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ARTICLE ADDENDUM

Ins and outs of Ca^{2+} transport by acidic organelles and cell migration

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ABSTRACT

Much contemporary evidence underscores the pathophysiological importance of Ca^{2+} handling by acidic organelles such as lysosomes. Whereas our knowledge of how Ca^{2+} is released from these acidic Ca^{2+} stores (the 'outs') is advancing, we know relatively little about how Ca^{2+} uptake is effected (the 'ins'). Here I highlight new work identifying animal Ca^{2+}/H^{+} (CAX) exchangers that localize to acidic organelles, mediate Ca^{2+} uptake and regulate cell migration *in vivo*. Continued molecular definition of the acidic Ca^{2+} store toolkit provides new insight into Ca^{2+}-dependent function.

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The so called 'acidic Ca^{2+} stores' are a morphologically eclectic cohort of Ca^{2+}- and H^{+}-replete organelles that, in addition to fulfilling their canonical functions, also serve as mobilizable stores of Ca^{2+}.[1,2] A well-studied example is the lysosome, acting as both a macronutrient recycling center and as a target Ca^{2+} store for the second messenger NAADP.[3] The list of Ca^{2+}-permeable channels expressed on lysosomes—the 'outs'—is steadily increasing. It includes the archetypal TRP mucolipins,[4] NAADP-regulated two-pore channels (TPCs)[5] and other ion channels thought generally to reside on the plasma membrane (TRPM2,[6] P2X4,[7] Cav2.1[8] and TRPA1[9]). These channels mediate a range of cellular processes including triggering of global Ca^{2+} changes and various trafficking events centered around endolysosomal fusion/fission.[1,2,10,11] Given emerging links to disease,[12,13] molecular and functional interest in Ca^{2+} release from acidic organelles is growing. But lagging behind (at least for the animal kingdom) is our understanding of the 'ins' i.e. how Ca^{2+} is taken up by acidic Ca^{2+} stores and its physiologic relevance.

Vacuoles are key acidic Ca^{2+} stores in plants, yeast and protists that are often likened to lysosomes of animal cells.[1] Vacuolar Ca^{2+} uptake is mediated by molecularly defined Ca^{2+}/H^{+} exchangers (CAXs) and P-type Ca^{2+} ATPases.[14] CAXs use the substantial proton gradient to drive the antiport of Ca^{2+} at high capacity in to the lumen. Knockout of CAX genes, for example in Arabidopsis, leads to a significant reduction in vacuolar Ca^{2+} loading, an associated increase in apoplastic (cell wall) Ca^{2+} concentration and reduced gas exchange, growth and fitness.[15,16] The existence of analogous CAXs have been proposed in animals based on early biochemical work in sea urchin eggs.[17] This study showed blockade of Ca^{2+} uptake into target NAADP-sensitive stores by agents that collapsed proton gradients such as bafilomycin A1(a V-type H^{+} ATPase inhibitor), but not by vanadate (a P-type Ca^{2+} ATPase inhibitor)[17] consistent with secondary active transport of Ca^{2+}. Indeed, such a proposal has received widespread support where Ca^{2+} release by NAADP or NAADP-forming agonists is consistently blocked by bafilomycin A1 across a multitude of cells.[18-20] However, the molecular identity of animal CAXs has been somewhat of a mystery.

Recent work identified several putative animal CAXs through searches of the ever-increasing genomic sequences now at our disposal.[21] These genes were found in protostomes such as gastropods and polychaetes, and deuterostomes from basal animal species (reassuringly including the sea urchin, an echinoderm) through to amphibians and non-placental mammals. CAXs were cloned from the purple sea urchin and the African clawed frog. The latter was heterologously expressed in yeast where it was shown to possess Ca^{2+}-H^{+} activity

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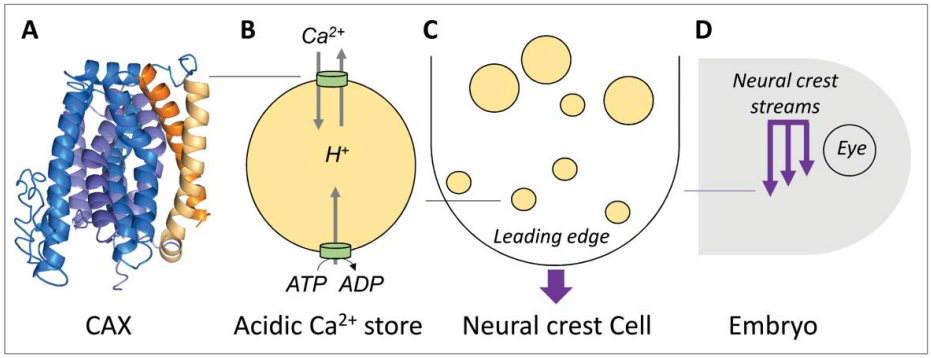

Figure 1. Ca^{2+}/H^{+} exchange by acidic organelles regulates cell migration *in vivo*. (A) Structural model of *Xenopus laevis* CAX based on crystal structure of VCX1. (B) Transport of H^{+} into acidic Ca^{2+} stores by a V-type ATPase (bottom) and its exchange for Ca^{2+} by CAX (top). (C) Location of acidic Ca^{2+} stores in a migrating neural crest cell. (D) Migration of neural crest streams in a developing frog embryo. Direction of migration in C-D is depicted by the arrows.

dependent upon on a conserved acidic residue within the transport core and the N-terminal 316 amino acids. Frog CAX localized to lysosomes when expressed in mammalian cells and tempered receptor-mediated Ca^{2+} signals[21] consistent with an analogous role for CAX in clearing Ca^{2+} elevations in response to osmotic stress in yeast.[22] In both frog[21] and zebrafish[23] embryos, transcripts for endogenous CAX were enriched in the neural crest. Within these highly migratory embryonic cells, CAX localized to yolk granules and small acidic vesicles (likely lysosomes).[21] The former finding is interesting as it was these very same lysosome-like organelles that were originally identified as NAADP-sensitive Ca^{2+} stores in sea urchin eggs.[17] Live cell imaging indicated that the smaller CAX-positive vesicles were highly mobile, often populating the leading edge of migrating neural crest cells.[21] Indeed, knockdown of CAX disrupted multiple cell migration processes in neural crest explants including focal adhesion formation, cell spreading and chemotaxis. Importantly, migration of the neural crest was also disrupted *in vivo*. Thus, this study[21] significantly furthers our understanding of how Ca^{2+} uptake by acidic Ca^{2+} stores impacts cellular function in animals and offers new opportunities for probing organellar Ca^{2+}/H^{+} exchange by molecular means (Fig. 1).

But what about Ca^{2+} uptake into acidic Ca^{2+} stores in human cells given the apparent lack of CAX homologues in placental mammals? It is formally possible (although in my opinion unlikely) that CAXs within our lineage have substantially diverged in sequence to make them invisible to current homology searches. Alternatively, Ca^{2+} uptake could be mediated through a novel protein with Ca^{2+}-H^{+} exchange activity,[24] or even through combinations of proteins (eg coupled Na^{+}/H^{+} and Na^{+}/Ca^{2+} exchange).[25] A recent study has suggested that lysosomal Ca^{2+} filling is achieved by neighboring IP_3-sensitive Ca^{2+} release channels on the ER but via a route that does not require a proton gradient.[26] Certainly, identified membrane contact sites between the ER and lysosomes would facilitate this[27,28] similar to their proposed role in amplifying lysosomal Ca^{2+} signals by the ER.[29] But the reported insensitivity of lysosomal Ca^{2+} uptake to bafilomycin A1 (assessed by monitoring Ca^{2+} signals evoked by the TRP mucolipin activator MLSA1),[26] is difficult to reconcile with previous studies; the findings are at odds not only with the aforementioned bafilomycin A1-sensitivity of NAADP action but also work by the same authors[30] and others[31] showing inhibition of MLSA1-evoked Ca^{2+} signals upon V-type H^{+} ATPase blockade. Clearly further work is required to clarify the mechanisms mediating lysosomal Ca^{2+} uptake in mammalian cells, the importance of which is underscored by functional evidence linking signaling through acidic Ca^{2+} stores to cell migration.[32,33]

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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