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Editorial

Acidic Ca^{2+} stores come to the fore

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ABSTRACT

Changes in the concentration of cytosolic Ca^{2+} form the basis of a ubiquitous signal transduction pathway. Accumulating evidence implicates acidic organelles in the control of Ca^{2+} dynamics in organisms across phyla. In this special issue, we discuss Ca^{2+} signalling by these "acidic Ca^{2+} stores" which include acidocalcisomes, vacuoles, the endo-lysosomal system, lysosome-related organelles, secretory vesicles and the Golgi complex. Ca^{2+} release from these morphologically very different organelles is mediated by members of the TRP channel superfamily and two-pore channels. Inositol trisphosphate and ryanodine receptors which are traditionally viewed as endoplasmic reticulum Ca^{2+} release channels can also mobilize acidic Ca^{2+} stores. Ca^{2+} uptake into acidic Ca^{2+} stores is driven by Ca^{2+} ATPases and Ca^{2+}/H^{+} exchangers. In animal cells, the Ca^{2+}-mobilizing messenger NAADP plays a central role in mediating Ca^{2+} signals from acidic Ca^{2+} stores through activation of two-pore channels. These signals are important for several physiological processes including muscle contraction and differentiation. Dysfunctional acidic Ca^{2+} stores have been implicated in diseases such as acute pancreatitis and lysosomal storage disorders. Acidic Ca^{2+} stores are therefore emerging as essential components of the Ca^{2+} signalling network and merit extensive further study.

1. Introduction

Ca^{2+} signals control a multitude of cellular events and derive from both the extracellular space and intracellular stores [1,2]. By far the best studied intracellular Ca^{2+} store is the endoplasmic reticulum (ER) with its well defined complement of Ca^{2+} pumps, buffers and Ca^{2+} release channels [1,2]. But it is clear that other organelles such as mitochondria and a variety of acidic compartments can also sequester and release Ca^{2+}. This Special Issue of *Cell Calcium* focuses on the role of acidic organelles in Ca^{2+} signalling. Organelles rich in both H^{+} and Ca^{2+}, the so called "acidic Ca^{2+} stores" include acidocalcisomes (best characterized in protists) and vacuoles (present in many organisms including plants and yeast). Organelles such as lysosomes and endosomes which are present in cells across phyla are also substantial acidic stores of Ca^{2+}. Together with lysosome-related organelles and secretory vesicles present in certain secretory cell types, and the ubiquitous Golgi complex (albeit mildly acidic) completes the line-up (Fig. 1). The functional grouping of this morphologically eclectic collection of organelles, and a brief overview of their roles played in Ca^{2+} signalling has recently been provided [3]. The aim of this special issue is to provide detail regarding each of these organelles with respect to Ca^{2+} handling with focus on the molecular mechanisms of Ca^{2+} uptake and release, and their physiological and patho-physiological roles.

2. Acidocalcisomes

The aptly named acidocalcisomes are small acidic organelles that contain high concentrations of Ca^{2+} [4]. They are also rich in phosphorous. They have been extensively studied in protists such as trypanosomes. These organelles play important physiological roles that include osmoregulation. Uptake of Ca^{2+} into these organelles is defined at the molecular level through the identification of Ca^{2+} ATPases but at present Ca^{2+}-permeable channels have evaded detection. The presence of acidocalcisomes has also been documented in animal cells and remarkably, prokaryotes. The latter may suggest that acidocalcisomes are primordial acidic Ca^{2+} stores. Clearly study of these organelles may shed light in to the working of other acidic Ca^{2+} stores. In particular, polyphosphate which is abundant in acidocalcisomes and known to bind cations including Ca^{2+}, may provide a conserved mechanism for buffering Ca^{2+} in acidic environments. Docampo and Moreno provides an overview of acidocalcisomes and their handling of Ca^{2+} [5].

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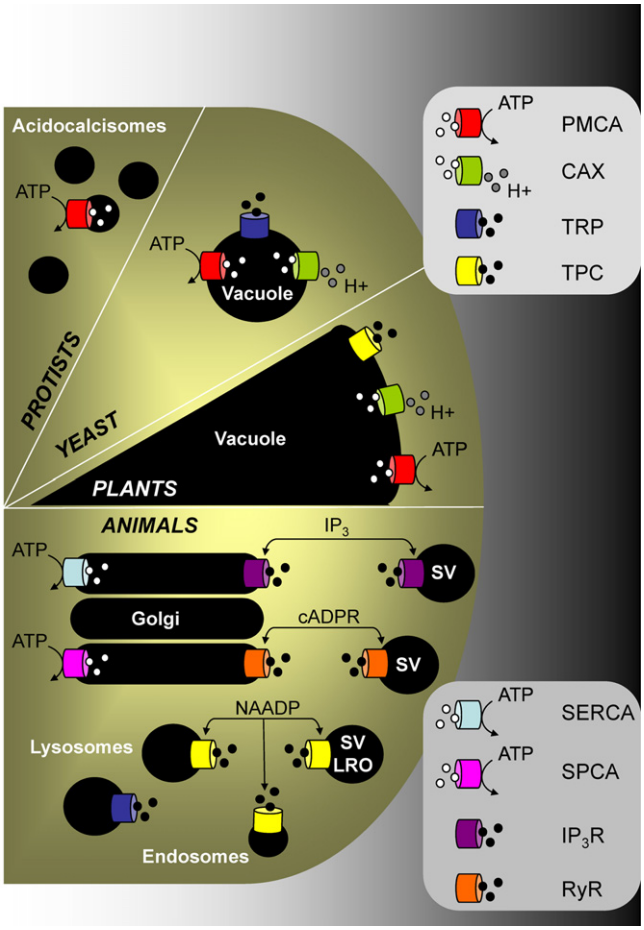

Fig. 1. The acidic Ca^{2+} stores. Schematic of cells from the indicated kingdoms showing their complement of acidic Ca^{2+} stores (black structures). Ca^{2+} pumps and channels where identified at the molecular level are depicted by the cylinders according to the keys on the right. SV, secretory vesicle; LRO, lysosome-related organelle.

3. Vacuoles

We next move to the plant and fungal worlds. Cells from both these organisms contain acidic vacuoles that represent the major store of Ca^{2+} within the cell. Ca^{2+} is the central signalling ion in plants and yeast and transduces many environmental and hormonal cues through oscillatory or sustained increases in cytosolic free Ca^{2+} concentration [6,7]. Peiter discusses vacuolar Ca^{2+} signalling in plants [8]. Several Ca^{2+}-permeable channels have been described on the plant vacuole through electrophysiological means but molecular correlates are lacking. The exception is the two-pore channel (TPC) which mediates the slow-vacuolar current [9]. Its importance is established in several physiological processes including stomatal closure. It is clear that TPCs are Ca^{2+}-permeable but whether plant TPCs mediate physiological Ca^{2+} signals in plants is debated.

In yeast, the best characterized Ca^{2+} release pathway from the vacuole at the molecular level is via the TRP channel, Yvc1 [10]. Cunningham discusses vacuolar Ca^{2+} signalling in yeast [11]. In this organism it is clear that Ca^{2+} signals can be sensed by calcineurin, which through the transcription factor Crz1, can regulate expression of the vacuolar Ca^{2+} uptake machinery thereby providing a feedback loop. The molecular basis for uptake of Ca^{2+} into vacuoles is detailed by Pittman [12]. This involves both ATP-driven Ca^{2+} pumps and Ca^{2+}–H^+ exchangers, and appears to be conserved in plants and fungi.

4. The endo-lysosomal system

We next move to the animal world, starting with the sea urchin egg. This cell type has been used extensively for Ca^{2+} signalling research. Notably, the sea urchin egg was the cell type in which the Ca^{2+} mobilizing properties of NAADP were discovered [13]. Moreover, it was in the sea urchin egg that it was first recognized that NAADP releases Ca^{2+} not from the ER but instead from an acidic, likely lysosomal-related organelle [14]. Despite the physical segregation of NAADP-sensitive Ca^{2+} stores from the ER, the two are functionally coupled in intact cells. Thus, NAADP provides a "trigger" release of Ca^{2+} which is then amplified by archetypal Ca^{2+}-sensitive Ca^{2+} release channels on the ER [15]. Morgan discusses the egg's portfolio of acidic organelles and relates them to NAADP action [16].

In mammalian cells, NAADP is also thought to trigger Ca^{2+} release from acidic stores of Ca^{2+} [17] This notion however is not without controversy since in contrast to sea urchin eggs, NAADP-mediated calcium signals in mammalian cells are often not observable following depletion/blockade of ER calcium stores [18]. One exciting development is the molecular identification of animal TPCs as targets for NAADP [19,20]. These channels localize the endo-lysosomal system akin to their plant counterparts which localize to the vacuole. Importantly, redirecting TPC2 to the plasma membrane through manipulation of a lysosomal targeting sequence fully dissociates Ca^{2+} release by NAADP from its subsequent amplification by the ER [21]. Patel et al. review the flurry of recent studies on animal TPCs in the context of NAADP-mediated Ca^{2+} signalling [22].

5. The secretory system

Platelets, like sea urchin eggs possess multiple types of acidic organelles that include dense granules (lysosome-related organelles) as well as lysosomes. NAADP has been shown to mobilize Ca^{2+} from acidic compartments in platelets [23]. Evidence has also been presented that Ca^{2+} uptake into acidic compartments stores is driven by a TBHQ-sensitive Ca^{2+} pump, possibly SERCA3 [24]. These findings, discussed by Rosado [25], are important since in contrast to plants, yeast and protozoans, the mechanism of Ca^{2+} uptake into acidic organelles in mammalian cells is unclear. As discussed by Pittman [12], vacuolar Ca^{2+} pumps appear to be more related to mammalian plasma membrane Ca^{2+} ATPases, and Ca^{2+}–H^+ exchangers have been lost in mammalian genomes. Nevertheless, Ca^{2+}-ATPase and Ca^{2+}–H^+ exchange activity has been detected in some acidic stores suggesting a possible conservation in mechanism perhaps through homologues which have yet to be identified at the molecular level [3].

Chromaffin cells and pancreatic acinar cells are secretory cell types of the adrenal medulla and exocrine pancreas, respectively. Both house secretory granules which contain substantial levels of Ca^{2+}. In adrenal chromaffin cells, much evidence reviewed by Yoo [26], suggests that Ca^{2+} can be mobilized from secretory granules through activation of inositol trisphosphate (IP_3) receptor/Ca^{2+} channels. Thus, the distribution of IP_3 receptors may not be limited to the ER. This is also likely true in highly polarized pancreatic acinar cells where in addition to NAADP, IP_3 (and also cyclic ADP-ribose) are capable of releasing Ca^{2+} from the apical pole through non-ER Ca^{2+} stores [27]. Acidic organelles found in this region include secretory granules, lysosomes and extensions of the Golgi, all of which were shown to accumulate Ca^{2+} and release Ca^{2+} in response to Ca^{2+} mobilizing messengers [28]. Petersen et al. discuss Ca^{2+} signalling by acidic compartments in the apical pole of pancreatic acinar cells [29].