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The origin and function of calmodulin regulated Ca^{2+} pumps in plants

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Abstract While Ca^{2+} signaling plays an important role in both plants and animals, the machinery that codes and decodes these signals have evolved to show interesting differences and similarities. For example, typical plant and animal cells both utilize calmodulin (CaM)-regulated Ca^{2+} pumps at the plasma membrane to help control cytoplasmic Ca^{2+} levels. However, in flowering plants this family of pumps has evolved with a unique structural arrangement in which the regulatory domain is located at the N-terminal instead of C-terminal end. In addition, some of the plant isoforms have evolved to function at endomembrane locations. For the 14 Ca^{2+} pumps present in the model plant *Arabidopsis*, molecular genetic analyses are providing exciting insights into their function in diverse aspects of plant growth and development.

Keywords P-type ATPase · Calcium · Calmodulin · Pollen · Tip growth

Abbreviations

ER	endoplasmic reticulum
PM	plasma membrane
TM	transmembrane
ACA	auto-inhibited Ca^{2+}ATPases
PMCA	Plasma Membrane Ca^{2+} ATPase
CaM	calmodulin

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Introduction

Ca^{2+} pumps and antiporters are utilized in eukaryotic cells to efflux Ca^{2+} from the cytosol, and thereby help regulate the distribution and dynamics of Ca^{2+} within and outside the cell. At present, three major subgroups of P-type Ca^{2+} pumps have been delineated based on amino acid sequence similarities: group P_{2A} or "ER-type"(e.g. SERCAs in animals), P_{2B} or "PM-type" (eg. PMCA, Plasma Membrane Ca^{2+} ATPase), and the secretory pathway Ca^{2+} ATPases (e.g. SPCA in mammals and PMR1 in *Saccharomyces cerevisiae*) (Okorokova-Facanha et al. 2003; Palmgren and Axelsen 1998; Van Baelen et al. 2004). In a model plant, *Arabidopsis thaliana*, there are 14 genes encoding Ca^{2+} pumps (Baxter et al. 2003). Four of these pumps are classified as P_{2A} (ER-type), and ten as P_{2B} (PMCA-like). Interestingly, there is no evidence for an SPCA homolog in *Arabidopsis*, and none has yet been identified in sequence databases for other land plants.

The focus of this review is on the evolution and function of the PM-type (P_{2B}) pumps in plants. In addition to overall sequence similarity differences, there are two important structural features that distinguish a typical plant P_{2B} from P_{2A}: 1) The presence of a calmodulin (CaM)-regulated autoinhibitory domain (Sze et al. 2000) (Fig. 1), and 2) differences in the residues that are predicted to coordinate Ca^{2+} ions in the transmembrane domain (TM) (Guerini et al. 2000; Toyoshima and Inesi 2004; Toyoshima et al. 2000). These differences contribute to the fact that P_{2A} and P_{2B} pumps are regulated by different signaling systems and provide functionally distinct ion transport capabilities.

Evolution

Within the P_{2B} family, there are evolutionarily distinct subgroups providing the expectation of isoforms with

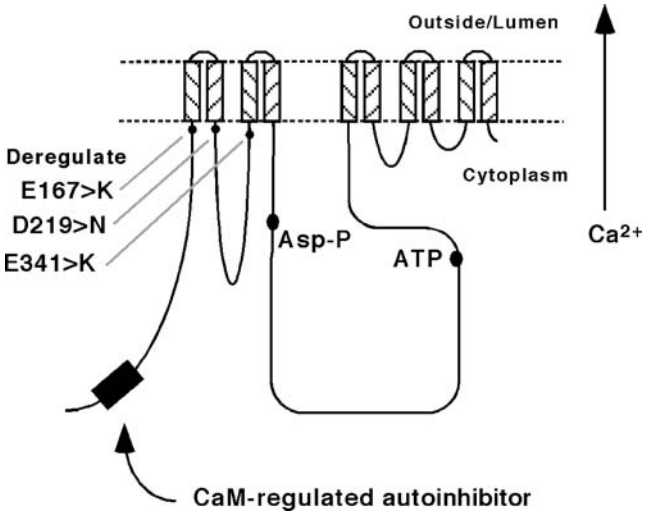

Fig. 1 Topology model for a typical plant ACA. The CaM-regulated autoinhibitor is located at the N-terminal end. The three mutations shown deregulate ACA2 and are significant because they lie outside of the region defined as the autoinhibitor. For reference, the sites of the phospho-Asp and ATP binding are marked

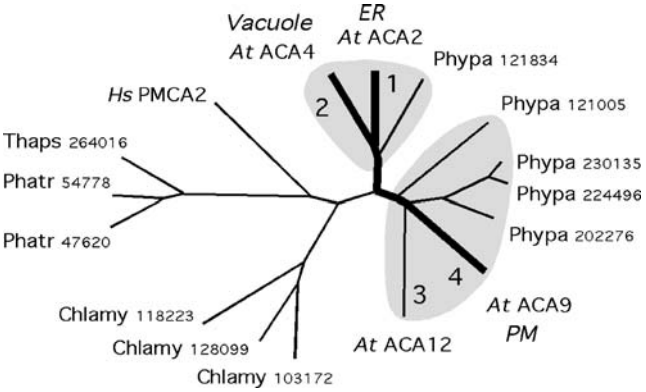

Fig. 2 Relationship tree supporting the evolutionary origin of ACAs at a point before the emergence of vascular plants. ACA-related gene models were obtained (8/2007) from the DOE Joint Genome Institute (http://genome.jgi-psf.org) with accession numbers indicated for "Chlamy" *Chlamydomonas reinhardtii,* "Phatr" *Phaeodactylum tricornutum,* "Thaps" *Thalassiosira pseudonana,* and "Phypa" *Physcomitrella patens ssp patens.* The human Hs PMCA2 corresponds to NCBI accession NP_001674. The plant ACAs shown represent subgroups 1 (*ACA2*, At4g37640), 2 (*ACA4*, At2g41560), 3 (*ACA12*, At3g63380, and 4 (*ACA9*, At3g21180) (Baxter et al. 2003). Similar trees were obtained with gene alignments made with either ClustalW, Clustal V, or Jotun-Hein using default parameters. All nodes are supported by bootstrap values exceeding 96/100 with trees drawn using Mega4 (http://www.megasoftware.net/)

fundamental differences in regulation and cellular functions (Palmgren and Axelsen 1998). For example, all P_{2B} related pumps analyzed from land plants have their putative autoinhibitory (R) domains located at the N-terminal end, in contrast to C-terminal locations in animal PMCAs (Baxter et al. 2003). In addition, vascular plant ACAs show at least three different subgroups that correlate with differences in subcellular locations (PM, ER, Vacuole), while animal PMCAs are exclusively localized to the plasma membrane (Fig. 2). To avoid the confusion of using a "PM-name" to describe a vacuolar or ER pump, the plant P_{2B} pumps have been called ACAs, for *A*utoinhibited *C*alcium *A*TPases.

A genomic comparison of ACAs in *Arabidopsis* (eudicot) and rice (monocot) identified four distinct subgroups that appear to be conserved in flowering plants (Baxter et al. 2003). Current evidence suggests that members of subgroup 1 (e.g. *AtACA2*) are localized to the ER (Hong et al. 1999), subgroup 2 (e.g. *ACA4* and *11*) to the Vacuole (Geisler et al. 2000; Lee et al. 2007), and subgroup 4 (e.g. *ACA8*, and *9*) to the PM (Bonza et al. 2000; Schiott et al. 2004) (Fig. 2). While cytological evidence establishing a localization for a member of subgroup 3 is still not available, a PM location has been proposed based on evidence (Harper, unpublished) that a transgene encoding *ACA12* can rescue a pollen defect resulting from a knockout of *ACA9*, which does have cytological evidence supporting a PM location (Schiott et al. 2004).

The unique structural arrangement that distinguishes a plant ACA from an animal PMCA can also be seen in four of the five P_{2B} pumps predicted from the *Physcomitrella patens ssp patens* genome sequence (Fig. 2). *Physcomitrella* is a moss that split away from "higher plants" very early before the evolution of a vascular system. Four of the predicted ACA-like pumps have a long N-terminal domain comparable to an *Arabidopsis* ACA, as well as significant conservation of key residues implicated in autoinhibition of ACAs (Harper, unpublished). A 5th isoform which lacks a long N-terminal domain may represent a truncated gene model (jgi|Phpa1_1|121055|) since its overall homology is still more similar to an ACA than any other subgroup of Ca^{2+} pumps. The observation that *Physcomitrella* has an ACA-like isoform most similar to ones found in the endomembranes of flowering plants, supports the hypothesis that the origin of distinct subgroups specialized for endomembrane or plasma membrane functions occurred before the evolution of vascular plants.

To test whether ACAs were present in more distantly related unicellular green algae and diatoms, we analyzed predicted P-type Ca^{2+} pumps from the genome sequences available for *Chlamydomonas reinhardtii, Phaeodactylum tricornutum, Thalassiosira pseudonana*. While predicted P_{2B} Ca pumps were found in each of these organisms, none of these pumps aligned within the subgroups defined by the land plants (Fig. 2). In contrast, they appear more similar to an animal PMCA (e.g. *Hs* PMCA2). This is consistent to the observation that the genomes from two diatoms and *Chlamydomona*s have many genes and cellular process more similar to animals than land plants (Armbrust et al. 2004; Scala et al. 2002). This analysis suggests that the evolution of ACAs may have occurred after the proliferation

of single cell photosynthetic organisms, and just before the emergence of more complex multicellular land plants.

A genome survey of "green organisms" also reveals a number of predicted P-type ATPases that may have diverged from the established Ca^{2+} pump subfamilies. For example, three predicted pumps from *Physcomitrella* all showed the characteristic "PEGL" signature found in the fourth transmembrane domain of all P_{2A} and P_{2B} Ca^{2+} pumps, but their overall sequence identities are most similar to the ENA sodium pump family characterized in yeast. While one of these genes (*PpENA1*, cDNA accession AJ564254, gene model jgi|Phypa1_1|105562|) has been shown to encode a functional sodium efflux pump (Benito and Rodriguez-Navarro 2003), the hypothesis that it may also pump Ca^{2+} has not been tested.

Another evolutionary surprise was the identification in maize of an ER-type (P_{2A}) Ca^{2+} pump (CAP1) that acquired a CaM binding site at its C-terminus (Subbaiah and Sachs 2000). At present no other example of this variant has emerged. However, in vitro assays indicate that this pump is stimulated by Ca^{2+}/CaM. Thus, along with the ACAs and PMCAs, there are now at least three structurally distinct groups of Ca^{2+} pumps that have evolved to be directly activated by CaM.

Regulation of activity

A simple working model for regulation of P_{2B} Ca^{2+} pumps is that the autoinhibitory domain (R for regulatory domain) interacts with one or more region of the pump and either blocks conformational changes required for the catalytic cycle, or access of Ca^{2+} to the pore domain, or both (Baekgaard et al. 2005, 2006; Carafoli 1994). Activation is proposed to occur when CaM binds to a portion of the autoinhibitor and disrupts its blocking interaction. Since domain swapping experiments with an animal PMCA indicated that the R domain can function at either end of the pump, it has been assumed that the N-terminal position of the R domain in ACA does not necessitate a novel mechanism of regulation (Adamo and Grimaldi 1998). Nevertheless, subtle differences in the interactions of R domains with the pump may still confer significantly different activation properties, consistent with the many different kinetic properties associated with splice variants of vertebrate PMCAs (Strehler et al. 2007).

It is also clear that CaM binding is not the only regulatory mechanism. For example, there is evidence that 14-3-3 can block the activity of certain PMCA isoforms (Domi et al. 2007; Rimessi et al. 2005). Many other examples of regulatory protein interaction and phospho-regulation have also been documented (e.g Bruce et al. 2002; Schuh et al. 2003; Wan et al. 2003). In plants, there is one example of an ACA pump whose activity can be inhibited through phosphorylation by a Ca^{2+} dependent protein kinase (CDPK) (Hwang et al. 2000). This suggests that the activity of this pump is tightly controlled by the positive and negative effects of two different Ca^{2+} signaling pathways, CaM and CDPKs, respectively. As with animal PMCAs, there is an expectation that many signaling pathways will converge to regulate Ca^{2+} pump activities in plant cells.

To identify structural features of an ACA pump responsible for autoinhibition, a random mutagenesis study was conducted with *AtACA2* (Curran et al. 2000). This genetic screen was made possible by using a yeast mutant (K616) whose growth on low Ca^{2+} media could only be rescued by constitutively active ACA mutants and not the wild-type autoinhibited pump. In addition to mapping out an autoinhibitor within the N-terminal domain, this screen also identified 3 cytosolic exposed residue (E167, D219, and E341) immediately adjacent to the TMs 1, 2 and 3, that when mutated resulted in a de-regulated pump (Fig. 1). In an animal PMCA, Bredeston and Adamo (Bredeston and Adamo 2004) have confirmed that an analogous mutation (D170N, corresponding to *ACA2* D219N) also created a deregulated pump. A careful characterization of the D170N mutant PMCA suggested that the autoinhibitory domain was not displaced by the mutation, but rather that the increased pump activity may arise from directly changing the accessibility of Ca^{2+} to the channel domain. Thus, it is not clear if these juxta-membrane mutations have identified a component of the natural regulatory system or simply a structural feature of the pump involved in ion selectivity. However, a D (or E) in the D219 analogous position appears to be highly conserved in both P_{2A} and P_{2B} pumps. For example, a D is present in all 26 representative P_{2B} pumps aligned by Palmgren and Axelsen (http://www.patbase.kvl.dk/), including mammalian PMCAs and the yeast PMC1. However, three notable exceptions have been identified in a subgroup of pumps conserved between rice and *Arabidopsis* (including At*ACA12* and *13*) (Baxter et al. 2003). These pumps all have a naturally occurring D>N variation. While the effect of this variation is not known, it is notable that regulatory domains for this subgroup are the most diverged of all the plant ACAs, including the recently identified examples in moss. This suggests that ACA-related pumps in which this region has diverged are either deregulated or have evolved a modified regulatory strategy.

Insights from expression profiling

More than 2,000 individual arrays experiments using the Affymetrix Ath1 genechip are available through public databases. A survey of these expression profiles for information on the *Arabidopsis* P_{2B} pumps supports the

hypothesis that most individual cell types express multiple isoforms for at least three of the four subfamilies. For example, in an analysis of 12 specific cell types found in roots (http://www.arexdb.org/), each cell type showed detectable expression for two or more different members from each subgroup 1, 2 and 4. This raises an expectation that the multiple isoforms will provide functional redundancy to most cell types in *Arabidopsis*.

Unlike the relatively constant and redundant expression for most *Arabidopsis* ACAs, members of subfamily 3 (*ACA12* and *13*) normally show very low or undetectable levels of expression. However, there are several examples where *ACA12* and *13* expression levels appear to be dramatically increased. For example, Fig. 3a shows an example where *ACA12* and *13* were induced 41 and 34-fold respectively in response to a pathogen stress, whereas the next most stimulated *ACA* was isoform *ACA2* with only a 5-fold induction. While it is not known why *ACA12* and *13* show such dramatic profiling changes, this may indicate a unique biochemical activity that is required only under special circumstances. This is consistent with the observation that members of subgroup 3 harbor a D>N variation (D219 in At *ACA2*) implicated in the regulation of pump activity (see above) (Baxter et al. 2003).

While other *ACAs* only show modest changes in expression levels, these changes are still interesting and potentially significant. For example, Fig. 3b shows *ACAs* with two different patterns of diurnal variation. The most striking is *ACA4*, which shows a night-time accumulation followed by a sudden drop as lights come on. *ACA10* shows a similar pattern, but with changes of much smaller magnitude. In contrast, *ACA8* shows relatively stable night-time expression levels, but rises to a peak around mid-day. Within the time resolution and data currently available, all other detectable *ACA* and *ECA*s show a pattern similar to a constitutively expressed gene such as *IPP2*.

Diurnal regulation is commonly divided in two different components: a circadian cycle that depends on the plant's "internal clock," or regulation due to light perception and photosynthesis. It is not yet clear whether the diurnal regulation seen for *ACA4*, *8* and *10* is dominated by clock or light regulation. However, two lines of evidence suggest that each isoform is under different regulatory controls. First, the diurnal rhythm seen for *ACA4* persisted even in the absence of a light/dark cycle, whereas the rhythms for *ACA 8* and *10* did not (http://www.ncbi.nlm.nih.gov/geo experiment GSE8365). Second, the rhythm for *ACA10*, but not *8* and *4*, appears to be linked to photosynthate accumulation. This difference was observed in the analysis of diurnal controlled genes in the context of a *pgm* mutant that lacks a functional phosphoglucomutase and cannot synthesize starch (Blasing et al. 2005). In the *pgm* mutant, sugars levels show an enhanced fluctuation throughout the day/night cycle. Many (>4,000) diurnally controlled genes, including *ACA10*, showed a corresponding enhanced fluctuation, indicating a transcriptional response to sugar levels. Together these experiments suggest that while *ACA4*

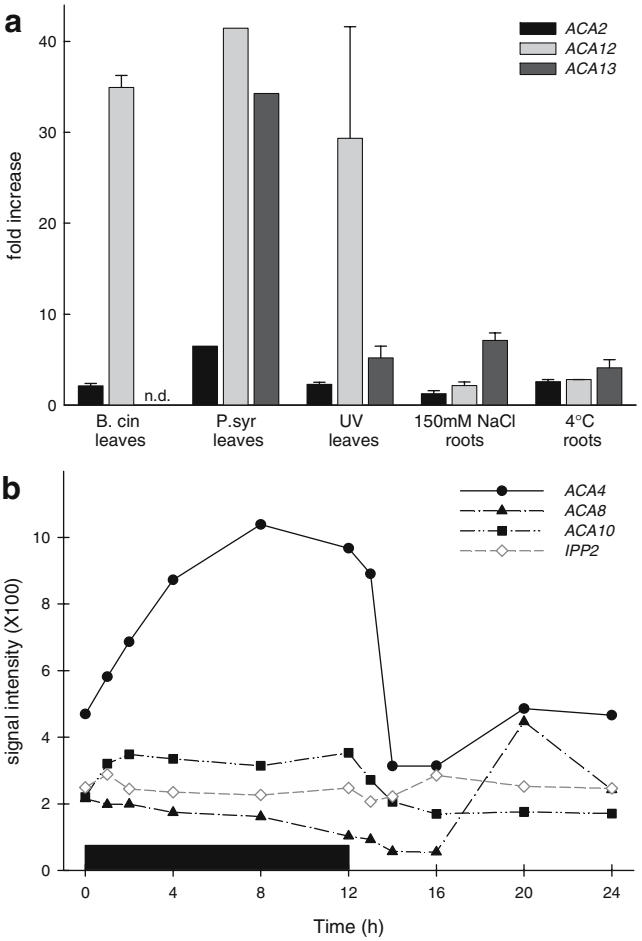

Fig. 3 Transcript expression profiling results showing examples of *ACA*s that respond to specific biotic or abiotic stresses or diurnal cycles. Data were obtained from Genechip Ath1 hybridization experiments available on public databases, GEO (http://www.ncbi.nlm.nih.gov/geo) (Barrett et al. 2007), NASC arrays (http://affymetrix.arabidopsis.info/narrays/experimentbrowse.pl) (Craigon et al. 2004), or ArrayExpress (http://www.ebi.ac.uk/microarray-as/aer). (**a**) Transcript levels for *ACA 2*, *12* and *13* in response to various examples of biotic and abiotic treatments. Plants were infected for 48 h by *Botrytis cinerea* (*B. cinerea*, NASC-167), for 6 h by *Pseudomonas syringae* strain avrRpm1 (*P. syr*, ArrayExpress E-MEXP-546, Bartsch et al. 2006), treated by unfiltered UV for 15 min and harvested 6 h later (UV, ArrayExpress E-MEXP-550, Ulm et al. 2004), treated for 6 h by 150 mM NaCl (NASC-140), and 4°C for 24 h (NASC-138). All NASC data presented here originated from the ATGenExpress research project (Kilian et al. 2007). Data (n=2 or 3) are expressed as a signal ratio between the value for the treatment and its control value or the detection threshold value. SD are indicated when available. "n.d.", gene called absent in the experiment. (**b**) Typical time dependent expression profile of *ACA 4*, *8*, *10* and the non-regulated *IPP2* (At3g02780). Data shown were obtained from GEO (GSE6174). Col-O plants were grown under 12 h day/night cycle (the black bar on the graph represents the night period). Three leaves from 20 individual plants were harvested and pooled into a single probe for chip hybridization. Similar pattern can be found in GEO experiment GDS1757

is closely linked to the internal circadian clock, *ACA8* and *10* are potentially more influenced by light and sugar levels, respectively. Interestingly, the hormone ABA, which can also exhibit diurnal variation (Novakova et al. 2005; Tallman 2004), has been shown to increase the expression of *ACA8*, but not *ACA10* (Cerana et al. 2006). Whether any expression changes seen for isoforms *ACA4*, *8*, and *10* have a biological function is not yet known, but there is accumulating evidence that diurnal changes in cytosolic Ca^{2+} may have an important function in the input and output of the circadian clock (Dodd et al. 2005, 2006; Love et al. 2004).

Knockout phenotypes

While multiple homozygous gene disruptions for all ten *ACA*s have been identified (Harper, unpublished), their characterization is still in progress. Nevertheless, the ability to isolate multiple homozygous gene disruptions for each of these pumps suggests that no individual pump is essential to the life cycle of the plant. This is in contrast to results with PMCA knockouts in mice that indicate an essential function for PMCA1 (Prasad et al. 2007). While this animal precedent would suggest that essential functions will eventually be uncovered in plants harboring multigene knockouts of redundant *ACA*s, it is nevertheless possible that P_{2B} pump are not essential in plants, but rather function to only modify various aspects of plant growth and development.

At present *aca9* is the only published example of a knockout phenotype for a plant *ACA*, in this case for a plasma membrane localized isoform (Schiott et al. 2004). Multiple independent gene disruptions all result in a greater than 3-fold reduction in seed set. This is caused by mutant pollen tubes that display at least two deficiencies. First, mutant tubes have a modest reduction in growth rate and distance potential, resulting in a small percentage of ovules that are out of reach of mutant tubes. However, even though most ovules do make contact with mutant tubes, in more than 50% of the interactions the tubes fail to discharge sperm cells into the ovules. Thus, the most significant defect is a disruption in pollen tube ovule-reception and sperm discharge.

While the underlying cellular defect in *aca9* mutant pollen tubes is still unknown, there is considerable evidence that Ca^{2+} signals regulate pollen tube tip growth (Campanoni and Blatt 2007; Cole and Fowler 2006; Dumas and Gaude 2006). Most recently, a mutation of a Ca^{2+} permeable cyclic nucleotide gated channel has been shown to be essential to pollen tube tip growth (Frietsch et al. 2007). Evidence indicates that this channel is asymmetrically localized to the growing tip, providing a potential mechanism for triggering a directional growth response at the growing tip. Since *ACA9* is also present in the plasma membrane, it is possible that its efflux activity may help regulate the dynamics of Ca^{2+} signals initiated by influx through CNGC18 and other Ca^{2+} channels.

While the potential signal modifying activity of *ACA9* is an attractive hypothesis, it is not the only way that a plasma membrane Ca^{2+} pump could function in tip growth. For example, *ACA9* may be required to prevent a toxic accumulation of Ca^{2+} in the cytoplasm (i.e. Ca^{2+}-overload hypothesis). While this remains a formal possibility, the pollen tube appears to have many different options for controlling cytoplasmic Ca^{2+} levels, including 6 other P-type Ca^{2+} pumps and several potential Ca^{2+}/proton exchangers (Bock et al. 2006). Another hypothesis is that *ACA9* provides a regulated Ca^{2+} efflux into the cell wall that may be critical to both tip growth and the cell–cell interactions that result in sperm discharge into the ovule.

Each of the above working models is consistent with three different functions outlined below that have been ascribed to animal PMCAs in the context of genetic knockouts and over-expression studies. 1) *Signaling*: Experimentally increasing the level of PMCA activity by over-expression has been shown to change Ca^{2+} signaling dynamics (Brini et al. 2000; Domi et al. 2007; Strehler et al. 2007). Thus, the activation of a Ca^{2+} pump can influence the information content of a Ca^{2+} signal. 2) *Prevent Ca^{2+} Overload*: The reduction in the amount of PMCA1 (haploinsufficiency) in PMCA4 null background can result in apoptosis in vascular smooth muscle cells, potentially caused by a cytoplasmic Ca^{2+} overload (Prasad et al. 2007). A Ca^{2+} overload has also been offered as an explanation for why a PMCA4 knockout results in a sperm motility problem leading to male infertility. 3) *Regulate Extracellular Ca^{2+}*: Evidence for a function of a PMCA in regulating the extracellular Ca^{2+} environment is provided by a *pmca2* knockout (Prasad et al. 2007). This mutation appears to specifically reduce the concentration of Ca^{2+} in milk by 60%. There is also evidence that the *pmca2* deafness and balance phenotypes correlate with a 5-fold reduction of Ca^{2+} in the endolymph surrounding the sensory epithelium in the inner ear.

Conclusion

The three general functions discussed above for Ca^{2+} pumps provide a starting point for understanding the isoform specific functions of each of the ten ACAs in *Arabidopsis*. While this starting point appears simple, the complexity lies in the fact that every cell is unique, with the potential to code and decode Ca^{2+} signals in different ways. In *Arabidopsis*, there are more than 400 proteins that can sense and respond to changes in Ca^{2+} levels (Harper and

Harmon 2005; Reddy and Reddy 2004). The expectation is that even subtle differences in the activity of Ca^{2+} influx and efflux systems will dramatically change how a plant develops or responds to its environment.

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