1126/scisignal.2007200> ra67.
- [90] J. Liu, Y.J. Zhao, W.H. Li, Y.N. Hou, T. Li, Z.Y. Zhao, C. Fang, S.L. Li, H.C. Lee, Cytosolic interaction of type III human CD38 with CIB1 modulates cellular cyclic ADP-ribose levels, *Proc. Natl. Acad. Sci. U. S. A.* 114 (2017) 8283–8288, <https://doi.org/10.1073/pnas.1703718114>.
- [91] 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 Ca<sup>2+</sup>-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>.
- [92] S. Bruzzone, L. Franco, L. Guida, E. Zocchi, P. Contini, A. Bisso, C. Usai, A. De Flora, A cell-restricted CD38-connexin 43 cross-talk affects NAD<sup>+</sup> and cyclic ADP-ribose metabolism and regulates intracellular calcium in 3T3 fibroblasts, *J. Biol. Chem.* 276 (2001) 48300–48308, <https://doi.org/10.1074/jbc.M107308200>.
- [93] L.L. Martucci, M. Amar, R. Chaussenot, G. Benet, O. Bauer, A. de Zélicourt, A. Nosjean, J.-M. Launay, J. Callebert, C. Sebrié, A. Galione, J.-M. Edeline, S. de la Porte, P. Fossier, S. Granon, C. Vaillend, J.-M. Cancela, A multiscale analysis in CD38 –/– mice unveils major prefrontal cortex dysfunctions, *FASEB J.* (2019), <https://doi.org/10.1096/fj.201800489R>.
- [94] H. Higashida, M. Hashii, Y. Tanaka, S. Matsukawa, Y. Higuchi, R. Gabata, M. Tsubomoto, N. Seishima, M. Teramachi, T. Kamijima, T. Hattori, O. Hori, C. Tsuji, S.M. Cherepanov, A.A. Shabalova, M. Gerasimenko, K. Minami, S. Yokoyama, S. Munesue, A. Harashima, Y. Yamamoto, A.B. Salmina, O. Lopatina, CD38, CD157, and RAGE as Molecular Determinants for Social Behavior, *Cells* 9 (2020) 62, <https://doi.org/10.3390/cells9010062>.
- [95] C. Ceni, N. Pochon, V. Brun, H. Muller-Steffner, A. Andrieux, D. Grunwald, F. Schuber, M. De Waard, F. Lund, M. Villaz, M.-J. Moutin, CD38-dependent ADP-ribosyl cyclase activity in developing and adult mouse brain, *Biochem. J.* 370 (2003) 175–183, <https://doi.org/10.1042/BJ020020604>.
- [96] M. Yamada, M. Mizuguchi, N. Otsuka, K. Ikeda, H. Takahashi, Ultrastructural localization of CD38 immunoreactivity in rat brain, *Brain Res* 756 (1997) 52–60, [https://doi.org/10.1016/s0006-8993\(97\)00117-0](https://doi.org/10.1016/s0006-8993(97)00117-0).
- [97] N. Braidy, A. Poljak, R. Grant, T. Jayasena, H. Mansour, T. Chan-Ling, G. J. Guillemin, G. Smythe, P. Sachdev, Mapping NAD(+) metabolism in the brain of ageing Wistar rats: potential targets for influencing brain senescence, *Biogerontology* 15 (2014) 177–198, <https://doi.org/10.1007/s10522-013-9489-5>.
- [98] M. Mizuguchi, N. Otsuka, M. Sato, Y. Ishii, S. Kon, M. Yamada, H. Nishina, T. Katada, K. Ikeda, Neuronal localization of CD38 antigen in the human brain, *Brain Res* 697 (1995) 235–240, [https://doi.org/10.1016/0006-8993\(95\)00085-t](https://doi.org/10.1016/0006-8993(95)00085-t).
- [99] C. Verderio, S. Bruzzone, E. Zocchi, E. Fedele, U. Schenk, A. De Flora, M. Matteoli, Evidence of a role for cyclic ADP-ribose in calcium signalling and neurotransmitter release in cultured astrocytes, *J. Neurochem.* 78 (2001) 646–657, <https://doi.org/10.1046/j.1471-4159.2001.00455.x>.
- [100] W. Kou, S. Banerjee, J. Eudy, L.M. Smith, R. Persidsky, K. Borgmann, L. Wu, N. Sakhija, M.S. Deshpande, T.F. Walseth, A. Ghorpade, CD38 regulation in activated astrocytes: implications for neuroinflammation and HIV-1 brain infection, *J. Neurosci. Res.* 87 (2009) 2326–2339, <https://doi.org/10.1002/jnr.22060>.
- [101] M.K. Mamik, S. Banerjee, T.F. Walseth, R. Hirte, L. Tang, K. Borgmann, A. Ghorpade, HIV-1 and IL-1β regulate astrocytic CD38 through mitogen-activated protein kinases and nuclear factor-κB signaling mechanisms, *J. Neuroinflammation* 8 (2011) 145, <https://doi.org/10.1186/1742-2094-8-145>.
- [102] Y. Ma, D. Wu, X. Ding, W. Ying, CD38 plays key roles in both antioxidation and cell survival of H2O2-treated primary rodent astrocytes, *Int. J. Physiol. Pathophysiol. Pharmacol.* 6 (2014) 102–108.
- [103] L. Mayo, J. Jacob-Hirsch, N. Amariglio, G. Rechavi, M.-J. Moutin, F.E. Lund, R. Stein, Dual role of CD38 in microglial activation and activation-induced cell death, *J. Immunol. Baltim. Md 1950* 181 (2008) 92–103, <https://doi.org/10.4049/jimmunol.181.1.92>.
- [104] Y. Ma, W. Cao, L. Wang, J. Jiang, H. Nie, B. Wang, X. Wei, W. Ying, Basal CD38/cyclic ADP-ribose-dependent signaling mediates ATP release and survival of microglia by modulating connexin 43 hemichannels, *Glia* 62 (2014) 943–955, <https://doi.org/10.1002/glia.22651>.
- [105] S. Guerreiro, A.-L. Privat, L. Bressac, D. Toulorge, CD38 in Neurodegeneration and Neuroinflammation, *Cells* 9 (2020), <https://doi.org/10.3390/cells9020471>.
- [106] S. Bruzzone, C. Verderio, U. Schenk, E. Fedele, E. Zocchi, M. Matteoli, A. De Flora, Glutamate-mediated overexpression of CD38 in astrocytes cultured with neurones, *J. Neurochem.* 89 (2004) 264–272, <https://doi.org/10.1111/j.1471-4159.2003.02326.x>.
- [107] T. Hattori, M. Kaji, H. Ishii, R. Jureepon, M. Takarada-Iemata, H. Minh Ta, T. Manh Le, A. Konno, H. Hirai, Y. Shiraishi, N. Ozaki, Y. Yamamoto, H. Okamoto, S. Yokoyama, H. Higashida, Y. Kitao, O. Hori, CD38 positively regulates postnatal development of astrocytes cell-autonomously and oligodendrocytes non-cell-autonomously, *Glia* 65 (2017) 974–989, <https://doi.org/10.1002/glia.23139>.
- [108] H.C. Lee, R. Aarhus, ADP-ribosyl cyclase: an enzyme that cyclizes NAD<sup>+</sup> into a calcium-mobilizing metabolite, *Cell Regul* 2 (1991) 203–209, <https://doi.org/10.1091/mcb.2.3.203>.
- [109] K. Nata, T. Sugimoto, A. Tohgo, T. Takamura, N. Noguchi, A. Matsuoka, T. Numakunai, K. Shikama, H. Yonekura, S. Takasawa, The structure of the Aplysia kurodai gene encoding ADP-ribosyl cyclase, a second-messenger enzyme, *Gene* 158 (1995) 213–218, [https://doi.org/10.1016/0378-1199\(95\)00095-n](https://doi.org/10.1016/0378-1199(95)00095-n).
- [110] Q. Liu, I.A. Kriksunov, R. Graeff, C. Munshi, H.C. Lee, Q. Hao, Crystal Structure of Human CD38 Extracellular Domain, *Structure* 13 (2005) 1331–1339, <https://doi.org/10.1016/j.str.2005.05.012>.
- [111] E. Ferrero, A.C. Faini, F. Malavasi, A phylogenetic view of the leukocyte ectonucleotidases, *Immunol. Lett.* 205 (2019) 51–58, <https://doi.org/10.1016/j.imlet.2018.06.008>.
- [112] H.C. Lee, Cyclic ADP-ribose and NAADP: fraternal twin messengers for calcium signaling, *Sci. China Life Sci.* 54 (2011) 699–711, <https://doi.org/10.1007/s11427-011-4197-3>.
- [113] L.C. Davis, A.J. Morgan, M. Ruas, J.L. Wong, R.M. Graeff, A.J. Poustka, H.C. Lee, G.M. Wessel, J. Parrington, A. Galione, Ca(2+) signaling occurs via second messenger release from intraorganelle synthesis sites, *Curr. Biol. CB* 18 (2008) 1612–1618, <https://doi.org/10.1016/j.cub.2008.09.024>.
- [114] S.P. Goodrich, H. Muller-Steffner, A. Osman, M.-J. Moutin, K. Kusser, A. Roberts, D.L. Woodland, T.D. Randall, E. Kellenberger, P.T. LoVerde, F. Schuber, F. E. Lund, Production of calcium-mobilizing metabolites by a novel member of the ADP-ribosyl cyclase family expressed in *Schistosoma mansoni*, *Biochemistry* 44 (2005) 11082–11097, <https://doi.org/10.1021/bi050704r>.
- [115] C. Ceni, N. Pochon, M. Villaz, H. Muller-Steffner, F. Schuber, J. Baratier, M. De Waard, M. Ronjat, M.-J. Moutin, The CD38-independent ADP-ribosyl cyclase from mouse brain synaptosomes: a comparative study of neonate and adult brain, *Biochem. J.* 395 (2006) 417–426, <https://doi.org/10.1042/BJ20051321>.
- [116] J.J. Kelu, S.E. Webb, A. Galione, A.L. Miller, Characterization of ADP-ribosyl cyclase 1-like (ARC1-like) activity and NAADP signaling during slow muscle cell development in zebrafish embryos, *Dev. Biol.* 445 (2019) 211–225, <https://doi.org/10.1016/j.ydbio.2018.11.005>.
- [117] H.C. Lee, Structure and enzymatic functions of human CD38, *Mol. Med. Camb. Mass.* 12 (2006) 317–323, <https://doi.org/10.2119/2006-00086.Lee>.
- [118] E. Ferrero, N. Lo Buono, A.L. Horenstein, A. Funaro, F. Malavasi, The ADP-ribosyl cyclases—the current evolutionary state of the ARCs, *Front. Biosci. Landmark Ed.* 19 (2014) 986–1002, <https://doi.org/10.2741/4262>.
- [119] H.R. Katz, P.A. LeBlanc, S.W. Russell, Two classes of mouse mast cells delineated by monoclonal antibodies, *Proc. Natl. Acad. Sci. U. S. A.* 80 (1983) 5916–5918, <https://doi.org/10.1073/pnas.80.19.5916>.
- [120] O. Muraoka, H. Tanaka, M. Itoh, K. Ishihara, T. Hirano, Genomic structure of human BST-1, *Immunol. Lett.* 54 (1996) 1–4, [https://doi.org/10.1016/s0165-2478\(96\)02633-8](https://doi.org/10.1016/s0165-2478(96)02633-8).
- [121] M. Itoh, K. Ishihara, H. Tomizawa, H. Tanaka, Y. Kobune, J. Ishikawa, T. Kaisho, T. Hirano, Molecular cloning of murine BST-1 having homology with CD38 and Aplysia ADP-ribosyl cyclase, *Biochem. Biophys. Res. Commun.* 203 (1994), <https://doi.org/10.1006/bbrc.1994.2325>.
- [122] Y. Hirata, N. Kimura, K. Sato, Y. Ohsugi, S. Takasawa, H. Okamoto, J. Ishikawa, T. Kaisho, K. Ishihara, T. Hirano, ADP ribosyl cyclase activity of a novel bone

- marrow stromal cell surface molecule, BST-1, FEBS Lett 356 (1994) 244–248, [https://doi.org/10.1016/0014-5793\(94\)01279-2](https://doi.org/10.1016/0014-5793(94)01279-2).
- [123] A.M. Hussain, H.C. Lee, C.F. Chang, Functional expression of secreted mouse BST-1 in yeast, Protein Expr. Purif. 12 (1998) 133–137, <https://doi.org/10.1006/prep.1997.0811>.
- [124] K. Ishihara, T. Hirano, BST-1/CD157 regulates the humoral immune responses in vivo, Chem. Immunol. 75 (2000) 235–255, <https://doi.org/10.1159/000058772>.
- [125] F. Malavasi, S. Deaglio, A. Funaro, E. Ferrero, A.L. Horenstein, E. Ortolan, T. Vaisitti, S. Aydin, Evolution and function of the ADP ribosyl cyclase/CD38 gene family in physiology and pathology, Physiol. Rev. 88 (2008) 841–886, <https://doi.org/10.1152/physrev.00035.2007>.
- [126] H.C. Lee, Cyclic ADP-ribose and nicotinic acid adenine dinucleotide phosphate (NAADP) as messengers for calcium mobilization, J. Biol. Chem. 287 (2012) 31633–31640, <https://doi.org/10.1074/jbc.R112.349464>.
- [127] O. Lopatina, T. Yoshihara, T. Nishimura, J. Zhong, S. Akther, A.A.K.M. Fakhru, M. Liang, C. Higashida, K. Sumi, K. Furuhara, Y. Inahata, J.-J. Huang, K. Koizumi, S. Yokoyama, T. Tsuji, Y. Petugina, A. Sunarov, A.B. Salmina, K. Hashida, Y. Kitao, O. Hori, M. Asano, Y. Kitamura, T. Kozaka, K. Shiba, F. Zhong, M.-J. Xie, M. Sato, K. Ishihara, H. Higashida, Anxiety- and depression-like behavior in mice lacking the CD157/BST1 gene, a risk factor for Parkinson's disease, Front. Behav. Neurosci. 8 (2014) 133, <https://doi.org/10.3389/fnbeh.2014.00133>.
- [128] H. Higashida, M. Liang, T. Yoshihara, S. Akther, A. Fakhru, C. Stanislav, T.-S. Nam, U.-H. Kim, S. Kasai, T. Nishimura, N. Al Mahmuda, S. Yokoyama, K. Ishihara, M. Gerasimenko, A. Salmina, J. Zhong, T. Tsuji, C. Tsuji, O. Lopatina, An immunohistochemical, enzymatic, and behavioral study of CD157/BST1 as a neuroregulator, BMC Neurosci 18 (2017) 35, <https://doi.org/10.1186/s12868-017-0350-7>.
- [129] M. Pehar, B.A. Harlan, K.M. Kilroy, M.R. Vargas, Nicotinamide Adenine Dinucleotide Metabolism and Neurodegeneration, Antioxid. Redox Signal. 28 (2018) 1652–1668, <https://doi.org/10.1089/ars.2017.7145>.
- [130] J. Gerdts, E.J. Brace, Y. Sasaki, A. DiAntonio, J. Milbrandt, SARM1 activation triggers axon degeneration locally via NAD<sup>+</sup> destruction, Science 348 (2015) 453–457, <https://doi.org/10.1126/science.1258366>.
- [131] D.W. Summers, D.A. Gibson, A. DiAntonio, J. Milbrandt, SARM1-specific motifs in the TIR domain enable NAD<sup>+</sup> loss and regulate injury-induced SARM1 activation, Proc. Natl. Acad. Sci. 113 (2016), <https://doi.org/10.1073/pnas.1601506113>. E6271–E6280.
- [132] K. Esumma, D.W. Summers, Y. Sasaki, X. Mao, A. DiAntonio, J. Milbrandt, The SARM1 Toll/Interleukin-1 Receptor Domain Possesses Intrinsic NAD<sup>+</sup> Cleavage Activity that Promotes Pathological Axonal Degeneration, Neuron 93 (2017), <https://doi.org/10.1016/j.neuron.2017.02.022>, 1334–1343.e5.
- [133] Z.Y. Zhao, X.J. Xie, W.H. Li, J. Liu, Z. Chen, B. Zhang, T. Li, S.L. Li, J.G. Lu, L. Zhang, L. Zhang, Z. Xu, H.C. Lee, Y.J. Zhao, A Cell-Permeant Mimetic of NMN Activates SARM1 to Produce Cyclic ADP-Ribose and Induce Non-apoptotic Cell Death, iScience 15 (2019) 452–466, <https://doi.org/10.1016/j.isci.2019.05.001>.
- [134] J. Gerdts, D.W. Summers, Y. Sasaki, A. DiAntonio, J. Milbrandt, Sarm1-mediated axon degeneration requires both SAM and TIR interactions, J. Neurosci. Off. J. Soc. Neurosci. 33 (2013) 13569–13580, <https://doi.org/10.1523/JNEUROSCI.1197-13.2013>.
- [135] Y. Sasaki, T.M. Engber, R.O. Hughes, M.D. Figley, T. Wu, T. Bosanac, R. Devraj, J. Milbrandt, R. Krauss, A. DiAntonio, cADPR is a gene dosage-sensitive biomarker of SARM1 activity in healthy, compromised, and degenerating axons, Exp. Neurol. 329 (2020), 113252, <https://doi.org/10.1016/j.expneuro.2020.113252>.
- [136] F. Gu, A. Krüger, H.G. Roggenkamp, R. Alpers, D. Lodygin, V. Jaquet, F. Möckl, L. C. Hernandez C, K. Winterberg, A. Bauche, A. Rosche, H. Grasberger, J.Y. Kao, D. Schetelig, R. Werner, K. Schröder, M. Carte, A.G. Bowie, S. Huber, C. Meier, H.-W. Mittrucker, J. Heeren, K.-H. Krause, A. Flügel, B.-P. Diercks, A.H. Guse, Dual NADPH oxidases DUOX1 and DUOX2 synthesize NAADP and are necessary for Ca<sup>2+</sup> signaling during T cell activation, Sci. Signal. 14 (2021), <https://doi.org/10.1126/scisignal.abe3800> eabe3800.
- [137] H.C. Lee, Physiological functions of cyclic ADP-ribose and NAADP as calcium messengers, Annu. Rev. Pharmacol. Toxicol. 41 (2001) 317–345, <https://doi.org/10.1146/annurev.pharmtox.41.1.317>.
- [138] O. Lopatina, H.-X. Liu, S. Amina, M. Hashii, H. Higashida, Oxytocin-induced elevation of ADP-ribosyl cyclase activity, cyclic ADP-ribose or Ca(2+) concentrations is involved in autoregulation of oxytocin secretion in the hypothalamus and posterior pituitary in male mice, Neuropharmacology 58 (2010) 50–55, <https://doi.org/10.1016/j.neuropharm.2009.06.012>.
- [139] J.P. Mothet, P. Fossier, F.M. Meunier, J. Stinnakre, L. Tauc, G. Baux, Cyclic ADP-ribose and calcium-induced calcium release regulate neurotransmitter release at a cholinergic synapse of Aplysia, J. Physiol. 507 (P2) (1998) 405–414, <https://doi.org/10.1111/j.1469-7793.1998.405bt.x>.
- [140] P. Chameau, Y. Van de Vrede, P. Fossier, G. Baux, Ryanodine-, IP3- and NAADP-dependent calcium stores control acetylcholine release, Pflügers Arch 443 (2001) 289–296, <https://doi.org/10.1007/s00420100691>.
- [141] S.M. Soares, M. Thompson, E.N. Chini, Role of the second-messenger cyclic-adenosine 5'-diphosphate-ribose on adrenocorticotropin secretion from pituitary cells, Endocrinology 146 (2005) 2186–2192, <https://doi.org/10.1210/en.2004-1298>.
- [142] D. Jin, H.-X. Liu, H. Hirai, T. Torashima, T. Nagai, O. Lopatina, N.A. Shnayder, K. Yamada, M. Noda, T. Seike, K. Fujita, S. Takasawa, S. Yokoyama, K. Koizumi, Y. Shiraishi, S. Tanaka, M. Hashii, T. Yoshihara, K. Higashida, M.S. Islam, N. Yamada, K. Hayashi, N. Noguchi, I. Kato, H. Okamoto, A. Matsushima, A. Salmina, T. Munesue, N. Shimizu, S. Mochida, M. Asano, H. Higashida, CD38 is critical for social behaviour by regulating oxytocin secretion, Nature 446 (2007) 41–45, <https://doi.org/10.1038/nature05526>.
- [143] M. Reyes-Harde, R. Empson, B.V. Potter, A. Galione, P.K. Stanton, Evidence of a role for cyclic ADP-ribose in long-term synaptic depression in hippocampus, Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 4061–4066.
- [144] T. Budde, F. Sieg, K.H. Braunewell, E.D. Gundelfinger, H.C. Pape, Ca2+-induced Ca2+ release supports the relay mode of activity in thalamocortical cells, Neuron 26 (2000) 483–492, [https://doi.org/10.1016/S0896-6273\(00\)81180-0](https://doi.org/10.1016/S0896-6273(00)81180-0).
- [145] R. Bal, G. Ozturk, E.O. Etem, E. Eraslan, S. Ozaydin, Modulation of the excitability of stellate neurons in the ventral cochlear nucleus of mice by TRPM2 channels, Eur. J. Pharmacol. 882 (2020), 173163, <https://doi.org/10.1016/j.ejphar.2020.173163>.
- [146] S. Bezin, G. Charpentier, H.C. Lee, G. Baux, P. Fossier, J.-M. Cancela, Regulation of nuclear Ca2+ signaling by translocation of the Ca2+ messenger synthesizing enzyme ADP-ribosyl cyclase during neuronal depolarization, J. Biol. Chem. 283 (2008) 27859–27870, <https://doi.org/10.1074/jbc.M804701200>.
- [147] G.S. Young, E.L. Jacobson, J.B. Kirkland, Water maze performance in young male Long-Evans rats is inversely affected by dietary intakes of niacin and may be linked to levels of the NAD+ metabolite cADPR, J. Nutr. 137 (2007) 1050–1057, <https://doi.org/10.1093/jn/137.4.1050>.
- [148] M. Reyes-Harde, B.V. Potter, A. Galione, P.K. Stanton, Induction of hippocampal LTD requires nitric-oxide-stimulated PKG activity and Ca2+ release from cyclic ADP-ribose-sensitive stores, J. Neurophysiol. 82 (1999) 1569–1576, <https://doi.org/10.1152/jn.1999.82.3.1569>.
- [149] K.H. Braunewell, D. Manahan-Vaughan, Long-term depression: a cellular basis for learning? Rev. Neurosci. 12 (2001) 121–140, <https://doi.org/10.1515/reneuro.2001.12.2.121>.
- [150] J.M. Ding, G.F. Buchanan, S.A. Tischkau, D. Chen, L. Kuriashkina, L.E. Faiman, J. M. Alster, P.S. McPherson, K.P. Campbell, M.U. Gillette, A neuronal ryanodine receptor mediates light-induced phase delays of the circadian clock, Nature 394 (1998) 381–384, <https://doi.org/10.1038/28639>.
- [151] J. Yue, W. Wei, C.M.C. Lam, Y.-J. Zhao, M. Dong, L.-R. Zhang, L.-H. Zhang, H.-C. Lee, CD38/cADPR/Ca2+ pathway promotes cell proliferation and delays nerve growth factor-induced differentiation in PC12 cells, J. Biol. Chem. 284 (2009) 29335–29342, <https://doi.org/10.1074/jbc.M109.049767>.
- [152] W. Wei, Y. Lu, B. Hao, K. Zhang, Q. Wang, A.L. Miller, L.-R. Zhang, L.-H. Zhang, J. Yue, CD38 Is Required for Neural Differentiation of Mouse Embryonic Stem Cells by Modulating Reactive Oxygen Species, Stem Cells Dayt. Ohio. 33 (2015) 2664–2673, <https://doi.org/10.1002/stem.2057>.
- [153] T.P. Nelissen, R.A. Bamford, S. Tochitani, K. Akkus, A. Kudzinskas, K. Yokoi, H. Okamoto, Y. Yamamoto, J.P.H. Burbach, H. Matsuzaki, A. Oguro-Ando, CD38 is Required for Dendritic Organization in Visual Cortex and Hippocampus, Neuroscience 372 (2018) 114–125, <https://doi.org/10.1016/j.neuroscience.2017.12.050>.
- [154] T. Munesue, S. Yokoyama, K. Nakamura, A. Anitha, K. Yamada, K. Hayashi, T. Asaka, H.-X. Liu, D. Jin, K. Koizumi, M.S. Islam, J.-J. Huang, W.-J. Ma, U.-H. Kim, S.-J. Kim, K. Park, D. Kim, M. Kikuchi, Y. Ono, H. Nakatani, S. Suda, T. Miyachi, H. Hirai, A. Salmina, Y.A. Pichugina, A.A. Soumarakov, N. Takei, N. Mori, M. Tsuji, T. Sugiyama, K. Yagi, M. Yamagishi, T. Sasaki, H. Yamasue, N. Kato, R. Hashimoto, M. Taniike, Y. Hayashi, J. Hamada, S. Suzuki, A. Ooi, M. Noda, Y. Kamiyama, M.A. Kido, O. Lopatina, M. Hashii, S. Amina, F. Malavasi, E.J. Huang, J. Zhang, N. Shimizu, T. Yoshikawa, A. Matsushima, Y. Minabe, H. Higashida, Two genetic variants of CD38 in subjects with autism spectrum disorder and controls, Neurosci. Res. 67 (2010) 181–191, <https://doi.org/10.1016/j.neures.2010.03.004>.
- [155] N. Akimoto, Y. Kamiyama, M. Yamafuji, K. Fujita, T. Seike, M.A. Kido, S. Yokoyama, H. Higashida, M. Noda, Immunohistochemistry of CD38 in Different Cell Types in the Hypothalamus and Pituitary of Male Mice, Messenger 2 (2013) 54–61, <https://doi.org/10.1166/mnr.2013.1021>.
- [156] E. Courchesne, P.R. Mouton, M.E. Calhoun, K. Semendeferi, C. Ahrens-Barbeau, M.J. Hallet, C.C. Barnes, K. Pierce, Neuron number and size in prefrontal cortex of children with autism, JAMA 306 (2011) 2001–2010, <https://doi.org/10.1001/jama.2011.1638>.
- [157] C. Frith, What do imaging studies tell us about the neural basis of autism? Novartis Found. Symp. 251 (2003) 149–166, discussion 166–176, 281–297.
- [158] G. Tang, K. Gudsnuks, S.-H. Kuo, M.L. Cotrina, G. Rosoklja, A. Sosunov, M. S. Sonders, E. Kanter, C. Castagna, A. Yamamoto, Z. Yue, O. Arancio, B. S. Peterson, F. Champagne, A.J. Dwork, J. Goldman, D. Sulzer, Loss of mTOR-dependent macroautophagy causes autistic-like synaptic pruning deficits, Neuron 83 (2014) 1131–1143, <https://doi.org/10.1016/j.neuron.2014.07.040>.
- [159] T.E. Faust, G. Gunner, D.P. Schafer, Mechanisms governing activity-dependent synaptic pruning in the developing mammalian CNS, Nat. Rev. Neurosci. (2021), <https://doi.org/10.1038/s41583-021-00507-y>.
- [160] J. Piven, S. Arndt, J. Bailey, S. Havercamp, N.C. Andreasen, P. Palmer, An MRI study of brain size in autism, Am. J. Psychiatry. 152 (1995) 1145–1149, <https://doi.org/10.1176/ajp.152.8.1145>.
- [161] H.C. Hazlett, M. Poe, G. Gerig, R.G. Smith, J. Provenzale, A. Ross, J. Gilmore, J. Piven, Magnetic resonance imaging and head circumference study of brain size in autism: birth through age 2 years, Arch. Gen. Psychiatry. 62 (2005) 1366–1376, <https://doi.org/10.1001/archpsyc.62.12.1366>.
- [162] E. Redcay, E. Courchesne, When is the brain enlarged in autism? A meta-analysis of all brain size reports, Biol. Psychiatry. 58 (2005) 1–9, <https://doi.org/10.1016/j.biopsych.2005.03.026>.
- [163] R. Sacco, S. Gabriele, A.M. Persico, Head circumference and brain size in autism spectrum disorder: A systematic review and meta-analysis, Psychiatry Res 234 (2015) 239–251, <https://doi.org/10.1016/j.psychresns.2015.08.016>.

- [164] B.S. Khundrakpam, J.D. Lewis, P. Kostopoulos, F. Carbonell, A.C. Evans, Cortical Thickness Abnormalities in Autism Spectrum Disorders Through Late Childhood, Adolescence, and Adulthood: A Large-Scale MRI Study, *Cereb. Cortex N. Y. N* 1991 27 (2017) 1721–1731, <https://doi.org/10.1093/cercor/bhw038>.
- [165] C. Ecker, C.M. Pretzsch, A. Bletsch, C. Mann, T. Schaefer, S. Ambrosino, J. Tillmann, A. Yousaf, A. Chiocchetti, M.V. Lombardo, V. Warrier, N. Bast, C. Moessnang, S. Baumeister, F. Dell'Acqua, D.L. Floris, M. Zabihi, A. Marquand, F. Cliquet, C. Leblond, C. Moreau, N. Puts, T. Banaschewski, E.J.H. Jones, L. Mason, S. Bölte, A. Meyer-Lindenberg, A.M. Persico, S. Durston, S. Baron-Cohen, W. Spooren, E. Loth, C.M. Freitag, T. Charman, G. Dumas, T. Bourgeron, C.F. Beckmann, J.K. Buitelaar, D.G.M. Murphy, Interindividual Differences in Cortical Thickness and Their Genomic Underpinnings in Autism Spectrum Disorder, *Am. J. Psychiatry* (2021), <https://doi.org/10.1176/appi.ajp.2021.20050630>.
- [166] S. Kim, T. Kim, H.-R. Lee, E.-H. Jang, H.-H. Ryu, M. Kang, S.-Y. Rah, J. Yoo, B. Lee, J.-I. Kim, C.S. Lim, S.J. Kim, U.-H. Kim, Y.-S. Lee, B.-K. Kaang, Impaired learning and memory in CD38 null mutant mice, *Mol. Brain.* 9 (2016) 16, <https://doi.org/10.1186/s13041-016-0195-5>.
- [167] E. Seu, A. Lang, R.J. Rivera, J.D. Jentsch, Inhibition of the norepinephrine transporter improves behavioral flexibility in rats and monkeys, *Psychopharmacology (Berl.)* 202 (2009) 505–519, <https://doi.org/10.1007/s00213-008-1250-4>.
- [168] S. Winter, M. Dieckmann, K. Schwabe, Dopamine in the prefrontal cortex regulates rats behavioral flexibility to changing reward value, *Behav. Brain Res.* 198 (2009) 206–213, <https://doi.org/10.1016/j.bbr.2008.10.040>.
- [169] M.V. Puig, A.T. Gulleedge, Serotonin and prefrontal cortex function: neurons, networks, and circuits, *Mol. Neurobiol.* 44 (2011) 449–464, <https://doi.org/10.1007/s12035-011-8214-0>.
- [170] T. Curry, P. Egeto, H. Wang, A. Podnos, D. Wasserman, J. Yeomans, Dopamine receptor D2 deficiency reduces mouse pup ultrasonic vocalizations and maternal responsiveness, *Genes Brain Behav* 12 (2013) 397–404, <https://doi.org/10.1111/gbb.12037>.
- [171] M.V. Puig, T. Gener, Serotonin Modulation of Prefronto-Hippocampal Rhythms in Health and Disease, *ACS Chem. Neurosci.* 6 (2015) 1017–1025, <https://doi.org/10.1021/cn500350e>.
- [172] O. Borodovitsyna, M. Flaminii, D. Chandler, Noradrenergic Modulation of Cognition in Health and Disease, *Neural Plast* 2017 (2017), <https://doi.org/10.1155/2017/6031478>.
- [173] K. Cambon, R. Dos-Santos Coura, L. Groc, A. Carbon, D. Weissmann, J. P. Changeux, J.F. Pujol, S. Granon, Aggressive behavior during social interaction in mice is controlled by the modulation of tyrosine hydroxylase expression in the prefrontal cortex, *Neuroscience* 171 (2010) 840–851, <https://doi.org/10.1016/j.neuroscience.2010.09.015>.
- [174] R.S. Coura, A. Cressant, J. Xia, F. de Chaumont, J.C. Olivo-Marin, Y. Pelloux, J. W. Dalley, S. Granon, Nonaggressive and adapted social cognition is controlled by the interplay between noradrenergic and nicotinic receptor mechanisms in the prefrontal cortex, *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* 27 (2013) 4343–4354, <https://doi.org/10.1096/fj.13-231084>.
- [175] P.R. Albert, F. Vahid-Ansari, C. Luckhardt, Serotonin-prefrontal cortical circuitry in anxiety and depression phenotypes: pivotal role of pre- and post-synaptic 5-HT1A receptor expression, *Front. Behav. Neurosci.* 8 (2014) 199, <https://doi.org/10.3389/fnbeh.2014.00199>.
- [176] M.-R. Zarrindast, F. Khakpaei, The Modulatory Role of Dopamine in Anxiety-like Behavior, *Arch. Iran. Med.* 18 (2015) 591–603, <https://doi.org/0151809/ AIM.009>.
- [177] T. Hotta, K. Asai, K. Fujita, T. Kato, H. Higashida, Membrane-bound form of ADP-ribosyl cyclase in rat cortical astrocytes in culture, *J. Neurochem.* 74 (2000) 669–675, <https://doi.org/10.1046/j.1471-4159.2000.740669.x>.
- [178] C. Farina, F. Aloisi, E. Meini, Astrocytes are active players in cerebral innate immunity, *Trends Immunol.* 28 (2007) 138–145, <https://doi.org/10.1016/j.it.2007.01.005>.
- [179] E.E. Tuppo, H.R. Arias, The role of inflammation in Alzheimer's disease, *Int. J. Biochem. Cell Biol.* 37 (2005) 289–305, <https://doi.org/10.1016/j.biocel.2004.07.009>.
- [180] F. Casamenti, C. Prosperi, C. Scali, L. Giovannelli, M.A. Colivicchi, M.S. Faussone-Pellegrini, G. Pepeu, Interleukin-1beta activates forebrain glial cells and increases nitric oxide production and cortical glutamate and GABA release in vivo: implications for Alzheimer's disease, *Neuroscience* 91 (1999) 831–842, [https://doi.org/10.1016/s0306-4522\(98\)00680-0](https://doi.org/10.1016/s0306-4522(98)00680-0).
- [181] P. Schubert, K. Rudolph, Interfering with the pathologic activation of microglial cells and astrocytes in dementia, *Alzheimer Dis. Assoc. Disord.* 12 (Suppl 2) (1998) S21–S28.
- [182] C.C. Chao, S. Hu, P.K. Peterson, Glia, cytokines, and neurotoxicity, *Crit. Rev. Neurobiol.* 9 (1995) 189–205.
- [183] M. Jana, J.A. Anderson, R.N. Saha, X. Liu, K. Pahan, Regulation of inducible nitric oxide synthase in proinflammatory cytokine-stimulated human primary astrocytes, *Free Radic. Biol. Med.* 38 (2005) 655–664, <https://doi.org/10.1016/j.freeradbiomed.2004.11.021>.
- [184] P. Bezzi, M. Domercq, L. Brambilla, R. Galli, D. Schols, E. De Clercq, A. Vescovi, G. Bagetta, G. Kollias, M. Meldolesi, A. Volterra, CXCR4-activated astrocyte glutamate release via TNFalpha: amplification by microglia triggers neurotoxicity, *Nat. Neurosci.* 4 (2001) 702–710, <https://doi.org/10.1038/89490>.
- [185] M. Deshpande, J. Zheng, K. Borgmann, R. Persidsky, L. Wu, C. Schellpeper, A. Ghorpade, Role of activated astrocytes in neuronal damage: potential links to HIV-1-associated dementia, *Neurotox. Res.* 7 (2005) 183–192, <https://doi.org/10.1007/BF03036448>.
- [186] A. Ghorpade, S. Holter, K. Borgmann, R. Persidsky, L. Wu, HIV-1 and IL-1 beta regulate Fas ligand expression in human astrocytes through the NF-kappa B pathway, *J. Neuroimmunol.* 141 (2003) 141–149, [https://doi.org/10.1016/s0165-5728\(03\)00222-4](https://doi.org/10.1016/s0165-5728(03)00222-4).
- [187] Y. Joe, Y. Chen, J. Park, H.-J. Kim, S.-Y. Rah, J. Ryu, G.J. Cho, H.-S. Choi, S. W. Ryter, J.W. Park, U.-H. Kim, H.T. Chung, Cross-talk between CD38 and TTP Is Essential for Resolution of Inflammation during Microbial Sepsis, *Cell Rep* 30 (2020), <https://doi.org/10.1016/j.celrep.2019.12.090>, 1063–1076.e5.
- [188] N. Bodrato, L. Franco, C. Fresia, L. Guida, C. Usai, A. Salis, I. Moreschi, C. Ferraris, C. Verderio, G. Basile, S. Bruzzone, S. Scarfi, A. De Flora, E. Zocchi, Abscisic acid activates the murine microglial cell line N9 through the second messenger cyclic ADP-ribose, *J. Biol. Chem.* 284 (2009) 14777–14787, <https://doi.org/10.1074/jbc.M802604200>.
- [189] S. Banerjee, T.F. Walseth, K. Borgmann, L. Wu, K.R. Bidasee, M.S. Kannan, A. Ghorpade, CD38/cyclic ADP-ribose regulates astrocyte calcium signaling: implications for neuroinflammation and HIV-1-associated dementia, *J. Neuroimmune Pharmacol. Off. J. Soc. Neuroimmune Pharmacol.* 3 (2008) 154–164, <https://doi.org/10.1007/s11481-008-9105-7>.
- [190] P.K. Aley, H.J. Murray, J.P. Boyle, H.A. Pearson, C. Peers, Hypoxia stimulates Ca<sup>2+</sup> release from intracellular stores in astrocytes via cyclic ADP ribose-mediated activation of ryanodine receptors, *Cell Calcium* 39 (2006) 95–100, <https://doi.org/10.1016/j.ceca.2005.09.009>.
- [191] K. Hayakawa, E. Esposito, X. Wang, Y. Terasaki, Y. Liu, C. Xing, X. Ji, E.H. Lo, Transfer of mitochondria from astrocytes to neurons after stroke, *Nature* 535 (2016) 551–555, <https://doi.org/10.1038/nature18928>.
- [192] L. Gao, Z. Zhang, J. Lu, G. Pei, Mitochondria Are Dynamically Transferring Between Human Neural Cells and Alexander Disease-Associated GFAP Mutations Impair the Astrocytic Transfer, *Front. Cell. Neurosci.* 13 (2019) 316, <https://doi.org/10.3389/fncel.2019.00316>.
- [193] J.-H. Park, E.H. Lo, K. Hayakawa, Endoplasmic Reticulum Interaction Supports Energy Production and Redox Homeostasis in Mitochondria Released from, Astrocytes, *Transl. Stroke Res.* (2021), <https://doi.org/10.1007/s12975-021-00892-7>.
- [194] M. Yamasaki, R. Masgrau, A.J. Morgan, G.C. Churchill, S. Patel, S.J.H. Ashcroft, A. Galione, Organelle selection determines agonist-specific Ca<sup>2+</sup> signals in pancreatic acinar and beta cells, *J. Biol. Chem.* 279 (2004) 7234–7240, <https://doi.org/10.1074/jbc.M31108200>.
- [195] E. Brailoiu, J.L. Hoard, C.M. Filipeanu, G.C. Brailoiu, S.L. Dun, S. Patel, N.J. Dun, Nicotinic acid adenine dinucleotide phosphate potentiates neurite outgrowth, *J. Biol. Chem.* 280 (2005) 5646–5650, <https://doi.org/10.1074/jbc.M408746200>.
- [196] N.P. Kinnear, F.-X. Boittin, J.M. Thomas, A. Galione, A.M. Evans, Lysosome-sarcoplasmic reticulum junctions. A trigger zone for calcium signaling by nicotinic acid adenine dinucleotide phosphate and endothelin-1, *J. Biol. Chem.* 279 (2004) 54319–54326, <https://doi.org/10.1074/jbc.M406132200>.
- [197] F. Zhang, G. Zhang, M.Y. Zhang, M.J. Koeberl, E. Wallander, P.-L. Li, Production of NAADP and its role in Ca<sup>2+</sup> mobilization associated with lysosomes in coronary arterial myocytes, *Am. J. Physiol. Heart Circ. Physiol.* 291 (2006) H274–H282, <https://doi.org/10.1152/ajpheart.01064.2005>.
- [198] V. Pandey, C.-C. Chuang, A.M. Lewis, P.K. Aley, E. Brailoiu, N.J. Dun, G. C. Churchill, S. Patel, Recruitment of NAADP-sensitive acidic Ca<sup>2+</sup> stores by glutamate, *Biochem. J.* 422 (2009) 503–512, <https://doi.org/10.1042/BJ20090194>.
- [199] T.L. Thai, G.C. Churchill, W.J. Arendshorst, NAADP receptors mediate calcium signaling stimulated by endothelin-1 and norepinephrine in renal afferent arterioles, *Am. J. Physiol. Renal Physiol.* 297 (2009) F510–F516, <https://doi.org/10.1152/ajprenal.00116.2009>.
- [200] S. Patel, Function and dysfunction of two-pore channels, *Sci. Signal.* 8 (2015), <https://doi.org/10.1126/scisignal.aab3134> re7.
- [201] A. Galione, NAADP Receptors, *Cold Spring Harb. Perspect. Biol.* 11 (2019), <https://doi.org/10.1101/cshperspect.a035071>.
- [202] Y. Lin-Moshier, T.F. Walseth, D. Churamani, S.M. Davidson, J.T. Slama, R. Hooper, E. Brailoiu, S. Patel, J.S. Marchant, Photoaffinity labeling of nicotinic acid adenine dinucleotide phosphate (NAADP) targets in mammalian cells, *J. Biol. Chem.* 287 (2012) 2296–2307, <https://doi.org/10.1074/jbc.M111.305813>.
- [203] T.F. Walseth, Y. Lin-Moshier, P. Jain, M. Ruas, J. Parrington, A. Galione, J. S. Marchant, J.T. Slama, Photoaffinity labeling of high affinity nicotinic acid adenine dinucleotide phosphate (NAADP)-binding proteins in sea urchin egg, *J. Biol. Chem.* 287 (2012) 2308–2315, <https://doi.org/10.1074/jbc.M111.305653>.
- [204] T.F. Walseth, Y. Lin-Moshier, K. Weber, J.S. Marchant, J.T. Slama, A.H. Guse, Nicotinic Acid Adenine Dinucleotide 2'-Phosphate (NAADP) Binding Proteins in T-Lymphocytes, *Messenger Los Angel. Calif Print.* 1 (2012) 86–94, <https://doi.org/10.1166/msr.2012.R008>.
- [205] M. Ruas, L.C. Davis, C.-C. Chen, A.J. Morgan, K.-T. Chuang, T.F. Walseth, C. Grimm, C. Gamham, T. Powell, N. Platt, F.M. Platt, M. Biel, C. Wahl-Schott, J. Parrington, A. Galione, Expression of Ca<sup>2+</sup>-permeable two-pore channels rescues NAADP signalling in TPC-deficient cells, *EMBO J* 34 (2015) 1743–1758, <https://doi.org/10.1522/embj.201490009>.
- [206] T.Y. Asfaha, G.S. Gunaratne, M.E. Johns, J.S. Marchant, T.F. Walseth, J.T. Slama, The synthesis and characterization of a clickable-photoactive NAADP analog active in human cells, *Cell Calcium* 83 (2019), <https://doi.org/10.1016/j.ceca.2019.102060>.
- [207] G.S. Gunaratne, P. Su, J.S. Marchant, J.T. Slama, T.F. Walseth, 5-Azido-8-ethynyl-NAADP: A bifunctional, clickable photoaffinity probe for the identification of

- NAADP receptors, *Biochim. Biophys. Acta Mol. Cell Res.* 1866 (2019) 1180–1188, <https://doi.org/10.1016/j.bbamcr.2018.11.017>.
- [208] de Duve, The Nobel Prize in Physiology or Medicine 1974, NobelPrize.Org (1974). <https://www.nobelprize.org/prizes/medicine/1974/summary/> (accessed May 17, 2021).
- [209] K. Ogawa, N. Mizuno, M. Okamoto, Morphology and Cytochemistry of Lysosomes, *Proc. Jpn. Histochem. Assoc.* 1960 (1960) 15–20, <https://doi.org/10.1267/ahc1960.1960.15>.
- [210] K. Ogawa, N. Mizuno, M. Okamoto, Lysosomes in cultured cells, *J. Histochem. Cytochem.* 9 (1961), <https://doi.org/10.1177/9.2.202>, 202–202.
- [211] A.B. Novikoff, Lysosomes in nerve cells. The Neuron. Edited by Hyden H, (1967).
- [212] K. Furuta, X.L. Yang, J.S. Chen, S.R. Hamilton, J.T. August, Differential expression of the lysosome-associated membrane proteins in normal human tissues, *Arch. Biochem. Biophys.* 365 (1999) 75–82, <https://doi.org/10.1006/abbi.1999.1147>.
- [213] R.G. Parton, K. Simons, C.G. Dotti, Axonal and dendritic endocytic pathways in cultured neurons, *J. Cell Biol.* 119 (1992) 123–137, <https://doi.org/10.1083/jcb.119.1.123>.
- [214] R.D. Pace, D.J. Britt, J. Mercurio, A.M. Foster, L. Djavaherian, V. Hoffmann, D. Abebe, J.S. Bonifacino, Synaptic Vesicle Precursors and Lysosomes Are Transported by Different Mechanisms in the Axon of Mammalian Neurons, *Cell Rep* 31 (2020), <https://doi.org/10.1016/j.celrep.2020.107775>.
- [215] M. Kuijpers, D. Azarnia Tehran, V. Haucke, T. Soykan, The axonal endolysosomal and autophagic systems, *J. Neurochem.* 158 (2021) 589–602, <https://doi.org/10.1111/jnc.15287>.
- [216] O. Monteiro, U.K. Wiegand, M. Ludwig, Vesicle degradation in dendrites of magnocellular neurones of the rat supraoptic nucleus, *Neurosci. Lett.* 489 (2011) 30–33, <https://doi.org/10.1016/j.neulet.2010.11.060>.
- [217] Z. Padamsey, L. McGuinness, N.J. Emptage, Inhibition of lysosomal Ca<sup>2+</sup> signalling disrupts dendritic spine structure and impairs wound healing in neurons, *Commun. Integr. Biol.* 10 (2017), [https://doi.org/10.1080/19420889.2017.1344802 e1344802](https://doi.org/10.1080/19420889.2017.1344802).
- [218] M.S. Goo, L. Sancho, N. Slepak, D. Boassa, T.J. Deerinck, M.H. Ellisman, B. L. Bloodgood, G.N. Patrick, Activity-dependent trafficking of lysosomes in dendrites and dendritic spines, *J. Cell Biol.* 216 (2017) 2499–2513, <https://doi.org/10.1083/jcb.201704068>.
- [219] F. Tsuruta, T. Okajima, S. Yano, T. Chiba, Quantification of Endosome and Lysosome Motilities in Cultured Neurons Using Fluorescent Probes, *J. Vis. Exp. JOVE.* (2017), <https://doi.org/10.3791/55488>.
- [220] T. Farfel-Becker, J.C. Roney, X.-T. Cheng, S. Li, S.R. Cuddy, Z.-H. Sheng, Neuronal Soma-Derived Degradative Lysosomes Are Continuously Delivered to Distal Axons to Maintain Local Degradation Capacity, *Cell Rep* 28 (2019), <https://doi.org/10.1016/j.celrep.2019.06.013>, 51–64.e4.
- [221] K.R. Croce, A. Yamamoto, A role for autophagy in Huntington's disease, *Neurobiol. Dis.* 122 (2019) 16–22, <https://doi.org/10.1016/j.nbd.2018.08.010>.
- [222] J.-Y. Koh, H.N. Kim, J.J. Hwang, Y.-H. Kim, S.E. Park, Lysosomal dysfunction in proteinopathic neurodegenerative disorders: possible therapeutic roles of cAMP and zinc, *Mol. Brain.* 12 (2019) 18, <https://doi.org/10.1186/s13041-019-0439-2>.
- [223] V. Tedeschi, T. Petrozziello, A. Seundo, Calcium Dyshomeostasis and Lysosomal Ca<sup>2+</sup> Dysfunction in Amyotrophic Lateral Sclerosis, *Cells* 8 (2019) 1216, <https://doi.org/10.3390/cells8101216>.
- [224] R.A. Nixon, D.-S. Yang, J.-H. Lee, Neurodegenerative lysosomal disorders: a continuum from development to late age, *Autophagy* 4 (2008) 590–599, <https://doi.org/10.4161/auto.6259>.
- [225] E. Lloyd-Evans, A.J. Morgan, X. He, D.A. Smith, E. Elliot-Smith, D.J. Silience, G. C. Churchill, E.H. Schuchman, A. Galione, F.M. Platt, Niemann-Pick disease type C1 is a sphingosine storage disease that causes deregulation of lysosomal calcium, *Nat. Med.* 14 (2008) 1247–1255, <https://doi.org/10.1038/nm.1876>.
- [226] S. Gowrishankar, P. Yuan, Y. Wu, M. Schrag, S. Paradise, J. Grutzendler, P. De Camilli, S.M. Ferguson, Massive accumulation of luminal protease-deficient axonal lysosomes at Alzheimer's disease amyloid plaques, *Proc. Natl. Acad. Sci. U. S. A.* 112 (2015), <https://doi.org/10.1073/pnas.1510329112>, E3699–3708.
- [227] Y.C. Wong, E.L.F. Holzbaur, Autophagosome dynamics in neurodegeneration at a glance, *J. Cell Sci.* 128 (2015) 1259–1267, <https://doi.org/10.1242/jcs.161216>.
- [228] L.N. Hockey, B.S. Kilpatrick, E.R. Eden, Y. Lin-Moshier, G.C. Brailoiu, E. Brailoiu, C.E. Futter, A.H. Schapira, J.S. Marchant, S. Patel, Dysregulation of lysosomal morphology by pathogenic LRRK2 is corrected by TPC2 inhibition, *J. Cell Sci.* 128 (2015) 232–238, <https://doi.org/10.1242/jcs.164152>.
- [229] P. Rivero-Ríos, M. Romo-Lozano, R. Fasiczka, Y. Naaldijk, S. Hilfiker, LRRK2-Related Parkinson's Disease Due to Altered Endolysosomal Biology With Variable Lewy Body Pathology: A Hypothesis, *Front. Neurosci.* 14 (2020) 556, <https://doi.org/10.3389/fnins.2020.00556>.
- [230] M.T. Bassi, M. Manzoni, E. Monti, M.T. Pizzo, A. Ballabio, G. Borsani, Cloning of the gene encoding a novel integral membrane protein, mucolipidin-and identification of the two major founder mutations causing mucolipidosis type IV, *Am. J. Hum. Genet.* 67 (2000) 1110–1120, [https://doi.org/10.1016/S0002-9297\(07\)62941-3](https://doi.org/10.1016/S0002-9297(07)62941-3).
- [231] M. Sun, E. Goldin, S. Stahl, J.L. Falardeau, J.C. Kennedy, J.S. Acierno, C. Bove, C. R. Kaneski, J. Nagle, M.C. Bromley, M. Colman, R. Schiffmann, S. A. Slaugenhaupt, Mucolipidosis type IV is caused by mutations in a gene encoding a novel transient receptor potential channel, *Hum. Mol. Genet.* 9 (2000) 2471–2478, <https://doi.org/10.1093/hmg/9.17.2471>.
- [232] J.M. LaPlante, J. Falardeau, M. Sun, M. Kanazirska, E.M. Brown, S. A. Slaugenhaupt, P.M. Vassilev, Identification and characterization of the single channel function of human mucolipin-1 implicated in mucolipidosis type IV, a disorder affecting the lysosomal pathway, *FEBS Lett.* 532 (2002) 183–187, [https://doi.org/10.1016/s0014-5793\(02\)03670-0](https://doi.org/10.1016/s0014-5793(02)03670-0).
- [233] X.-P. Dong, X. Cheng, E. Mills, M. Delling, F. Wang, T. Kurz, H. Xu, The type IV mucolipidosis-associated protein TRPML1 is an endolysosomal iron release channel, *Nature* 455 (2008) 992–996, <https://doi.org/10.1038/nature07311>.
- [234] W. Stoortvogel, G.J. Strous, H.J. Geuze, V. Oorschot, A.L. Schwartz, Late endosomes derive from early endosomes by maturation, *Cell* 65 (1991) 417–427, [https://doi.org/10.1016/0092-8674\(91\)90459-c](https://doi.org/10.1016/0092-8674(91)90459-c).
- [235] I. Mellman, Endocytosis and molecular sorting, *Annu. Rev. Cell Dev. Biol.* 12 (1993) 575–625, <https://doi.org/10.1146/annurev.cellbio.12.1.575>.
- [236] J.P. Luzio, B.A. Rous, N.A. Bright, P.R. Pryor, B.M. Mullock, R.C. Piper, Lysosome-endosome fusion and lysosome biogenesis, *J. Cell Sci.* 113 (Pt 9) (2000) 1515–1524.
- [237] C. Lafourcade, K. Sobo, S. Kieffer-Jaquinod, J. Garin, F.G. van der Goot, Regulation of the V-ATPase along the endocytic pathway occurs through reversible subunit association and membrane localization, *PloS One* 3 (2008), [https://doi.org/10.1371/journal.pone.0002758 e2758](https://doi.org/10.1371/journal.pone.0002758).
- [238] M.E. Maxson, S. Grinstein, The vacuolar-type H<sup>+</sup>-ATPase at a glance - more than a proton pump, *J. Cell Sci.* 127 (2014) 4987–4993, <https://doi.org/10.1242/jcs.158550>.
- [239] J. Huotari, A. Helenius, Endosome maturation, *EMBO J.* 30 (2011) 3481–3500, <https://doi.org/10.1038/embj.2011.286>.
- [240] H. Xu, D. Ren, Lysosomal physiology, *Annu. Rev. Physiol.* 77 (2015) 57–80, <https://doi.org/10.1146/annurev-physiol-021014-071649>.
- [241] F.L. Bygrave, A. Benedetti, What is the concentration of calcium ions in the endoplasmic reticulum? *Cell Calcium* 19 (1996) 547–551, [https://doi.org/10.1016/s0143-4160\(96\)90064-0](https://doi.org/10.1016/s0143-4160(96)90064-0).
- [242] J.V. Gerasimenko, A.V. Tepikin, O.H. Petersen, O.V. Gerasimenko, Calcium uptake via endocytosis with rapid release from acidifying endosomes, *Curr. Biol.* CB. 8 (1998) 1335–1338, [https://doi.org/10.1016/s0960-9822\(07\)00565-9](https://doi.org/10.1016/s0960-9822(07)00565-9).
- [243] K.A. Christensen, J.T. Myers, J.A. Swanson, pH-dependent regulation of lysosomal calcium in macrophages, *J. Cell Sci.* 115 (2002) 599–607.
- [244] S. Patel, R. Docampo, Acidic calcium stores open for business: expanding the potential for intracellular Ca<sup>2+</sup> signaling, *Trends Cell Biol.* 20 (2010) 277–286, <https://doi.org/10.1016/j.tcb.2010.02.003>.
- [245] J.K. Pittman, Vacuolar Ca(2+) uptake, *Cell Calcium* 50 (2011) 139–146, <https://doi.org/10.1016/j.ceca.2011.01.004>.
- [246] M. Melchiorra, J.K. Pittman, R. Mayor, S. Patel, Ca<sup>2+</sup>/H<sup>+</sup> exchange by acidic organelles regulates cell migration in vivo, *J. Cell Biol.* 212 (2016) 803–813, <https://doi.org/10.1083/jcb.201510019>.
- [247] J.J. López, C. Camello-Almaraz, J.A. Pariente, G.M. Salido, J.A. Rosado, Ca<sup>2+</sup> accumulation into acidic organelles mediated by Ca<sup>2+</sup>- and vacuolar H<sup>+</sup>-ATPases in human platelets, *Biochem. J.* 390 (2005) 243–252, <https://doi.org/10.1042/BJ20050168>.
- [248] J.J. López, I. Jardín, R. Bobe, J.A. Pariente, J. Enouf, G.M. Salido, J.A. Rosado, STIM1 regulates acidic Ca<sup>2+</sup> store refilling by interaction with SERCA3 in human platelets, *Biochem. Pharmacol.* 75 (2008) 2157–2164, <https://doi.org/10.1016/j.bcp.2008.03.010>.
- [249] C.I. López-Sanjurjo, S.C. Tovey, D.L. Prole, C.W. Taylor, Lysosomes shape Ins(1,4,5)P<sub>3</sub>-evoked Ca<sup>2+</sup> signals by selectively sequestering Ca<sup>2+</sup> released from the endoplasmic reticulum, *J. Cell Sci.* 126 (2013) 289–300, <https://doi.org/10.1242/jcs.116103>.
- [250] C.I. López-Sanjurjo, S.C. Tovey, C.W. Taylor, Rapid recycling of Ca<sup>2+</sup> between IP<sub>3</sub>-sensitive stores and lysosomes, *PLoS One* 9 (2014), [https://doi.org/10.1371/journal.pone.0111275 e111275](https://doi.org/10.1371/journal.pone.0111275).
- [251] A.G. Garrity, W. Wang, C.M. Collier, S.A. Levey, Q. Gao, H. Xu, The endoplasmic reticulum, not the pH gradient, drives calcium refilling of lysosomes, *Elife* 5 (2016), <https://doi.org/10.7554/elife.15887>.
- [252] V. Ronco, D.M. Potenza, F. Dentì, S. Vullo, G. Gagliano, M. Tognolina, G. Guerra, P. Pinton, A.A. Genazzani, L. Mapelli, D. Lim, F. Moccia, A novel Ca<sup>2+</sup>-mediated cross-talk between endoplasmic reticulum and acidic organelles: implications for NAADP-dependent Ca<sup>2+</sup> signalling, *Cell Calcium* 57 (2015) 89–100, <https://doi.org/10.1016/j.ceca.2015.01.001>.
- [253] P. Atakpa, N.B. Thillaipalappan, S. Matarakga, D.L. Prole, C.W. Taylor, IP<sub>3</sub> Receptors Preferentially Associate with ER-Lysosome Contact Sites and Selectively Deliver Ca<sup>2+</sup> to Lysosomes, *Cell Rep.* 25 (2018), <https://doi.org/10.1016/j.celrep.2018.11.064>, 3180–3193.e7.
- [254] V. Tedeschi, M.J. Sisalli, T. Petrozziello, L.M.T. Canzoniero, A. Seundo, Lysosomal calcium is modulated by STIM1/TRPML1 interaction which participates to neuronal survival during ischemic preconditioning, *FASEB J.* Off. Publ. Fed. Am. Soc. Exp. Biol. 35 (2021), [https://doi.org/10.1096/fj.202001886R e21277](https://doi.org/10.1096/fj.202001886R).
- [255] J.R. Friedman, J.R. Dibenedetto, M. West, A.A. Rowland, G.K. Voeltz, Endoplasmic reticulum-endosome contact increases as endosomes traffic and mature, *Mol. Biol. Cell.* 24 (2013) 1030–1040, <https://doi.org/10.1091/mbc.E12-10-0733>.
- [256] B.S. Kilpatrick, E.R. Eden, A.H. Schapira, C.E. Futter, S. Patel, Direct mobilisation of lysosomal Ca<sup>2+</sup> triggers complex Ca<sup>2+</sup> signals, *J. Cell Sci.* 126 (2013) 60–66, <https://doi.org/10.1242/jcs.118836>.
- [257] N. Fameli, O.A. Ogunbayo, C. van Breemen, A.M. Evans, Cytoplasmic nanojunctions between lysosomes and sarcoplasmic reticulum are required for specific calcium signaling, *F1000Research.* 3 (2014) 93. [10.12688/f1000research.ch.3720.1](https://doi.org/10.12688/f1000research.ch.3720.1).
- [258] D. Aston, R.A. Capel, K.L. Ford, H.C. Christian, G.R. Mirams, E.A. Rog-Zielinska, P. Kohl, A. Galione, R.A.B. Burton, D.A. Terrar, High resolution structural evidence suggests the Sarcoplasmic Reticulum forms microdomains with Acidic Stores (lysosomes) in the heart, *Sci. Rep.* 7 (2017), <https://doi.org/10.1038/srep40620>, 40620.

- [259] A. Blocker, F.F. Severin, J.K. Burkhardt, J.B. Bingham, H. Yu, J.C. Olivo, T. A. Schroer, A.A. Hyman, G. Griffiths, Molecular requirements for bi-directional movement of phagosomes along microtubules, *J. Cell Biol.* 137 (1997) 113–129, <https://doi.org/10.1083/jcb.137.1.113>.
- [260] I. Jordens, M. Fernandez-Borja, M. Marsman, S. Dusseljee, L. Janssen, J. Calafat, H. Janssen, R. Wubbolt, J. Neefjes, The Rab7 effector protein RILP controls lysosomal transport by inducing the recruitment of dynein-dynactin motors, *Curr. Biol.* 11 (2001) 1680–1685, [https://doi.org/10.1016/s0960-9822\(01\)00531-0](https://doi.org/10.1016/s0960-9822(01)00531-0).
- [261] B.M. Schwenk, C.M. Lang, S. Hogl, S. Tahirovic, D. Orozco, K. Rentzsch, S. F. Lichtenthaler, C.C. Hoogenraad, A. Capell, C. Haass, D. Edbauer, The FTLD risk factor TMEM106B and MAP6 control dendritic trafficking of lysosomes, *EMBO J* 33 (2014) 450–467, <https://doi.org/10.1002/embj.201385857>.
- [262] F. Tsuruta, R.E. Dolmetsch, PIKfyve mediates the motility of late endosomes and lysosomes in neuronal dendrites, *Neurosci. Lett.* 605 (2015) 18–23, <https://doi.org/10.1016/j.neulet.2015.07.021>.
- [263] J.S. Bonifacino, J. Neefjes, Moving and positioning the endolysosomal system, *Curr. Opin. Cell Biol.* 47 (2017) 1–8, <https://doi.org/10.1016/j.ceb.2017.01.008>.
- [264] Y. Han, M. Li, F. Qiu, M. Zhang, Y.-H. Zhang, Cell-permeable organic fluorescent probes for live-cell long-term super-resolution imaging reveal lysosome-mitochondrion interactions, *Nat. Commun.* 8 (2017) 1307, <https://doi.org/10.1038/s41467-017-01503-6>.
- [265] W. Peng, Y.C. Wong, D. Krainc, Mitochondria-lysosome contacts regulate mitochondrial Ca<sup>2+</sup> dynamics via lysosomal TRPML1, *Proc. Natl. Acad. Sci. U. S. A.* 117 (2020) 19266–19275, <https://doi.org/10.1073/pnas.2003236117>.
- [266] D.M. Sabatini, Twenty-five years of mTOR: Uncovering the link from nutrients to growth, *Proc. Natl. Acad. Sci. U. S. A.* 114 (2017) 11818–11825, <https://doi.org/10.1073/pnas.1716173114>.
- [267] Y.C. Wong, S. Kim, W. Peng, D. Krainc, Regulation and Function of Mitochondria-Lysosome Membrane Contact Sites in Cellular Homeostasis, *Trends Cell Biol.* 29 (2019) 500–513, <https://doi.org/10.1016/j.tcb.2019.02.004>.
- [268] 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<sup>(+)</sup> channels to adapt to metabolic state, *Cell* 152 (2013) 778–790, <https://doi.org/10.1016/j.cell.2013.01.023>.
- [269] D. Höglunger, T. Burgoyne, E. Sanchez-Heras, P. Hartwig, A. Colaco, J. Newton, C. E. Futter, S. Spiegel, F.M. Platt, E.R. Eden, NPC1 regulates ER contacts with endocytic organelles to mediate cholesterol egress, *Nat. Commun.* 10 (2019), <https://doi.org/10.1038/s41467-019-12152-2>, 4276.
- [270] N. Plotegher, M.R. Duchen, Crosstalk between Lysosomes and Mitochondria in Parkinson's Disease, *Front. Cell Dev. Biol.* 5 (2017) 110, <https://doi.org/10.3389/fcell.2017.00110>.
- [271] B.S. Kilpatrick, J. Magalhaes, M.S. Beavan, A. McNeill, M.E. Gegg, M.W.J. Cleeter, D. Bloor-Young, G.C. Churchill, M.R. Duchen, A.H. Schapira, S. Patel, Endoplasmic reticulum and lysosomal Ca<sup>2+</sup> stores are remodelled in GBA1-linked Parkinson disease patient fibroblasts, *Cell Calcium* 59 (2016) 12–20, <https://doi.org/10.1016/j.ceca.2015.11.002>.
- [272] S. Kim, Y.C. Wong, F. Gao, D. Krainc, Dysregulation of mitochondria-lysosome contacts by GBA1 dysfunction in dopaminergic neuronal models of Parkinson's disease, *Nat. Commun.* 12 (2021) 1807, <https://doi.org/10.1038/s41467-021-22113-3>.
- [273] M. Schrader, L.F. Godinho, J.L. Costello, M. Islinger, The different facets of organelle interplay—an overview of organelle interactions, *Front. Cell Dev. Biol.* 3 (2015) 56, <https://doi.org/10.3389/fcell.2015.00056>.
- [274] J.K. Jaiswal, N.W. Andrews, S.M. Simon, Membrane proximal lysosomes are the major vesicles responsible for calcium-dependent exocytosis in nonsecretory cells, *J. Cell Biol.* 159 (2002) 625–635, <https://doi.org/10.1083/jcb.200208154>.
- [275] K.A. Toops, A. Lakkaraju, Let's play a game of chutes and ladders: Lysosome fusion with the epithelial plasma membrane, *Commun. Integr. Biol.* 6 (2013), <https://doi.org/10.4161/cib.24474> e24474.
- [276] M. Corrotte, T. Castro-Gomes, A.B. Koushik, N.W. Andrews, Approaches for plasma membrane wounding and assessment of lysosome-mediated repair responses, *Methods Cell Biol.* 126 (2015) 139–158, <https://doi.org/10.1016/bs.mcb.2014.11.009>.
- [277] M. Encarnação, L. Espada, C. Escrevente, D. Mateus, J. Ramalho, X. Michelet, I. Santarino, V.W. Hsu, M.B. Brenner, D.C. Barral, O.V. Vieira, A Rab3a-dependent complex essential for lysosome positioning and plasma membrane repair, *J. Cell Biol.* 213 (2016) 631–640, <https://doi.org/10.1083/jcb.201511093>.
- [278] X. Michelet, A. Tuli, H. Gan, C. Geadas, M. Sharma, H.G. Remold, M.B. Brenner, Lysosome-Mediated Plasma Membrane Repair Is Dependent on the Small GTPase Arl8b and Determines Cell Death Type in Mycobacterium tuberculosis Infection, *J. Immunol. Baltim. Md* 1950 200 (2018) 3160–3169, <https://doi.org/10.4049/jimmunol.1700029>.
- [279] L. Hui, N.H. Geiger, D. Bloor-Young, G.C. Churchill, J.D. Geiger, X. Chen, Release of calcium from endolysosomes increases calcium influx through N-type calcium channels: Evidence for acidic store-operated calcium entry in neurons, *Cell Calcium* 58 (2015) 617–627, <https://doi.org/10.1016/j.ceca.2015.10.001>.
- [280] J.J. López, N. Dionisio, A. Berna-Erro, C. Galán, G.M. Salido, J.A. Rosado, Two-pore channel 2 (TPC2) modulates store-operated Ca<sup>2+</sup> entry, *Biochim. Biophys. Acta BBA - Mol. Cell Res.* 1823 (2012) 1976–1983, <https://doi.org/10.1016/j.bbamcr.2012.08.002>.
- [281] A. D'Amore, A.A. Hanbashi, S. Di Agostino, F. Palombi, A. Sacconi, A. Voruganti, M. Taggi, R. Canipari, G. Blandino, J. Parrington, A. Filippini, Loss of Two-Pore Channel 2 (TPC2) Expression Increases the Metastatic Traits of Melanoma Cells by a Mechanism Involving the Hippo Signalling Pathway and Store-Operated Calcium Entry, *Cancers* 12 (2020) 2391, <https://doi.org/10.3390/cancers12092391>.
- [282] H. Zbidi, I. Jardin, G.E. Woodard, J.J. Lopez, A. Berna-Erro, G.M. Salido, J. A. Rosado, STIM1 and STIM2 Are Located in the Acidic Ca<sup>2+</sup> Stores and Associates with Orai1 upon Depletion of the Acidic Stores in Human Platelets\*, *J. Biol. Chem.* 286 (2011) 12257–12270, <https://doi.org/10.1074/jbc.M110.190694>.
- [283] L. Sbano, M. Bonora, S. Marchi, F. Baldassari, D.L. Medina, A. Ballabio, C. Giorgi, P. Pinton, TFEB-mediated increase in peripheral lysosomes regulates store-operated calcium entry, *Sci. Rep.* 7 (2017), <https://doi.org/10.1038/srep40797>, 40797.
- [284] P.C. Trivedi, J.J. Bartlett, T. Pulinilkunnil, Lysosomal Biology and Function: Modern View of Cellular Debris Bin, *Cells* 9 (2020) 1131, <https://doi.org/10.3390/cells9051131>.
- [285] N. Tugba Durlu-Kandilci, M. Ruas, K.-T. Chuang, A. Brading, J. Parrington, A. Galione, TPC2 proteins mediate nicotinic acid adenine dinucleotide phosphate (NAADP)- and agonist-evoked contractions of smooth muscle, *J. Biol. Chem.* 285 (2010) 24925–24932, <https://doi.org/10.1074/jbc.M110.129833>.
- [286] V. García-Rúa, M.F. Otero, P.V. Lear, D. Rodríguez-Péras, S. Feijóo-Bandín, T. Noguera-Moreno, M. Calaza, M. Álvarez-Barredo, A. Mosquera-Leal, J. Parrington, J. Brugada, M. Portolés, M. Rivera, J.R. González-Juanatey, F. Lago, Increased expression of fatty-acid and calcium metabolism genes in failing human heart, *PloS One* 7 (2012) e37505, <https://doi.org/10.1371/journal.pone.0037505>.
- [287] J.J. Kelu, H.L.H. Chan, S.E. Webb, A.H.H. Cheng, M. Ruas, J. Parrington, A. Galione, A.L. Miller, Two-Pore Channel 2 activity is required for slow muscle cell-generated Ca<sup>2+</sup> signaling during myogenesis in intact zebrafish, *Int. J. Dev. Biol.* 59 (2015) 313–325, <https://doi.org/10.1387/ijdb.150206am>.
- [288] J.J. Kelu, S.E. Webb, J. Parrington, A. Galione, A.L. Miller, Ca<sup>2+</sup> release via two-pore channel type 2 (TPC2) is required for slow muscle cell myofibrilllogenesis and myotomal patterning in intact zebrafish embryos, *Dev. Biol.* 425 (2017) 109–129, <https://doi.org/10.1016/j.ydbio.2017.03.031>.
- [289] L.C. Davis, A.J. Morgan, J.-L. Chen, C.M. Snead, D. Bloor-Young, E. Shenderov, M. N. Stanton-Humphreys, S.J. Conway, G.C. Churchill, J. Parrington, V. Cerundolo, A. Galione, NAADP activates two-pore channels on T cell cytolytic granules to stimulate exocytosis and killing, *Curr. Biol.* 22 (2012) 2331–2337, <https://doi.org/10.1016/j.cub.2012.10.035>.
- [290] Z.-H. Zhang, Y.-Y. Lu, J. Yue, Two pore channel 2 differentially modulates neural differentiation of mouse embryonic stem cells, *PloS One* 8 (2013), <https://doi.org/10.1371/journal.pone.0066077> e66077.
- [291] A.L. Ambrosio, J.A. Boyle, S.M. Di Pietro, TPC2 mediates new mechanisms of platelet dense granule membrane dynamics through regulation of Ca<sup>2+</sup> release, *Mol. Biol. Cell.* 26 (2015) 3263–3274, <https://doi.org/10.1091/mbc.E15-01-0058>.
- [292] S.E. Webb, J.J. Kelu, A.L. Miller, Role of Two-Pore Channels in Embryonic Development and Cellular Differentiation, *Cold Spring Harb. Perspect. Biol.* 12 (2020), <https://doi.org/10.1101/cshperspect.a035170> a035170.
- [293] W.J. Foster, H.B.C. Taylor, Z. Padamsey, A.F. Jeans, A. Galione, N.J. Emptage, Hippocampal mGluR1-dependent long-term potentiation requires NAADP-mediated acidic store Ca<sup>2+</sup> signaling, *Sci. Signal.* 11 (2018), <https://doi.org/10.1126/scisignal.aat0903>.
- [294] 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>.
- [295] 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.* 20 (2010) 703–709, <https://doi.org/10.1016/j.cub.2010.02.049>.
- [296] M.X. Zhu, J. Ma, J. Parrington, A. Galione, A.M. Evans, TPCs: Endolysosomal channels for Ca<sup>2+</sup> mobilization from acidic organelles triggered by NAADP, *FEBS Lett.* 584 (2010) 1966–1974, <https://doi.org/10.1016/j.febslet.2010.02.028>.
- [297] K. Ishibashi, M. Suzuki, M. Imai, Molecular cloning of a novel form (two-repeat) protein related to voltage-gated sodium and calcium channels, *Biochem. Biophys. Res. Commun.* 270 (2000) 370–376, <https://doi.org/10.1006/bbrc.2000.2435>.
- [298] P.A. Anderson, R.M. Greenberg, Phylogeny of ion channels: clues to structure and function, *Comp. Biochem. Physiol. B Biochem. Mol. Biol.* 129 (2001) 17–28, [https://doi.org/10.1016/s1096-4959\(01\)00376-1](https://doi.org/10.1016/s1096-4959(01)00376-1).
- [299] E. Peifer, F.J.M. Maathuis, L.N. Mills, H. Knight, J. Pelloux, A.M. Hetherington, D. Sanders, The vacuolar Ca<sup>2+</sup>-activated channel TPC1 regulates germination and stomatal movement, *Nature* 434 (2005) 404–408, <https://doi.org/10.1038/nature03381>.
- [300] 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 Ca<sup>2+</sup> and Na<sup>+</sup> channels, *Sci. Signal.* 7 (2014), <https://doi.org/10.1126/scisignal.2005450> ra109.
- [301] S. Patel, X. Cai, Evolution of acidic Ca<sup>2+</sup> stores and their resident Ca<sup>2+</sup>-permeable channels, *Cell Calcium* 57 (2015) 222–230, <https://doi.org/10.1016/j.ceca.2014.12.005>.
- [302] V. Rybalchenko, M. Ahuja, J. Coblenz, D. Churamani, S. Patel, K. Kiselyov, S. Mualem, Membrane potential regulates nicotinic acid adenine dinucleotide phosphate (NAADP) dependence of the pH- and Ca<sup>2+</sup>-sensitive organelar two-

- pore channel TPC1, *J. Biol. Chem.* 287 (2012) 20407–20416, <https://doi.org/10.1074/jbc.M112.359612>.
- [303] F. Ye, L. Xu, X. Li, W. Zeng, N. Gan, C. Zhao, W. Yang, Y. Jiang, J. Guo, Voltage-gating and cytosolic Ca<sup>2+</sup> activation mechanisms of *Arabidopsis* two-pore channel AtTPC1, *Proc. Natl. Acad. Sci. U. S. A.* 118 (2021), <https://doi.org/10.1073/pnas.2113946118> e2113946118.
- [304] S.J. Pitt, T.M. Funnell, M. Sitsapesan, E. Venturi, K. Rieddorf, M. Ruas, A. Ganesan, R. Gosain, G.C. Churchill, M.X. Zhu, J. Parrington, A. Galione, R. Sitsapesan, TPC2 is a novel NAADP-sensitive Ca<sup>2+</sup> release channel, operating as a dual sensor of luminal pH and Ca<sup>2+</sup>, *J. Biol. Chem.* 285 (2010) 35039–35046, <https://doi.org/10.1074/jbc.M110.156927>.
- [305] 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<sup>+</sup> channels, *Elife* 8 (2019), <https://doi.org/10.7554/elife.51423>.
- [306] E. Brailoiu, T. Rahman, D. Churamani, D.L. Prole, G.C. Brailoiu, R. Hooper, C. W. Taylor, S. Patel, An NAADP-gated two-pore channel targeted to the plasma membrane uncouples triggering from amplifying Ca<sup>2+</sup> signals, *J. Biol. Chem.* 285 (2010) 38511–38516, <https://doi.org/10.1074/jbc.M110.162073>.
- [307] M. Schieder, K. Rötzer, A. Brüggemann, M. Biel, C.A. Wahl-Schott, Characterization of two-pore channel 2 (TPCN2)-mediated Ca<sup>2+</sup> currents in isolated lysosomes, *J. Biol. Chem.* 285 (2010) 21219–21222, <https://doi.org/10.1074/jbc.C110.143123>.
- [308] 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>.
- [309] C.S.-K. Lee, B.C.-K. Tong, C.W.-H. Cheng, H.C.-H. Hung, K.-H. Cheung, Characterization of Two-Pore Channel 2 by Nuclear Membrane Electrophysiology, *Sci. Rep.* 6 (2016) 20282, <https://doi.org/10.1038/srep20282>.
- [310] S. Gerndt, C.-C. Chen, Y.-K. Chao, Y. Yuan, S. Burgstaller, A. Scotto Rosato, E. Krogsæter, 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>.
- [311] A. Jha, M. Ahuja, S. Patel, E. Brailoiu, S. Muallem, Convergent regulation of the lysosomal two-pore channel-2 by Mg<sup>2+</sup>, NAADP, PI(3,5)P<sub>2</sub> and multiple protein kinases, *EMBO J* 33 (2014) 501–511, <https://doi.org/10.1002/embj.201387035>.
- [312] S.J. Pitt, A.K.M. Lam, K. Rieddorf, A. Galione, R. Sitsapesan, Reconstituted human TPC1 is a proton-permeable ion channel and is activated by NAADP or Ca<sup>2+</sup>, *Sci. Signal.* 7 (2014) <https://doi.org/10.1126/scisignal.2004854> ra46.
- [313] C. Cang, K. Aranda, D. Ren, A non-inactivating high-voltage-activated two-pore Na<sup>+</sup> channel that supports ultra-long action potentials and membrane bistability, *Nat. Commun.* 5 (2014), <https://doi.org/10.1038/ncomms6015>, 5015.
- [314] A.J. Morgan, A. Galione, Two-pore channels (TPCs): current controversies, *BioEssays News Rev. Mol. Cell. Dev. Biol.* 36 (2014) 173–183, <https://doi.org/10.1002/bies.201300118>.
- [315] M. Yamasaki, J.M. Thomas, G.C. Churchill, C. Garnham, A.M. Lewis, J.-M. Cancela, S. Patel, A. Galione, Role of NAADP and cADPR in the induction and maintenance of agonist-evoked Ca<sup>2+</sup> spiking in mouse pancreatic acinar cells, *Curr. Biol.* 15 (2005) 874–878, <https://doi.org/10.1016/j.cub.2005.04.033>.
- [316] 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–C239, <https://doi.org/10.1152/ajpcell.00638.2005>.
- [317] M. Mushtaq, T.-S. Nam, U.-H. Kim, Critical role for CD38-mediated Ca<sup>2+</sup> signaling in thrombin-induced procoagulant activity of mouse platelets and hemostasis, *J. Biol. Chem.* 286 (2011) 12952–12958, <https://doi.org/10.1074/jbc.M110.207100>.
- [318] A. Macgregor, M. Yamasaki, S. Rakovic, L. Sanders, R. Parkesh, G.C. Churchill, A. Galione, D.A. Terrar, NAADP controls cross-talk between distinct Ca<sup>2+</sup> stores in the heart, *J. Biol. Chem.* 282 (2007) 15302–15311, <https://doi.org/10.1074/jbc.M611167200>.
- [319] J. Hermann, M. Bender, D. Schumacher, M.S. Woo, A. Shaposhnykov, S. C. Rosenkranz, V. Kuryshev, C. Meier, A.H. Guse, M.A. Friese, M. Freichel, V. Tsvilovsky, Contribution of NAADP to Glutamate-Evoked Changes in Ca<sup>2+</sup> Homeostasis in Mouse Hippocampal Neurons, *Front. Cell Dev. Biol.* 8 (2020), <https://doi.org/10.3389/fcell.2020.00496>, 496.
- [320] E. Naylor, A. Arredouani, S.R. Vasudevan, A.M. Lewis, R. Parkesh, A. Mizote, D. Rosen, J.M. Thomas, M. Izumi, A. Ganesan, A. Galione, G.C. Churchill, Identification of a chemical probe for NAADP by virtual screening, *Nat. Chem. Biol.* 5 (2009) 220–226, <https://doi.org/10.1038/nchembio.150>.
- [321] A. Favia, M. Desideri, G. Gambara, A. D'Alessio, M. Ruas, B. Esposito, D. Del Bufalo, J. Parrington, E. Ziparo, F. Palombi, A. Galione, A. Filippini, VEGF-induced neoangiogenesis is mediated by NAADP and two-pore channel-2-dependent Ca<sup>2+</sup> signaling, *Proc. Natl. Acad. Sci. U. S. A.* 111 (2014) E4706–E4715, <https://doi.org/10.1073/pnas.1406029111>.
- [322] D. Rosen, A.M. Lewis, A. Mizote, J.M. Thomas, P.K. Aley, S.R. Vasudevan, R. Parkesh, A. Galione, M. Izumi, A. Ganesan, G.C. Churchill, Analogues of the nicotinic acid adenine dinucleotide phosphate (NAADP) antagonist Ned-19 indicate two binding sites on the NAADP receptor, *J. Biol. Chem.* 284 (2009) 34930–34934, <https://doi.org/10.1074/jbc.M109.016519>.
- [323] R.A. Capel, E.L. Bolton, W.K. Lin, D. Aston, Y. Wang, W. Liu, X. Wang, R.-A. B. Burton, D. Bloor-Young, K.-T. Shade, M. Ruas, J. Parrington, G.C. Churchill, M. Lei, A. Galione, D.A. Terrar, Two-pore Channels (TPC2s) and Nicotinic Acid Adenine Dinucleotide Phosphate (NAADP) at Lysosomal-Sarcoplasmic Reticular Junctions Contribute to Acute and Chronic β-Adrenoceptor Signaling in the Heart, *J. Biol. Chem.* 290 (2015) 30087–30098, <https://doi.org/10.1074/jbc.M115.684076>.
- [324] G.J.S. Pereira, H. Hirata, G.M. Firmino, L.G. do Carmo, C. Bincoletto, S.W. Han, R. S. Stilhano, R.P. Ureshino, D. Bloor-Young, G. Churchill, M. Piacentini, S. Patel, S. S. Smalli, Nicotinic Acid Adenine Dinucleotide Phosphate (NAADP) Regulates Autophagy in Cultured Astrocytes, *J. Biol. Chem.* 286 (2011) 27875–27881, <https://doi.org/10.1074/jbc.C110.216580>.
- [325] K.-H. Park, B.-J. Kim, A.I. Shawl, M.-K. Han, H.C. Lee, U.-H. Kim, Autocrine/paracrine function of nicotinic acid adenine dinucleotide phosphate (NAADP) for glucose homeostasis in pancreatic β-cells and adipocytes, *J. Biol. Chem.* 288 (2013) 35548–35558, <https://doi.org/10.1074/jbc.M113.489278>.
- [326] A.C. Heidemann, C.G. Schipke, H. Kettenmann, Extracellular application of nicotinic acid adenine dinucleotide phosphate induces Ca<sup>2+</sup> signaling in astrocytes *in situ*, *J. Biol. Chem.* 280 (2005) 35630–35640, <https://doi.org/10.1074/jbc.M507338200>.
- [327] M. Barceló-Tornés, A.M. Lewis, A. Gubert, D. Barneda, D. Bloor-Young, F. Picatoste, G.C. Churchill, E. Claro, R. Masgrau, NAADP mediates ATP-induced Ca<sup>2+</sup> signals in astrocytes, *FEBS Lett.* 585 (2011) 2300–2306, <https://doi.org/10.1016/j.febslet.2011.05.062>.
- [328] A.J. Morgan, Y. Yuan, S. Patel, A. Galione, Does lysosomal rupture evoke Ca<sup>2+</sup> release? A question of pores and stores, *Cell Calcium* 86 (2020), 102139, <https://doi.org/10.1016/j.ceca.2019.102139>.
- [329] R.T. Mallmann, N. Klugbauer, Genetic Inactivation of Two-Pore Channel 1 Impairs Spatial Learning and Memory, *Behav. Genet.* 50 (2020) 401–410, <https://doi.org/10.1007/s10519-020-10011-1>.
- [330] J.J. Kelu, S.E. Webb, A. Galione, A.L. Miller, TPC2-mediated Ca<sup>2+</sup> signaling is required for the establishment of synchronized activity in developing zebrafish primary motor neurons, *Dev. Biol.* 438 (2018) 57–68, <https://doi.org/10.1016/j.ydbio.2018.02.011>.
- [331] C. Guo, S.E. Webb, C.M. Chan, A.L. Miller, TPC2-mediated Ca<sup>2+</sup> signaling is required for axon extension in caudal primary motor neurons in zebrafish embryos, *J. Cell Sci.* 133 (2020), jcs244780, <https://doi.org/10.1242/jcs.244780>.
- [332] A.A. Genazzani, R.M. Empson, A. Galione, Unique inactivation properties of NAADP-sensitive Ca<sup>2+</sup> release, *J. Biol. Chem.* 271 (1996) 11599–11602, <https://doi.org/10.1074/jbc.271.20.11599>.
- [333] P. Netcharoensirisut, C. Abrahamian, R. Tang, C.-C. Chen, A.S. Rosato, W. Beyers, Y.-K. Chao, A. Filippini, S. Di Pietro, K. Bartel, M. Biel, A.M. Vollmar, K. Umehara, W. De-Eknakul, C. Grimm, Flavonoids increase melanin production and reduce proliferation, migration and invasion of melanoma cells by blocking endolysosomal/melanosomal TPC2, *Sci. Rep.* 11 (2021) 8515, <https://doi.org/10.1038/s41598-021-88196-6>.
- [334] M. Müller, S. Gerndt, Y.-K. Chao, T. Zisis, O.N.P. Nguyen, A. Gerwien, N. Urban, C. Müller, F.A. Gegenfurtner, F. Geisslinger, C. Ortler, C.-C. Chen, S. Zahler, M. Biel, M. Schaefer, C. Grimm, F. Bracher, A.M. Vollmar, K. Bartel, Gene editing and synthetically accessible inhibitors reveal role for TPC2 in HCC cell proliferation and tumor growth, *Cell Chem. Biol.* 28 (2021), <https://doi.org/10.1016/j.chembiol.2021.01.023>, 1119–1131.e27.
- [335] Y. Sakurai, A.A. Kolokoltsov, C.-C. Chen, M.W. Tidwell, W.E. Bauta, N. Klugbauer, C. Grimm, C. Wahl-Schott, M. Biel, R.A. Davey, Ebola virus. Two-pore channels control Ebola virus host cell entry and are drug targets for disease treatment, *Science* 347 (2015) 995–998, <https://doi.org/10.1126/science.1258758>.
- [336] I. Pafumi, M. Festa, F. Papacci, L. Lagostena, C. Giunta, V. Gutta, L. Cornara, A. Favia, F. Palombi, F. Gambale, A. Filippini, A. Carpaneto, Naringenin Impairs Two-Pore Channel 2 Activity And Inhibits VEGF-Induced Angiogenesis, *Sci. Rep.* 7 (2017) 5121, <https://doi.org/10.1038/s41598-017-04974-1>.
- [337] K. Wiśniewski, H. Car, S)-3,5-DHPG: A Review, *CNS Drug Rev* 8 (2002) 101–116, <https://doi.org/10.1111/j.1527-3458.2002.tb00218.x>.
- [338] H. Lavreyens, R. Wouters, F. Bischoff, S. Nóbrega Pereira, X. Langlois, S. Blokland, M. Somers, L. Dillen, A.S.J. Lesage, JNJ16259685, a highly potent, selective and systemically active mGlu1 receptor antagonist, *Neuropharmacology* 47 (2004) 961–972, <https://doi.org/10.1016/j.neuropharm.2004.08.007>.
- [339] S.-Y. Rah, K.-H. Park, M.-K. Han, M.-J. Im, U.-H. Kim, Activation of CD38 by interleukin-8 signaling regulates intracellular Ca<sup>2+</sup> level and motility of lymphokine-activated killer cells, *J. Biol. Chem.* 280 (2005) 2888–2895, <https://doi.org/10.1074/jbc.M40952200>.
- [340] J. Drach, T. McQueen, H. Engel, M. Andreeff, K.A. Robertson, S.J. Collins, F. Malavasi, K. Mehta, Retinoic acid-induced expression of CD38 antigen in myeloid cells is mediated through retinoic acid receptor-alpha, *Cancer Res* 54 (1994) 1746–1752.
- [341] K. Kontani, H. Nishina, Y. Ohoka, K. Takahashi, T. Katada, NAD glycohydrolase specifically induced by retinoic acid in human leukemic HL-60 cells. Identification of the NAD glycohydrolase as leukocyte cell surface antigen CD38, *J. Biol. Chem.* 268 (1993) 16895–16898.
- [342] E. Blacher, B. Ben Baruch, A. Levy, N. Geva, K.D. Green, S. Garneau-Tsodikova, M. Fridman, R. Stein, Inhibition of glioma progression by a newly discovered CD38 inhibitor, *Int. J. Cancer.* 136 (2015) 1422–1433, <https://doi.org/10.1002/ijc.29095>.
- [343] C.D. Haffner, J.D. Becherer, E.E. Boros, R. Cadilla, T. Carpenter, D. Cowan, D. N. Deaton, Y. Guo, W. Harrington, B.R. Henke, M.R. Jeune, I. Kaldor, N. Milliken, K.G. Petrov, F. Preugschat, C. Schulte, B.G. Shearer, T. Shearer, T.L. Smalley, E. L. Stewart, J.D. Stuart, J.C. Ulrich, Discovery, Synthesis, and Biological

- Evaluation of Thiazoloquin(az)olin(on)es as Potent CD38 Inhibitors, *J. Med. Chem.* 58 (2015) 3548–3571, <https://doi.org/10.1021/jm502009h>.
- [344] Y. Jiang, T. Liu, C.-H. Lee, Q. Chang, J. Yang, Z. Zhang, The NAD+-mediated self-inhibition mechanism of pro-neurodegenerative SARM1, *Nature* 588 (2020) 658–663, <https://doi.org/10.1038/s41586-020-2862-z>.
- [345] A. Loreto, M. Di Stefano, M. Gering, L. Conforti, Wallerian Degeneration Is Executed by an NMN-SARM1-Dependent Late Ca(2+) Influx but Only Modestly Influenced by Mitochondria, *Cell Rep* 13 (2015) 2539–2552, <https://doi.org/10.1016/j.celrep.2015.11.032>.
- [346] M. Di Stefano, I. Nascimento-Ferreira, G. Orsomando, V. Mori, J. Gilley, R. Brown, L. Janeckova, M.E. Vargas, L.A. Worrell, A. Loreto, J. Tickle, J. Patrick, J.R. M. Webster, M. Marangoni, F.M. Carpi, S. Puccirelli, F. Rossi, W. Meng, A. Sagasti, R.R. Ribchester, G. Magni, M.P. Coleman, L. Conforti, A rise in NAD precursor nicotinamide mononucleotide (NMN) after injury promotes axon degeneration, *Cell Death Differ* 22 (2015) 731–742, <https://doi.org/10.1038/cdd.2014.164>.
- [347] Y. Sasaki, J. Zhu, Y. Shi, W. Gu, B. Kobe, T. Ve, A. DiAntonio, J. Milbrandt, Nicotinic acid mononucleotide is an allosteric SARM1 inhibitor promoting axonal protection, 2021. [10.1101/2021.07.15.452560](https://doi.org/10.1101/2021.07.15.452560).
- [348] R.O. Hughes, T. Bosanac, X. Mao, T.M. Engber, A. DiAntonio, J. Milbrandt, R. Devraj, R. Krauss, Small Molecule SARM1 Inhibitors Recapitulate the SARM1–/– Phenotype and Allow Recovery of a Metastable Pool of Axons Fated to Degenerate, *Cell Rep* 34 (2021), 108588, <https://doi.org/10.1016/j.celrep.2020.108588>.
- [349] T.F. Walshet, H.C. Lee, Synthesis and characterization of antagonists of cyclic-ADP-ribose-induced Ca2+ release, *Biochim. Biophys. Acta.* 1178 (1993) 235–242, [https://doi.org/10.1016/0167-4889\(93\)90199-y](https://doi.org/10.1016/0167-4889(93)90199-y).
- [350] J.M. Cancela, O.H. Petersen, The cyclic ADP ribose antagonist 8-NH2-cADP-ribose blocks cholecystokinin-evoked cytosolic Ca2+ spiking in pancreatic acinar cells, *Pflugers Arch* 435 (1998) 746–748, <https://doi.org/10.1007/s004240050578>.
- [351] O. Thastrup, P.J. Cullen, B.K. Drøbak, M.R. Hanley, A.P. Dawson, Thapsigargin, a tumor promoter, discharges intracellular Ca2+ stores by specific inhibition of the endoplasmic reticulum Ca2+(+)-ATPase, *Proc. Natl. Acad. Sci. U. S. A.* 87 (1990) 2466–2470, <https://doi.org/10.1073/pnas.87.7.2466>.
- [352] G.A. Moore, D.J. McConkey, G.E. Kass, P.J. O'Brien, S. Orrenius, 2,5-Di(tert-butyl)-1,4-benzodihydroquinoine—a novel inhibitor of liver microsomal Ca2+ sequestration, *FEBS Lett* 224 (1987) 331–336, [https://doi.org/10.1016/0014-5793\(87\)80479-9](https://doi.org/10.1016/0014-5793(87)80479-9).
- [353] N.W. Seidler, I. Jona, M. Vegh, A. Martonosi, Cyclopiazonic acid is a specific inhibitor of the Ca2+-ATPase of sarcoplasmic reticulum, *J. Biol. Chem.* 264 (1989) 17816–17823.
- [354] D.E. Goeger, R.T. Riley, J.W. Dorner, R.J. Cole, Cyclopiazonic acid inhibition of the Ca2+-transport ATPase in rat skeletal muscle sarcoplasmic reticulum vesicles, *Biochem. Pharmacol.* 37 (1988) 978–981, [https://doi.org/10.1016/0006-2952\(88\)90195-5](https://doi.org/10.1016/0006-2952(88)90195-5).
- [355] T. Maruyama, T. Kanaji, S. Nakade, T. Kanno, K. Mikoshiba, 2APB, 2-aminoethoxydiphenyl borate, a membrane-penetrable modulator of Ins(1,4,5)P3-induced Ca2+ release, *J. Biochem. (Tokyo)* 122 (1997) 498–505, <https://doi.org/10.1093/oxfordjournals.jbchem.a021780>.
- [356] J. Gafni, J.A. Munsch, T.H. Lam, M.C. Catlin, L.G. Costa, T.F. Molinski, I. N. Pessah, Xestospingins: potent membrane permeable blockers of the inositol 1,4,5-trisphosphate receptor, *Neuron* 19 (1997) 723–733, [https://doi.org/10.1016/s0896-6273\(00\)80384-0](https://doi.org/10.1016/s0896-6273(00)80384-0).
- [357] E.C. Toescu, S.C. O'Neill, O.H. Petersen, D.A. Eisner, Caffeine inhibits the agonist-evoked cytosolic Ca2+ signal in mouse pancreatic acinar cells by blocking inositol trisphosphate production, *J. Biol. Chem.* 267 (1992) 23467–23470, [https://doi.org/10.1016/S0021-9258\(18\)35860-5](https://doi.org/10.1016/S0021-9258(18)35860-5).
- [358] J.R. Brorson, D. Bleakman, S.J. Gibbons, R.J. Miller, The properties of intracellular calcium stores in cultured rat cerebellar neurons, *J. Neurosci. Off. J. Soc. Neurosci.* 11 (1991) 4024–4043.
- [359] B.R. Fruen, J.R. Mickelson, C.F. Louis, Dantrolene inhibition of sarcoplasmic reticulum Ca2+ release by direct and specific action at skeletal muscle ryanodine receptors, *J. Biol. Chem.* 272 (1997) 26965–26971, <https://doi.org/10.1074/jbc.272.43.26965>.
- [360] A.J. Ricci, Y.-C. Wu, R. Fettiplace, The Endogenous Calcium Buffer and the Time Course of Transducer Adaptation in Auditory Hair Cells, *J. Neurosci.* 18 (1998) 8261–8277, <https://doi.org/10.1523/JNEUROSCI.18-20-08261.1998>.
- [361] R.Y. Tsien, New calcium indicators and buffers with high selectivity against magnesium and protons: design, synthesis, and properties of prototype structures, *Biochemistry* 19 (1980) 2396–2404, <https://doi.org/10.1021/bi00552a018>.
- [362] N. Stockbridge, EGTA, Comput. Biol. Med. 17 (1987) 299–304, [https://doi.org/10.1016/0010-4825\(87\)90019-9](https://doi.org/10.1016/0010-4825(87)90019-9).
- [363] F.S. Sadek, R.W. Schmid, C.N. Reiley, Visual egta titration of calcium in the, presence of magnesium, *Talanta* 2 (1959) 38–51, [https://doi.org/10.1016/0039-9140\(59\)80028-X](https://doi.org/10.1016/0039-9140(59)80028-X).
- [364] 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>.
- [365] M. Samie, X. Wang, X. Zhang, A. Goschka, X. Li, X. Cheng, E. Gregg, M. Azar, Y. Zhuo, A.G. Garrity, Q. Gao, S. Slaugenhaupt, J. Pickel, S.N. Zolov, L. S. Weisman, G.M. Lenk, S. Titus, M. Bryant-Genevier, N. Southall, M. Juan, M. Ferrer, H. Xu, A TRP channel in the lysosome regulates large particle phagocytosis via focal exocytosis, *Dev. Cell.* 26 (2013) 511–524, <https://doi.org/10.1016/j.devcel.2013.08.003>.
- [366] E.J. Bowman, A. Siebers, K. Altendorf, Baflomycins: a class of inhibitors of membrane ATPases from microorganisms, animal cells, and plant cells, *Proc. Natl. Acad. Sci. U. S. A.* 85 (1988) 7972–7976, <https://doi.org/10.1073/pnas.85.21.7972>.
- [367] L.C. Davis, A.J. Morgan, A. Galione, NAADP-regulated two-pore channels drive phagocytosis through endo-lysosomal Ca2+ nanodomains, calcineurin and dynamin, *EMBO J* (2020), <https://doi.org/10.1525/embj.2019104058>.
- [368] M. Jadot, C. Colmant, S. Wattiaux-De Coninck, R. Wattiaux, Intralysosomal hydrolysis of glycyl-l-phenylalanine 2-naphthylamide, *Biochem. J.* 219 (1984) 965–970, <https://doi.org/10.1042/bj2190965>.
- [369] C.J. Penny, K. Vassileva, A. Jha, Y. Yuan, X. Chee, E. Yates, M. Mazzon, B. S. Kilpatrick, S. Muallem, M. Marsh, T. Rahman, S. Patel, Mining of Ebola virus entry inhibitors identifies approved drugs as two-pore channel pore blockers, *Biochim. Biophys. Acta Mol. Cell Res.* 1866 (2019) 1151–1161, <https://doi.org/10.1016/j.bbamcr.2018.10.022>.
- [370] S. Patel, E. Braillouin, Triggering of Ca2+ signals by NAADP-gated two-pore channels: a role for membrane contact sites? *Biochem. Soc. Trans.* 40 (2012) 153–157, <https://doi.org/10.1042/BST2010693>.
- [371] M.X. Zhu, J. Ma, J. Parrington, P.J. Craft, A. Galione, A.M. Evans, Calcium signaling via two-pore channels: local or global, that is the question, *Am. J. Physiol. Cell Physiol.* 298 (2010) C430–C441, <https://doi.org/10.1152/ajpcell.00475.2009>.
- [372] 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), <https://doi.org/10.1038/srep43900>, 43900.
- [373] J.M. Cancela, F. Van Coppenolle, A. Galione, A.V. Tepikin, O.H. Petersen, Transformation of local Ca2+ spikes to global Ca2+ transients: the combinatorial roles of multiple Ca2+ releasing messengers, *EMBO J* 21 (2002) 909–919, <https://doi.org/10.1093/emboj/21.5.909>.
- [374] W. Dammermann, A.H. Guse, Functional ryanodine receptor expression is required for NAADP-mediated local Ca2+ signaling in T-lymphocytes, *J. Biol. Chem.* 280 (2005) 21394–21399, <https://doi.org/10.1074/jbc.M413085200>.
- [375] T.P. Collins, R. Bayliss, G.C. Churchill, A. Galione, D.A. Terrar, NAADP influences excitation-contraction coupling by releasing calcium from lysosomes in atrial myocytes, *Cell Calcium* 50 (2011) 449–458, <https://doi.org/10.1016/j.ceca.2011.07.007>.
- [376] N.P. Kinnear, C.N. Wyatt, J.H. Clark, P.J. Craft, S. Fleischer, L.H. Jeyakumar, G.F. Nixon, A.M. Evans, Lysosomes co-localize with ryanodine receptor subtype 3 to form a trigger zone for calcium signalling by NAADP in rat pulmonary arterial smooth muscle, *Cell Calcium* 44 (2008) 190–201, <https://doi.org/10.1016/j.ceca.2007.11.003>.
- [377] B.-P. Diercks, R. Werner, D. Schetelig, I.M.A. Wolf, A.H. Guse, High-Resolution Calcium Imaging Method for Local Calcium Signaling, *Methods Mol. Biol.* Clifton NJ. 1929 (2019) 27–39, [https://doi.org/10.1007/978-1-4939-9030-6\\_3](https://doi.org/10.1007/978-1-4939-9030-6_3).
- [378] J.M. Cancela, Specific Ca2+ signaling evoked by cholecystokinin and acetylcholine: the roles of NAADP, cADPR, and IP3, *Annu. Rev. Physiol.* 63 (2001) 99–117, <https://doi.org/10.1146/annurev.physiol.63.1.99>.
- [379] G.C. Churchill, A. Galione, NAADP induces Ca2+ oscillations via a two-pool mechanism by priming IP3- and cADPR-sensitive Ca2+ stores, *EMBO J* 20 (2001) 2666–2671, <https://doi.org/10.1093/emboj/20.11.2666>.
- [380] A. Arredouani, M. Ruas, S.C. Collins, R. Parkesh, F. Clough, T. Pillinger, G. Colart, K. Rieddorf, A. Royle, P. Johnson, M. Braun, Q. Zhang, W. Sones, K. Shimomura, A.J. Morgan, A.M. Lewis, K.-T. Chuang, R. Tunn, J. Gadea, L. Teboul, P.M. Heister, P.W. Tynan, E.A. Bellomo, G.A. Rutter, P. Rorsman, G. C. Churchill, J. Parrington, A. Galione, Nicotinic Acid Adenine Dinucleotide Phosphate (NAADP) and Endolysosomal Two-pore Channels Modulate Membrane Excitability and Stimulus-Secretion Coupling in Mouse Pancreatic β Cells, *J. Biol. Chem.* 290 (2015) 21376–21392, <https://doi.org/10.1074/jbc.M115.671248>.
- [381] E. Arlt, M. Fraticelli, V. Tsvilovsky, W. Nadolni, A. Breit, T.J. O'Neill, S. Resenberger, G. Wennemuth, C. Wahl-Schott, M. Biel, C. Grimm, M. Freichel, T. Gudermann, N. Klugbauer, I. Boekhauer, S. Zierler, TPC1 deficiency or blockade augments systemic anaphylaxis and mast cell activity, *Proc. Natl. Acad. Sci. U. S. A.* 117 (2020) 18068–18078, <https://doi.org/10.1073/pnas.1920122117>.
- [382] M. Ruas, K.-T. Chuang, L.C. Davis, A. Al-Douri, P.W. Tynan, R. Tunn, L. Teboul, A. Galione, J. Parrington, TPC1 has two variant isoforms, and their removal has different effects on endo-lysosomal functions compared to loss of TPC2, *Mol. Cell. Biol.* 34 (2014) 3981–3992, <https://doi.org/10.1128/MCB.00113-14>.
- [383] C. Grimm, L.M. Holdt, C.-C. Chen, S. Hassan, C. Müller, S. Jörs, H. Cuny, S. Kissing, B. Schröder, E. Butz, B. Northoff, J. Castonguay, C.A. Luber, M. Moser, S. Spahn, R. Lüllmann-Rauch, C. Fendel, N. Klugbauer, O. Griesbeck, A. Haas, M. Mann, F. Bracher, D. Teupser, P. Saftig, M. Biel, C. Wahl-Schott, High susceptibility to fatty liver disease in two-pore channel 2-deficient mice, *Nat. Commun.* 5 (2014), <https://doi.org/10.1038/ncomms5699>, 4699.
- [384] 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>.
- [385] F. Moccia, E. Zuccolo, F. Di Nezza, G. Pellavio, P.S. Faris, S. Negri, A. De Luca, U. Laforenza, L. Ambrosone, V. Rosti, G. Guerra, Nicotinic acid adenine dinucleotide phosphate activates two-pore channel TPC1 to mediate lysosomal Ca2+ release in endothelial colony-forming cells, *J. Cell. Physiol.* 236 (2021) 688–705, <https://doi.org/10.1002/jcp.29896>.
- [386] S. Patel, G.C. Churchill, T. Sharp, A. Galione, Widespread distribution of binding sites for the novel Ca2+-mobilizing messenger, nicotinic acid adenine

- dinucleotide phosphate, in the brain, *J. Biol. Chem.* 275 (2000) 36495–36497, <https://doi.org/10.1074/jbc.C000458200>.
- [387] G.J.S. Pereira, M. Antonioli, H. Hirata, R.P. Ureshino, A.R. Nascimento, C. Bincoletto, T. Vescovo, M. Piacentini, G.M. Fimia, S.S. Smaili, Glutamate induces autophagy via the two-pore channels in neural cells, *Oncotarget* 8 (2017) 12730–12740, <https://doi.org/10.18632/oncotarget.14404>.
- [388] P.K. Aley, A.M. Mikolajczyk, B. Munz, G.C. Churchill, A. Galione, F. Berger, Nicotinic acid adenine dinucleotide phosphate regulates skeletal muscle differentiation via action at two-pore channels, *Proc. Natl. Acad. Sci. U. S. A.* 107 (2010) 19927–19932, <https://doi.org/10.1073/pnas.1007381107>.
- [389] A. Arredouani, A.M. Evans, J. Ma, J. Parrington, M.X. Zhu, A. Galione, An emerging role for NAADP-mediated Ca<sup>2+</sup> signaling in the pancreatic β-cell, *Islets* 2 (2010) 323–330, <https://doi.org/10.4161/isl.2.5.12747>.
- [390] E. Brailoiu, M.D. Miyamoto, N.J. Dun, Nicotinic acid adenine dinucleotide phosphate enhances quantal neurosecretion at the frog neuromuscular junction: possible action on synaptic vesicles in the releasable pool, *Mol. Pharmacol.* 60 (2001) 718–724.
- [391] E. Brailoiu, S. Patel, N.J. Dun, Modulation of spontaneous transmitter release from the frog neuromuscular junction by interacting intracellular Ca(2+) stores: critical role for nicotinic acid adenine dinucleotide phosphate (NAADP), *Biochem. J.* 373 (2003) 313–318, <https://doi.org/10.1042/BJ20030472>.
- [392] L. McGuinness, S.J. Bardo, N.J. Emptage, The lysosome or lysosome-related organelle may serve as a Ca<sup>2+</sup> store in the boutons of hippocampal pyramidal cells, *Neuropharmacology* 52 (2007) 126–135, <https://doi.org/10.1016/j.neuropharm.2006.07.029>.
- [393] W. Bildl, T. Strassmaier, H. Thurm, J. Andersen, S. Eble, D. Oliver, M. Knipper, M. Mann, U. Schulte, J.P. Adelman, B. Fakler, Protein kinase CK2 is coassembled with small conductance Ca(2+)-activated K<sup>+</sup> channels and regulates channel gating, *Neuron* 43 (2004) 847–858, <https://doi.org/10.1016/j.neuron.2004.08.033>.
- [394] D. Allen, B. Fakler, J. Maylie, J.P. Adelman, Organization and regulation of small conductance Ca<sup>2+</sup>-activated K<sup>+</sup> channel multiprotein complexes, *J. Neurosci. Off. J. Soc. Neurosci.* 27 (2007) 2369–2376, <https://doi.org/10.1523/JNEUROSCI.3565-06.2007>.
- [395] E. Brailoiu, D. Churamani, V. Pandey, G.C. Brailoiu, F. Tuluc, S. Patel, N.J. Dun, Messenger-specific role for nicotinic acid adenine dinucleotide phosphate in neuronal differentiation, *J. Biol. Chem.* 281 (2006) 15923–15928, <https://doi.org/10.1074/jbc.M602249200>.
- [396] K. Singaravelu, J.W. Deitmer, Calcium mobilization by nicotinic acid adenine dinucleotide phosphate (NAADP) in rat astrocytes, *Cell Calcium* 39 (2006) 143–153, <https://doi.org/10.1016/j.ceca.2005.10.001>.
- [397] P.-H. Lin, P. Duann, S. Komazaki, K.H. Park, H. Li, M. Sun, M. Sermersheim, K. Gumpfer, J. Parrington, A. Galione, A.M. Evans, M.X. Zhu, J. Ma, Lysosomal two-pore channel subtype 2 (TPC2) regulates skeletal muscle autophagic signaling, *J. Biol. Chem.* 290 (2015) 3377–3389, <https://doi.org/10.1074/jbc.M114.608471>.
- [398] 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-Lleti, 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/JPhysiol.2013.327132>.
- [399] O.A. Ogunbayo, J. Duan, J. Xiong, Q. Wang, X. Feng, J. Ma, M.X. Zhu, A.M. Evans, mTORC1 controls lysosomal Ca<sup>2+</sup> release through the two-pore channel TPC2, *Sci. Signal.* 11 (2018), <https://doi.org/10.1126/scisignal.aao5775>.
- [400] K.M. Neely Kayala, G.D. Dickinson, A. Minassian, K.C. Walls, K.N. Green, F. M. Laferla, Presenilin-null cells have altered two-pore calcium channel expression and lysosomal calcium: implications for lysosomal function, *Brain Res* 1489 (2012) 8–16, <https://doi.org/10.1016/j.brainres.2012.10.036>.
- [401] Y. Lu, B. Hao, R. Graeff, J. Yue, NAADP/TPC2/Ca(2+) Signaling Inhibits Autophagy, *Commun. Integr. Biol.* 6 (2013), <https://doi.org/10.4161/cib.27595> e27595.
- [402] Y. Sancak, L. Bar-Peled, R. Zoncu, A.L. Markhard, S. Nada, D.M. Sabatini, Ragulator-Rag complex targets mTORC1 to the lysosomal surface and is necessary for its activation by amino acids, *Cell* 141 (2010) 290–303, <https://doi.org/10.1016/j.cell.2010.02.024>.
- [403] V.I. Korolchuk, D.C. Rubinsztein, Regulation of autophagy by lysosomal positioning, *Autophagy* 7 (2011) 927–928, <https://doi.org/10.4161/auto.7.18562>.
- [404] R. Zoncu, L. Bar-Peled, A. Efeyan, S. Wang, Y. Sancak, D.M. Sabatini, mTORC1 senses lysosomal amino acids through an inside-out mechanism that requires the vacuolar H(+)-ATPase, *Science* 334 (2011) 678–683, <https://doi.org/10.1126/science.1207056>.
- [405] T.A. Longden, F. Dabertrand, M. Koide, A.L. Gonzales, N.R. Tykocki, J.E. Brayden, D. Hill-Eubanks, M.T. Nelson, Capillary K<sup>+</sup>-sensing initiates retrograde hyperpolarization to increase local cerebral blood flow, *Nat. Neurosci.* 20 (2017) 717–726, <https://doi.org/10.1038/nn.4533>.
- [406] A.D. Hogan-Cann, P. Lu, C.M. Anderson, Endothelial NMDA receptors mediate activity-dependent brain hemodynamic responses in mice, *Proc. Natl. Acad. Sci. U. S. A.* 116 (2019) 10229–10231, <https://doi.org/10.1073/pnas.1902647116>.
- [407] G. Garthwaite, K. Bartus, D. Malcolm, D. Goodwin, M. Kolb-Sielecka, M. Kolb-Sielecka, C. Dooldeniya, J. Garthwaite, Signaling from blood vessels to CNS axons through nitric oxide, *J. Neurosci. Off. J. Soc. Neurosci.* 26 (2006) 7730–7740, <https://doi.org/10.1523/JNEUROSCI.1528-06.2006>.
- [408] R.D. Broadwell, B.J. Balin, M. Salzman, Transcytotic pathway for blood-borne protein through the blood-brain barrier, *Proc. Natl. Acad. Sci. U. S. A.* 85 (1988) 632–636, <https://doi.org/10.1073/pnas.85.2.632>.
- [409] G.C. Brailoiu, B. Gurzu, X. Gao, R. Parkesh, P.K. Aley, D.I. Trifa, A. Galione, N. J. Dun, M. Madesh, S. Patel, G.C. Churchill, E. Brailoiu, Acidic NAADP-sensitive calcium stores in the endothelium: agonist-specific recruitment and role in regulating blood pressure, *J. Biol. Chem.* 285 (2010) 37133–37137, <https://doi.org/10.1074/jbc.C110.169763>.
- [410] E. Zuccolo, D.A. Kheder, D. Lim, A. Perna, F.D. Nezza, L. Botta, G. Scarpellino, S. Negri, S. Martinotti, T. Soda, G. Forcaia, L. Riboni, E. Ranzato, G. Sancini, L. Ambrosone, E. D'Angelo, G. Guerra, F. Moccia, Glutamate triggers intracellular Ca<sup>2+</sup> oscillations and nitric oxide release by inducing NAADP- and InsP3-dependent Ca<sup>2+</sup> release in mouse brain endothelial cells, *J. Cell. Physiol.* 234 (2019) 3538–3554, <https://doi.org/10.1002/jcp.26953>.
- [411] E. Zuccolo, U. Laforenza, S. Negri, L. Botta, R. Berra-Romani, P. Faris, G. Scarpellino, G. Forcaia, G. Pellavio, G. Sancini, F. Moccia, Muscarinic M5 receptors trigger acetylcholine-induced Ca<sup>2+</sup> signals and nitric oxide release in human brain microvascular endothelial cells, *J. Cell. Physiol.* 234 (2019) 4540–4562, <https://doi.org/10.1002/jcp.27234>.
- [412] S. Negri, P. Faris, G. Pellavio, L. Botta, M. Orgiu, G. Forcaia, G. Sancini, U. Laforenza, F. Moccia, Group 1 metabotropic glutamate receptors trigger glutamate-induced intracellular Ca<sup>2+</sup> signals and nitric oxide release in human brain microvascular endothelial cells, *Cell. Mol. Life Sci. CMLS.* 77 (2020) 2235–2253, <https://doi.org/10.1007/s00018-019-03284-1>.
- [413] S. Negri, P. Faris, C. Maniezza, G. Pellavio, P. Spaiardi, L. Botta, U. Laforenza, G. Biella, D.F. Moccia, NMDA receptors elicit flux-independent intracellular Ca<sup>2+</sup> signals via metabotropic glutamate receptors and flux-dependent nitric oxide release in human brain microvascular endothelial cells, *Cell Calcium* 99 (2021), <https://doi.org/10.1016/j.ceca.2021.102454>, 102454.
- [414] R. Berra-Romani, P. Faris, G. Pellavio, M. Orgiu, S. Negri, G. Forcaia, V. Var-Gaz-Guadarrama, M. Garcia-Carrasco, L. Botta, G. Sancini, U. Laforenza, F. Moccia, Histamine induces intracellular Ca<sup>2+</sup> oscillations and nitric oxide release in endothelial cells from brain microvascular circulation, *J. Cell. Physiol.* 235 (2020) 1515–1530, <https://doi.org/10.1002/jcp.29071>.
- [415] A.J. Morgan, L.C. Davis, S.K.T.Y. Wagner, A.M. Lewis, J. Parrington, G. C. Churchill, A. Galione, Bidirectional Ca<sup>2+</sup> signaling occurs between the endoplasmic reticulum and acidic organelles, *J. Cell Biol.* 200 (2013) 789–805, <https://doi.org/10.1083/jcb.201204078>.
- [416] S. Navarro-Serna, A. Hachem, A. Canha-Gouveia, A. Hanbashi, G. Garrappa, J. S. Lopes, E. París-Oller, L. Sarrías-Gil, C. Flores-Flores, A. Bassett, R. Sánchez, P. Bermúdez-Alvarez, C. Matás, R. Romar, J. Parrington, J. Gadea, Generation of Nonmosaic, Two-Pore Channel 2 Biallelic Knockout Pigs in One Generation by CRISPR-Cas9 Microinjection Before Oocyte Insemination, *CRISPR J* 4 (2021) 132–146, <https://doi.org/10.1089/crispr.2020.0078>.
- [417] JM Cancela, et al., Two different but converging messenger pathways to intracellular Ca(2+) release: the roles of nicotinic acid adenine dinucleotide phosphate, cyclic ADP-ribose and inositol trisphosphate, *The EMBO journal* (2000), <https://doi.org/10.1093/emboj/19.11.2549>.