Plant Signaling & Behavior 9:11, e973818; December 1, 2014; © 2014 Taylor & Francis Group, LLC

Calcium signaling and biotic defense responses in plants

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Calcium (Ca^{2+}) acts as an important second messenger in plant cells. Cytosolic free Ca^{2+} concentration in plant cells changes rapidly and dynamically in response to various endogenous or environmental cues. Elevation in calcium concentration in plant cells is an essential early event during plant defense responses. Alterations in the Ca^{2+} concentration are sensed by Ca^{2+}-binding proteins, including calmodulin, calcium-dependent protein kinases and calcineurin B-like proteins, which relay or decode the encoded Ca^{2+} signals into specific cellular and physiological responses in order to survive challenges by pathogens. Genetic and functional studies have revealed that Ca^{2+} signaling plays both positive and negative roles in regulating the establishment of defense responses. Furthermore, recent studies revealed that actions of Ca^{2+}-mediated signaling could be regulated by other cell signaling systems such as the ubiquitin-proteasome system to mount precise and prompt plant defense responses.

Keywords: calcium signaling, calmodulin, CaM-binding proteins, CDPKs, plant defense

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Submitted: 06/20/2014

Revised: 08/08/2014

Accepted: 08/12/2014

http://dx.doi.org/10.4161/15592324.2014.973818

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Transient and drastic changes in intracellular Ca^{2+} concentration in plant cells upon pathogen infection have been shown to be an essential early signaling event for plant defense responses.[1,2] The information encoded by the Ca^{2+} transients is interpreted by Ca^{2+}-binding proteins into specific physiological responses to cope with pathogen attacks.[3] This mini-review summarizes the current knowledge on the roles of Ca^{2+} signaling-encoding and decoding networks during plant-pathogen interactions.

Ca^{2+} transients: an essential early event during plant-pathogen interactions

In unstimulated cells, cytosolic Ca^{2+} concentrations are usually maintained at lower levels, around 100 nM.[4] Elevation in calcium concentration in plant cells is an early event upon pathogen challenge and is believed to be caused by Ca^{2+} influx into cytosol.[5] Ca^{2+} transients have been observed in both compatible and incompatible plant-pathogen interactions. Changes in cytosolic Ca^{2+} concentration had been monitored in *Nicotiana plumbaginifolia* cells following treatment of cryptogein, an elicitor secreted by oomycete *Phytophthora cryptogea.*[6] Other elicitors such as Pep-13 peptide from *P. megasperma* and an oligopeptide elicitor derived from a cell wall protein of *P. sojae* were also shown to induce Ca^{2+} transients in suspension-cultured cells of parsley.[7-9] Changes in Ca^{2+} concentration had also been detected during effector-triggered immunity (ETI), specifically in the incompatible interactions between *Pseudomonas syringae pv. tomato* (containing *avrRpm1*) and *RPM1* in *Arabidopsis.*[10] Interestingly, the pattern and dynamics of changes in Ca^{2+} concentrations were quite different in compatible and incompatible plant-pathogen interactions,[2] which may be related to the distinct defense responses in pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI) and effector-triggered immunity (ETI). These changes in intracellular Ca^{2+} concentration were shown to correlate with the subsequent defense related physiological responses in host cells such as production of reactive oxygen species (ROS) and nitric oxide (NO), as well as induced expression of PR genes.

Calmodulin (CaM) and CaM-binding proteins in plant defense responses

Changes in Ca^{2+} concentrations evoked by a specific stimulus is usually perceived by sensor proteins which interpret the encoded Ca^{2+} signals with signature features into appropriate molecular and biochemical responses.[11] In plants, there are diverse Ca^{2+}-binding proteins that serve as sensors to monitor cellular Ca^{2+} changes. Calmodulins belong to a primary and prototypical class of calcium sensor in all eukaryotic cells. It has 2 separate globular domains, each having a pair of EF-hands, connected by a flexible helical region, so each CaM binds to 4 Ca^{2+} ions. Generally, CaM has no catalytic activities of its own, but upon binding to Ca^{2+} via the EF-hand motif it changes its configuration leading to exposure of hydrophobic regions that form high affinity binding sites for downstream target proteins.[12] Hence, CaM functions by binding and regulating the activities of various downstream CaM-binding proteins (CaMBPs). Thus, CaMBPs provide another level of specificity for Ca^{2+} signaling since different CaMBPs trigger specific physiological responses.[3]

AtSR1/CAMTA3 in *Arabidopsis* is one of the best-studied CaMBPs involved in plant defense. The early ethylene-responsive gene, *NtER1*, an ortholog of *AtSR1*, was first identified in tobacco plants.[13] Later, 6 homologs of NtER1, AtSR1–6/CAMTA1–6, were identified in *Arabidopsis* and found to be induced rapidly and differently by various external stimuli.[14, 15] Further functional analysis of one of these genes, *AtSR1*, connected Ca^{2+} signals directly to plant pathogen defense response through negative regulation of the activation of pathway of the well-known plant defense hormone, salicylic acid (SA).[16,17] SA is recognized as a necessary endogenous signal mediating plant defense against pathogens. Detailed studies revealed that *EDS1*, a positive regulator of SA biosynthesis, is a direct target of AtSR1. Most importantly, the CaM-binding to AtSR1 is required for its proper function in suppressing the expression of EDS1ref.[16] The negative regulation of plant immunity by Ca^{2+}/CaM/AtSR1 is believed to prevent mis-activation of plant defense or to balance defense response. In addition, genetic screening for *Arabidopsis* mutants led to the discoveries of gain-of-function mutation of AtSR1, and confirming the negative role of AtSR1 in plant defense.[18,19] In addition, barley CaM-binding protein, MLO, acts as a repressor of plant defense against powdery mildew, and also, CaM-binding to MLO is important for its negative regulation of plant defense.[20]

Another CaM-binding transcription factor, CBP60g, has also been shown to be involved in plant defense by regulating SA biosynthesis. Unlike AtSR1, CBP60g plays a positive role in SA-mediated defense response.[21-23] CBP60 is believed to bind to and activate the expression of SA biosynthesis gene *ICS1*, providing a direct channel for Ca^{2+} signal to activate defense responses.

Identification and functional characterization of other CaMBPs revealed that Ca^{2+}/CaM also regulate other aspects of plant defense. Pathogen attacks induce rapid production of nitric oxide (NO) in plants, which serves as a modulator of disease resistance by triggering hypersensitive cell death and activating the expression of several defense genes.[24] AtNOS1 (nitric oxide synthase) in *Arabidopsis* contains CaM-binding motifs and Ca^{2+}/CaM is necessary for the full activation of the enzyme.[25] Furthermore, the *atnos1* mutant exhibited more susceptibility to pathogenic bacteria, thus *AtNOS1* may serve as a hub linking Ca^{2+}/CaM signaling to NO-mediated defense response. Besides, rapid production of reactive oxygen species (ROS) is another early event during plant response to pathogen invasion, and accumulation of ROS is critical for the onset of hypersensitive response (HR) which limits the spread of disease from the infection site. Ca^{2+} influx has been shown to be necessary for the controlled generation of H_2O_2.[26] NAD kinase was found to be a CaMBP involved in the generation of elicitor-induced ROS burst. The possible underlying mechanism is that NAD kinase activated by Ca^{2+}/CaM enhanced ROS production by increasing the NAD(H)/NADP(H) ratio.[27]

Besides canonic CaMs, there are multiple (50 in *Arabidopsis*) CaM-like proteins (CMLs) in plants which contain EF-hand motifs but no other known functional domains and share at least 16% amino acid identity with CaM.[28] In contrast to the 7 *CaM* genes which are uniformly and highly expressed, the expression patterns of different *CMLs* vary at developmental stages, in different tissues and in response to environmental stimuli, indicating that distinct CMLs in plants may have specific roles.[28] Recently, the *Arabidopsis* CML9 was reported to act as a positive regulator of plant defense against different strains of bacterial pathogen *P. syringae*[29]

Ubiquitin-proteasome system (UPS) is another signaling pathway that is well conserved in different organisms.[30] UPS is one of the best characterized pathways for selective protein degradation and it has been connected to almost all aspects of plant biology.[31] Furthermore, UPS has been shown to play both positive and negative regulation on plant defense responses. UPS has been reported to be actively involved in plant immune responses by regulating the actions of defense-related hormones including jasmonate (JA), ethylene (ET) and SA.[32-35] In Arabidopsis, the U-box E3 ligases PUB12 and PUB13 have been shown to attenuate plant defense by promoting the protein degradation of pattern recognition receptor (PRR) Flagellin Sensing2 (FLS2).[36, 37] However, involvement of cross-talk between Ca^{2+} signaling and UPS in plant defense responses is not clear. Our recent study of Ca^{2+}/CaM/AtSR1 signaling revealed that an AtSR1-interaction protein, SR1IP1 which functions as substrate adaptor in E3 ligase, could contribute to the transient derepression of SA-mediated defense exerted by AtSR1/CAMTA3 at a time of necessity,[38] suggesting a mechanism of precise control on the establishment of plant immunity through the crosstalk between Ca^{2+}/CaM- and UPS-mediated signal pathways. In addition, other types of Ca^{2+}-binding proteins which are different from CaM or CMLs in structure and function are also known to play active roles in regulating plant immune responses.

Ca^{2+}-dependent protein kinase (CDPK) in plant-pathogen interactions

Another well-studied type of Ca^{2+} sensor-effector is Ca^{2+}-dependent protein kinase. The canonical structure of CDPK contains a Ca^{2+-}binding domain of 4 EF-hand motifs fused to the C-terminus of a Ser/Thr kinase domain with a junction of an autoinhibiotory domain (Harmon et al., 2000). The binding of Ca^{2+} to the EF-hand motif induces a conformational change leading to relief of the inhibition of kinase activity, so specific substrates are phosphorylated by CDPKs. Therefore, changes in Ca^{2+} concentrations are translated into phosphorylation events and eventually to downstream physiological responses.[39]

CDPKs have been shown to be involved in plant responses to abiotic and biotic stresses, as well as plant growth and development.[40] CDPKs participate in hormone signaling, oxidative burst and gene expression network to regulate plant defense responses.[41] The *Nicotiana tabaccum* NtCDPK2 was the first CDPK known to be involved in ETI triggered by the fungal elicitor *Avr9*.[42] The *Arabidopsis* AtCPK1 is able to phosphorylate phenylalanine ammonialyase (PAL) *in vitro,* and PAL has been shown to be a critical player in an alternate pathway to produce SA.[43] In *Arabidopsis*, the bacterial elicitor flg22 induced multiple CDPK activities. Furthermore, 4 AtCDPKs (AtCPK4, 5, 6, and 11) have been shown to function as early transcriptional regulators in PAMP signal pathways.[44] In addition, a subset of CDPKs were able to phosphorylate the NADPH oxidase isoform, RBOHD, indicating the involvement of CDPKs in ROS-mediated signal transduction.[45] Besides, a few CDPKs have been shown to be negative regulators in plant defense responses. Overexpression of *OsCPK12* in rice led to hypersensitivity to both virulent and avirulent blast fungi, probably due to compromised ROS production.[46] In summary, CDPKs serve as important Ca^{2+} sensors to translate the information to downstream processes during plant responses to pathogen challenges. CDPKs participate in plant defense by interacting and phosphorylating diverse substrates to regulate different aspects of immune responses.

Calcineurin B-like proteins (CBLs)

Calcineurin B-like proteins (CBLs) are plant-specific Ca^{2+} sensor proteins. CBLs are very similar to both the regulatory β subunit of calcineurin and neuronal calcium sensors.[47] CBLs contain EF-hand motifs as Ca^{2+}-binding domain and interact specifically with a family of Ser/Thr protein kinases, CBL-interacting protein kinases (CIPKs) to relay Ca^{2+}signals.[48,49] CIPKs are closely related to sucrose non-fermenting-like and cAMP-dependent kinases from other organisms. Protein interaction analysis identified a conserved 24-amino acid motif in the C-terminal non-kinase region of CIPKs that is sufficient and necessary to mediated CBL-CIPK interaction.[50] Recently, the tomato calcineurin B-like protein 10 (Cbl10)/ calcineurin B-like interacting protein kinase 6 (Cipk6) signaling module has been shown to be involved in ROS signaling during plant-pathogen interactions.[51] Besides, 2 CIPKs, OsCIPK14 and OsCIPK15, have been shown to participate in PTI.[52]

Conclusion

Changes in cytosolic Ca^{2+} concentrations in plant cells upon pathogen challenge has been observed for almost a decade and recognized as an early event essential for plant defense responses. Identification and analysis of CaM-binding proteins,CDPKs and other Ca^{2+} sensors revealed that Ca^{2+} signaling participates in diverse aspects of plant defense responses. Interestingly, it is known that Ca^{2+} signaling plays both positive and negative roles in plant-pathogen interactions. The complexity of Ca^{2+} signaling may be coordinated by other regulatory pathways including the ubiquitin/proteasome system to reach effective and balanced plant defense responses. Further functional studies of more signaling components in Ca^{2+} signaling may help to better understand its roles in plant immunity and help to improve disease resistance of crop plants.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Lorie Mochel and Ade Snider, Washington State University, for their help in preparing the manuscript.

Funding

This research was supported by National Science Foundation grant 1021344, and the National Science Foundation of China grant U1130304.

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