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Calcium signaling in plant defense

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Abstract

Calcium ions (Ca^{2+}) serve as ubiquitous second messengers, orchestrating various physiological and developmental processes in plants and other eukaryotes. Upon immune activation, spatiotemporal changes in cytosolic Ca^{2+} concentration, referred to as calcium signatures, play a crucial role in linking pathogen recognition to specific downstream intracellular immune responses. These signatures are generated via the coordinated activity of calcium-permeable channels, including cyclic nucleotide-gated channels, glutamate receptor-like channels, hyperosmolality-gated calcium-permeable channels, annexins, two-pore channels, and resistosomes derived from nucleotide-binding leucine-rich repeat receptors, as well as by mobilization from intracellular organelles. Meanwhile, Ca^{2+} pumps and antiporters maintain cytosolic homeostasis. Calcium signals are decoded by calcium sensors, such as calmodulins and calmodulin-like proteins, calcium-dependent protein kinases, calcineurin B-like proteins, and CBL-interacting protein kinases. This decoding triggers crucial downstream immune outputs, including reactive oxygen species production, defense gene expression, hormone modulation, and programmed cell death. Pathogens deploy effectors to modulate calcium influx, sensor function, or downstream signaling, highlighting calcium signaling as a primary target in host–pathogen interactions. This review summarizes the fundamental role of calcium signaling in plant defense, focusing on recent discoveries in signal decoding and pathogen counter-strategies, and aims to provide strategies for engineering disease-resistant crops.

KEYWORDS

calcium, calcium channels, calcium decoding, calcium sensors, plant immunity

1 | INTRODUCTION

Calcium ions (Ca^{2+}) serve as ubiquitous second messengers that regulate a wide range of physiological and developmental processes in plants, including cell division, elongation, tropic responses, fertilization, and adaptation to environmental stimuli.[1] The versatility of calcium signaling stems from its ability to transduce diverse stimuli into unique "calcium signatures," which are spatiotemporal changes in cytosolic Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$), characterized by specific amplitude, frequency, duration, and spatial distribution. These signatures are generated by the orchestrated opening and closing of calcium-permeable channels located on the plasma membrane and various organellar membranes. The calcium signals are then decoded by specific calcium-binding proteins, which initiate tailored cellular responses.[1,2]

In natural ecosystems, plants are incessantly challenged by diverse abiotic and biotic stresses. Throughout evolution, they have developed sophisticated immune systems to counteract these pervasive threats. Among them, pathogen-caused diseases pose a serious threat to global agriculture, leading to

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significant economic losses. The plant immune system plays a pivotal role in maintaining plant health by recognizing and responding to pathogenic invasions. Upon pathogen recognition, pathogen-associated molecular patterns (PAMPs) are detected by pattern recognition receptors (PRRs) located on the plasma membrane, activating PAMP-triggered immunity (PTI), a basal immune response that provides broad-spectrum resistance to pathogens.[3–6] PRRs encompass receptor-like kinases and receptor-like proteins. The well-characterized examples include flagellin sensing 2 and chitin elicitor receptor kinase 1 (CERK1), which activate downstream signaling cascades, often via receptor-like cytoplasmic kinases (RLCKs), leading to transcriptional activation of defense-related genes.[7–10] To evade PTI, pathogens secrete effectors into host cells to suppress immune responses and facilitate infection. In response, plants have evolved intracellular nucleotide-binding leucine-rich repeat receptors (NLRs) that specifically detect these effectors and trigger effector-triggered immunity (ETI).[6,11–14] ETI represents a more robust and sustained immune response, frequently regarded as a hypersensitive response (HR) and accompanied by localized cell death at the infection site, which subsequently activates the systemic acquired resistance (SAR).[15,16] Notably, recent studies have revealed a synergistic relationship between PTI and ETI, wherein each pathway mutually enhances the other, leading to amplified immunity.[17–22]

Both PTI and ETI trigger intracellular calcium fluxes, and functional studies show that disruption of these fluxes compromises immunity, underlining the indispensable role of calcium as an early signaling component in plant immunity. Upon pathogen recognition, the steep Ca^{2+} gradient between the apoplast and cytosol drives a rapid increase in $[Ca^{2+}]_{cyt}$, which is essential for activating calcium-dependent defense responses.[2,23] Several classical calcium-permeable channels are involved in this process, for example cyclic nucleotide-gated channels (CNGCs), glutamate receptor-like channels (GLRs), hyperosmolality-gated calcium-permeable channels (OSCAs), annexins (ANNs), two-pore channels (TPCs), and recently identified non-canonical channels formed by NLR resistosomes.[24–28] The specific "calcium signature" generated determines the diverse nature of downstream responses. For instance, transient increases may primarily promote basal resistance, whereas more prolonged or oscillatory Ca^{2+} elevations often trigger cell death.[29,30] These dynamic signals are precisely decoded by an array of calcium sensor proteins, including calmodulins and calmodulin-like proteins (CaMs/CMLs), calcium-dependent protein kinases (CDPKs/CPKs), calcineurin B-like proteins, and CBL-interacting protein kinases (CIPKs), which subsequently activate specific transcriptional and post-translational response pathways.[2,31,32] Importantly, calcium signaling is tightly integrated with other pivotal signaling pathways, including reactive oxygen species (ROS), phytohormones, and mitogen-activated protein kinase (MAPK) cascades, thereby forming a sophisticated and interconnected signaling network that ensures the specificity and robustness of the immune response.[33]

This review integrates recent advances in calcium signaling during plant immunity. We summarize the generation of distinct calcium signatures upon pathogen recognition, the precise decoding of these intricate signals by calcium sensor proteins, and the initiation of specific downstream immune outputs. Furthermore, we examine how pathogens manipulate host calcium signaling. Through this synthesis, we aim to provide a comprehensive reference for researchers in plant immunity, signal transduction, and crop improvement, ultimately supporting the development of disease-resistant crops.

2 | GENERATION OF CALCIUM SIGNATURES IN PLANT IMMUNITY

2.1 | Fundamental characteristics of calcium signaling in plant immunity

Ca^{2+} functions as a universal secondary messenger across all eukaryotic organisms and acts as an immediate and versatile signaling molecule in plant immunity, effectively transducing extracellular stimuli into specific intracellular responses. As a signaling molecule, the essential characteristics of calcium include its tight regulation of cytosolic concentration, rapid influx and efflux dynamics, and reversible binding to calcium sensors. Under resting conditions, cytosolic calcium concentrations are typically maintained at approximately 100 nM, whereas extracellular compartments or organellar stores maintain much higher concentrations (1–10 mM). Upon pathogen perception, there is a substantial elevation in cytosolic Ca^{2+} concentration, which rises to the micromolar range, forming a "calcium signature." These calcium signatures vary in amplitude, duration, frequency, and spatial distribution depending on the type of elicitor, the nature of the plant–pathogen interaction, and the tissue type.[2,34,35] Such features are critical for conferring downstream specificity in plant defense signaling. Ca^{2+} homeostasis is maintained by the coordinated action of calcium-permeable channels, pumps, and exchangers localized in the plasma membrane, vacuole, endoplasmic reticulum (ER), chloroplasts, and mitochondria. The cytosolic buffering capacity and the transient nature of calcium signaling together ensure signal specificity and prevent cytotoxicity.[2,36]

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2.2 | Calcium channels involved in plant immunity

Calcium influx is primarily mediated by diverse families of Ca^{2+}-permeable channels. These channels serve as critical conduits for elevating cytosolic calcium, precisely shaping the calcium signatures that are essential for decoding immune signals and triggering downstream defense pathways.

2.2.1 | CNGCs

Members of the CNGC family in plants are homologous to animal CNG ion channels activated by cyclic nucleotides.[37] CNGCs play pivotal roles in plant immune responses by mediating calcium influx and maintaining cytosolic Ca^{2+} homeostasis. Among them, CNGC2 and CNGC4 are well-characterized. The *Arabidopsis cngc2* and *cngc4* mutants, known as *defense, no death* (*dnd*), and *HR-like lesion mimic* (*dnd2*/*hlm*) mutants, respectively, exhibit constitutive defense responses, including spontaneous cell death and elevated salicylic acid (SA) levels.[38,39] CNGC2 and CNGC4 form a heteromeric channel that is repressed by CaM and activated through the phosphorylation of CNGC4, mediated by BOTRYTIS-INDUCED KINASE 1 (BIK1) upon the perception of PAMPs.[40,41] Notably, activation of the CNGC2-CNGC4 channel complex via P2K1-mediated phosphorylation connects extracellular ATP perception to calcium signaling during plant immune responses.[42] CNGC11 and CNGC12 have also been reported to contribute to the immune response, as demonstrated by the autoimmune *constitutive expresser of PR genes 22* mutant, which encodes a chimeric CNGC11-CNGC12 channel that triggers constitutive Ca^{2+} influx and defense activation due to the absence of the CNGC12 CaM-binding domain.[43–47] CNGC19 and CNGC20 form Ca^{2+}-conducting channels that promote BRI1-ASSOCIATED RECEPTOR KINASE 1 (BAK1)/SOMATIC EMBRYOGENESIS RECEPTOR KINASE 4 (SERK4)-mediated autoimmunity and cell death, but are destabilized by BAK1/SERK4-dependent phosphorylation.[48] They contribute unequally, with CNGC20 playing a dominant role, although both are required for the full autoimmune phenotype. Whereas dispensable for PTI, CNGC19 and CNGC20 contribute to defense against insects and beneficial microbial interactions, underscoring their broader roles in Ca^{2+}-dependent immune signaling.[49–51] In rice, OsCNGC9 confers resistance to *Magnaporthe oryzae* and is activated via phosphorylation by OsRLCK185.[52] Collectively, these findings highlight the central role of CNGCs in shaping calcium signaling dynamics during plant immunity.

2.2.2 | GLRs

GLRs are ligand-gated, Ca^{2+}-permeable channels in plants that are structurally related to mammalian ionotropic glutamate receptors but are gated by a range of amino acids.[53] *Arabidopsis* encodes 20 GLRs grouped into three clades, among which GLR3.3 and GLR3.6 have been shown to mediate Ca^{2+} influx in response to damage- and pathogen-associated signals.[54–56] It has been shown that *glr2.7*/*2.8*/*2.9* triple mutant exhibited reduced PAMP-triggered cytosolic Ca^{2+} elevation and reduced bacterial resistance while retaining normal abiotic stress responses, indicating a specific role for this clade in PTI.[57] GLRs participate in both local and systemic defense responses, including flg22 (a 22-amino acid peptide derived from bacterial flagellin)-induced stomatal closure and long-distance wound signaling. Apoplastic glutamate activates GLRs in distal tissues, triggering systemic Ca^{2+} waves and jasmonic acid (JA) signaling.[58,59] Mutants lacking *GLR3.3* and *GLR3.6* exhibit impaired systemic JA signaling and reduced expression of defense-related genes.[60] In tomato and cotton, homologs such as SlGLR3.5 and GhGLR4.8 play critical roles in systemic immune responses and ETI-like hypersensitive responses.[61,62] These findings highlight the broad functional scope of GLRs in integrating environmental and biotic signals through Ca^{2+}-based communication, although the activation mechanisms across different GLR clades remain to be fully elucidated.

2.2.3 | OSCAs

The OSCA family comprises mechanosensitive calcium-permeable channels involved in osmotic stress responses and plant immunity. Initially identified through heterologous expression and genetic screens, *Arabidopsis* OSCA1.1 and OSCA1.2 have been shown to mediate cytosolic Ca^{2+} influx in response to hyperosmotic stress and mechanical stimulation, functioning as evolutionarily conserved mechanosensitive channels belonging to the transmembrane protein 63 family.[63–66] Structural studies have revealed that OSCA proteins form homo-dimers with 11 transmembrane helices, resembling TMEM16 family proteins.[67,68] More recently, OSCA1.3 and OSCA1.7 have been shown to participate in PTI by promoting flg22-induced stomatal closure. This function is regulated through direct phosphorylation by BIK1, which specifically activates OSCA1.3/1.7 channel activity in guard cells. Notably, the *osca1.3*/*1.7* mutant exhibits impaired stomatal closure in response to flg22, but not to abscisic acid, suggesting that it plays a specialized role in immune-

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specific rather than general stomatal regulation.[69] The involvement of OSCAs in both osmotic sensing and immune signaling indicates a potential mechanistic link between water homeostasis and pathogen defense, warranting further investigation.

2.2.4 | ANNs

ANNs are a conserved family of Ca^{2+}- and phospholipid-binding proteins that can function as unconventional Ca^{2+}-permeable channels or transporters, despite lacking transmembrane domains.[70] In plants, ANNs are primarily located in the cytosol but associate with membranes in a Ca^{2+}-dependent manner.[71] The *Arabidopsis* genome encodes eight *ANN* genes involved in diverse processes, including ion transport, signal transduction, and stress responses.[72–74] ANN1 has been particularly implicated in plant immunity. It interacts with CERK1, which perceives chitin (a component of the fungal cell wall), to mediate chitin-induced Ca^{2+} influx. The *ann1* mutants exhibit enhanced ROS accumulation and MAPK activation, suggesting that ANN1 acts as a negative regulator of these immune responses.[75] ANN1 also contributes to extracellular ATP (eATP)-induced Ca^{2+} influx in roots and regulates systemic Ca^{2+} signaling.[76,77] Furthermore, *ANN* gene expression is upregulated by SA and pathogen infection. Heterologous expression of *Brassica juncea* ANN1 in tobacco enhances resistance to *Phytophthora parasitica*, further supporting its involvement in plant defense.[78,79]

2.2.5 | TPCs

In addition to plasma membrane-localized channels, intracellular compartments such as the vacuole also contribute to cytosolic Ca^{2+} elevation during plant immune responses. TPCs, which are conserved across plants and animals, function as slow vacuolar Ca^{2+} channels that are gated by voltage and cytosolic Ca^{2+} levels.[80,81] *Arabidopsis* encodes a single *TPC* gene, and gain-of-function mutations in *TPC1* enhance JA accumulation and resistance to *Botrytis cinerea*.[82] However, TPC1 appears to be dispensable for PAMP-triggered Ca^{2+} influx, raising questions regarding its precise role in PRR-mediated immunity.[83] Notably, TPC1 is required for both local and systemic Ca^{2+} signaling in response to wounding and herbivory, and its overactivation reduces aphid infestation.[56,84] In rice, OsTPC1 also promotes defense gene activation and HR upon elicitor treatment.[85] Although TPCs clearly contribute to defense and Ca^{2+} dynamics, the mechanistic coordination between vacuolar TPC1 activity and plasma membrane Ca^{2+} channels remains poorly understood.

2.2.6 | Pumps and antiporters

To restore cytosolic Ca^{2+} levels following immune activation, plants rely on Ca^{2+}-ATPases and Ca^{2+}/H^{+} antiporters. In *Arabidopsis*, the double mutant of the autoinhibited Ca^{2+}-ATPases (*ACA8*) and *ACA10* exhibits reduced flg22-induced Ca^{2+} influx, ROS bursts and altered transcriptional reprogramming.[86] Two tonoplast-localized Ca^{2+}-ATPase pumps, ACA4 and ACA11, act as negative regulators of flg22-triggered cytosolic Ca^{2+} elevations.[87] Concurrently, vacuolar Ca^{2+}/H^{+} exchangers (CAXs) are crucial for modulating Ca^{2+} signaling during stress responses. Isoforms such as AtCAX1 and AtCAX3 contribute to plant tolerance to cold, salinity, flooding, and pathogen attacks through dynamic regulatory mechanisms, including transcriptional regulation and phosphorylation by immune kinases such as BIK1.[88,89] Recent studies on sugarcane have further revealed that ScCAX4 negatively regulates plant disease resistance by modulating multiple defense signaling pathways, particularly JA signaling.[90] Analysis of sugarcane's response to *Sporisorium scitamineum* revealed that ScCAX2 and ScCAX3 play negative roles in disease resistance.[91] Together, these transport systems are essential for terminating calcium signals and maintaining immune homeostasis.

2.3 | Pathogen perception triggers calcium signaling

Upon pathogen recognition, plants rapidly induce Ca^{2+} influx across the plasma membrane and mobilize it from intracellular stores, including the vacuole, ER, chloroplasts, and others. This swift elevation of cytosolic Ca^{2+} is a foundational event in both PTI and ETI.[92,93] These Ca^{2+} transients form unique calcium signatures, with specific PAMPs such as flg22 and chitin, notably inducing distinct cytosolic Ca^{2+} signatures across different plant species.[94,95] These signatures are shaped by diverse combinations of calcium-permeable channels. For example, PTI typically elicits transient Ca^{2+} spikes, whereas ETI often features more robust and sustained oscillations.[18] Recent studies have shown that certain plant NLRs can oligomerize into resistosomes that act as Ca^{2+}-permeable pores, directly coupling effector recognition to Ca^{2+} influx during ETI.[24,96–98] Based on their N-terminal domains, NLRs are classified into coiled-coil NLRs (CNLs), Toll/interleukin-1 receptor (TIR)-domain NLRs (TNLs), and resistance to powdery mildew 8 (RPW8)-like NLRs (RNLs).[99] CNLs/RNLs form plasma membrane pores mediating Ca^{2+} influx. For example, upon recognizing the bacterial effector AvrAC, *Arabidopsis* CNL HOPZ-activated resistance 1 (ZAR1) assembles into a pentameric resistosome that inserts into the plasma membrane to mediate Ca^{2+} influx critical for the

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HR.[24,100] Similar pentameric structures are formed by wheat CNL Sr35, whereas the asterid helper NLR NRC4 assembles into a hexameric resistosome.[96,101,102] In contrast, TNLs such as RPP1 in *Arabidopsis* and Roq1 in *Nicotiana benthamiana* form tetrameric resistosomes upon effector recognition and signal via NAD^+ cleavage. This activates helper RNLs through ENHANCED DISEASE SUSCEPTIBILITY 1 complexes, in which EDS1–PHYTOALEXIN DEFICIENT 4 (PHYTOALEXIN DEFICIENT 4) associates with ACTIVATED DISEASE RESISTANCE 1 proteins and EDS1–SENESCENCE-ASSOCIATED GENE 101 associates with N REQUIRED GENE 1 proteins, leading to the formation of Ca^{2+}-conducting resistosomes, which are essential for HR.[25,103–107] Additionally, *Arabidopsis* mixed lineage kinase domain-like (AtMLKL1) promotes Ca^{2+} influx during TNL-triggered immunity, suggesting a conserved role for HeLo domains in immune Ca^{2+} signaling.[108] These findings highlight resistosome-mediated Ca^{2+} influx as a central component of ETI calcium signatures, distinguishing them from PTI-associated transients.

The vacuole, which stores over 90% of cellular Ca^{2+}, can release Ca^{2+} via TPCs, contributing to cytosolic calcium elevation during immune responses.[80] While the roles of ER calcium release channels, such as inositol 1,4,5-trisphosphate receptors and ryanodine receptors, are well-characterized in animals, their exact identities and functions in plants are still being clarified.[109–112] Recent studies identified the resistance gene *WeiTsing* (*WTS*), which encodes an ER-localized Ca^{2+}-permeable channel conferring broad-spectrum resistance against *Plasmodiophora brassicae* in *Arabidopsis* and *Brassica napus*.[113,114] WTS assembles into a pentameric resistosome-like complex that mediates Ca^{2+} release from the ER, and its channel activity is essential for triggering immune responses.[23,114] Recent studies also highlight the chloroplast as a dynamic calcium reservoir, where pathogen infection and PAMP perception can trigger stromal calcium signals linked to ROS production and retrograde signaling.[36,115,116] Ultimately, these dynamic patterns are integrated and decoded by calcium sensor proteins to activate appropriate downstream defense responses.

3 | DECODING CALCIUM SIGNALS IN PLANT IMMUNE PATHWAYS

The generation of calcium signatures in plant immunity is orchestrated through the tightly regulated activity of calcium-permeable channels and transporters, which coordinate cytosolic Ca^{2+} influx and efflux. However, the biological significance of these signatures hinges on their precise decoding by calcium sensor proteins, which translate transient calcium fluctuations into specific immune outputs. Plants employ several classes of calcium sensors to interpret these signatures, including CaMs/CMLs, CDPKs/CPKs, and CBLs-CIPKs. These sensor modules function in distinct ways during PTI and ETI, initiating tailored defense responses based on the nature and context of the Ca^{2+} signals. Once decoded, Ca^{2+} signals mediate a broad spectrum of downstream immune processes, including rapid generation of ROS, activation of defense-related gene expression, modulation of phytohormone signaling pathways, and execution of HR-associated programmed cell death. In addition, Ca^{2+} signaling contributes to the establishment of SAR, enabling long-lasting immunity throughout the plant. In this section, we summarize the major classes of calcium sensors involved in plant immunity and detail the multifaceted immune outputs governed by Ca^{2+}-mediated signaling cascades.

3.1 | CaMs/CMLs

Among calcium-binding proteins, CaMs and CMLs are well-characterized. CaM is composed of 148 amino acids and lacks intrinsic catalytic activity; however, it functions as a versatile calcium sensor. Upon Ca^{2+} binding, CaMs undergo conformational changes that enable interactions with a wide array of calmodulin-binding proteins, thereby modulating diverse cellular processes.[117] In *Arabidopsis,* CaM7 negatively regulates the CNGC2/4 calcium channel complex by binding to CNGC2 and maintaining the channel in a closed conformation. Upon PAMP perception, BIK1 phosphorylates CNGC4, relieving the inhibitory effect of CaM7 and enabling Ca^{2+} influx to activate immune signaling.[41] CaM also interacts with CAMTA3, a calmodulin-binding transcription factor that negatively regulates SA-dependent immune responses.[118] The calmodulin-like protein TOUCH3/TCH3 (CML12) relieves the autoinhibitory constraint of CPK5, thereby promoting its ability to phosphorylate CAM-BINDING PROTEIN 60-LIKE G (CBP60g), a key transcription factor in plant immunity, and enhancing resistance to soil-borne fungal pathogens.[119] Several other CMLs have also been implicated in plant immunity. Overexpression of the soybean CML SCaM-4 enhances resistance to a broad range of pathogens, including oomycetes, fungi, bacteria, and viruses.[120,121] In *Arabidopsis*, CML41 enhances defense against *Pseudomonas syringae* by promoting callose deposition at plasmodesmata in response to flagellin,[122] whereas CML24 is required for HR and PAMP-induced nitric oxide production during avirulent bacterial challenge.[123] Other CMLs, such as CML8 and CML9, positively regulate immune responses, although CML9 also negatively affects abiotic stress tolerance.[124–127] CML37 and CML42 function antagonistically in

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defense against *Spodoptera littoralis*, with CML37 enhancing resistance and CML42 acting as a negative regulator by modulating JA signaling.[128]

3.2 | CDPKs/CPKs

CDPKs/CPKs are plant-specific serine/threonine kinases that function as both sensors and transducers of calcium signals. Structurally, they possess a kinase domain fused to a calmodulin-like regulatory domain with EF-hand motifs (helix–loop–helix motifs), enabling direct activation upon Ca^{2+} binding. CDPKs respond rapidly to PAMP-induced cytosolic Ca^{2+} elevations and activate downstream signaling by phosphorylating a wide range of target proteins. In *Arabidopsis*, CPK5 phosphorylates CBP60g to enhance resistance to soilborne fungal pathogens.[119] CPK4, CPK5, CPK6, and CPK11 are essential for transcriptional reprogramming during immune responses and contribute to defense gene activation upon flagellin perception, whereas CPK5 also plays a critical role in SAR.[31,97,129–132] The rapid production of ROS is one of the earliest defense responses. The oxidative burst is primarily catalyzed by membrane-bound NADPH oxidases, notably RESPIRATORY BURST OXIDASE HOMOLOG D (RBOHD). In *Arabidopsis*, RBOHD activity is regulated via both direct binding of Ca^{2+} and phosphorylation by CPK5. The interaction between CPK5 and RBOHD is essential for fine-tuning ROS levels during PTI.[31,129,133] RBOHD activity is tightly regulated by multiple layers. RLCKs such as BIK1 directly phosphorylate RBOHD to promote ROS production, whereas PBS1-like 13 (PBL13) promotes its degradation via ubiquitination.[131,134–136] Concurrently, the lipid signal phosphatidic acid (PA) enhances both RBOHD activity and stability. The synthesis of PA is also kinase-regulated, with RLCKs promoting its production while MPK4 acts to inhibit it.[137–139] Additionally, CPK5 phosphorylates the transcription factor WRKY DNA-binding protein 33 (WRKY33), thereby regulating camalexin biosynthesis.[140] Recent studies have also revealed that CPK5 phosphorylates MICRORCHIDIA1 (MORC1), promoting its nuclear localization and subsequent activation of NPR1-TGA-dependent defense gene expression, thus establishing a Ca^{2+}-dependent signaling module that confers broad-spectrum disease resistance.[141] In contrast, CPK28 functions as a negative regulator of immunity. It phosphorylates the E3 ubiquitin ligases plant U-box protein 25 and PUB26, promoting the degradation of BIK1, a central cytoplasmic kinase in PTI, thereby dampening ROS production and immune signaling.[131,132,142] Beyond model species, CDPKs are also pivotal regulators of immune responses in crop plants. For instance, ScCDPK1 and ScCDPK8 in sugarcane exhibit auto-inhibitory activity, with their truncated forms strongly activating defense genes.[143] In citrus, CsCPK6 regulates defense against pathogens,[144] whereas in rice, OsCPK17 positively mediates immunity against bacterial pathogens[145] and OsCPK10 contributes to resistance against fungal pathogens.[146]

3.3 | CBL–CIPK networks

The CBL–CIPK system represents another calcium-decoding mechanism unique in plants. CBLs sense Ca^{2+} via EF-hand motifs and activate specific CIPKs, which phosphorylate downstream targets. Although initially characterized in the context of abiotic stress, recent studies have demonstrated their involvement in plant immunity. Vacuolar CAXs have emerged as key components in maintaining cytosolic Ca^{2+} homeostasis during immune activation. The CBL–CIPK module phosphorylates a conserved serine-rich cluster within the autoinhibitory domain of CAXs, enhancing Ca^{2+} efflux in *Arabidopsis*. This mechanism responds to elevated external Ca^{2+} and operates with the immune signaling cascade involving FLS2-BAK1, BIK1, and PBL1, all of which target the same serine cluster. Together, these calcium-dependent and immune-activated pathways finely tune cytosolic Ca^{2+} clearance during defense responses, ensuring a balance between immune activation and cellular homeostasis.[89]

4 | MODULATION OF CALCIUM SIGNALING BY PATHOGEN EFFECTORS

While plants rely on intricate calcium decoding systems to activate immunity, pathogens have evolved sophisticated strategies to modulate these signaling pathways. As calcium fluxes and decoding mechanisms are central to the activation of defense pathways, numerous pathogen-derived effectors target components of calcium signaling to suppress plant immunity.

For instance, the *Phytophthora infestans* effector Avrblb2 hijacks CaM or CML36 in *N. benthamiana* to suppress CNGC18-mediated Ca^{2+} influx.[147,148] Similarly, the transcription activator-like effector AvrXa10 from *Xanthomonas oryzae* triggers Xa10-dependent defense responses under conditions of ER Ca^{2+} depletion,[149] suggesting that manipulation of calcium homeostasis is a common virulence strategy among pathogens. The *P. syringae* effector HopE1 interacts with CaM to disrupt host defense, thereby promoting susceptibility.[150] Likewise, the fungal effector AvrPiz-t structurally mimics the Ca^{2+} sensor RESISTANCE OF RICE TO DISEASES1 (ROD1), which enhances catalase activity to scavenge ROS in a Ca^{2+}-dependent manner. By imitating ROD1, AvrPiz-t suppresses H_2O_2 accumulation and weakens rice immunity to promote fungal infection.[151–153] Similarly, the effector RipAB from *Ralstonia solanacearum* downregulates

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the expression of calcium signaling genes in potato to promote full virulence.[154] Pathogen effectors can also directly target host immune components of calcium signaling. For example, *Verticillium dahliae* effector VdSCP41 targets the SA signaling regulators CBP60g and SARD1 by binding to the C-terminal region of CBP60g and inhibiting its transcriptional activity.[119,155–157] The *Phytophthora sojae* effector PsCRN108 suppresses the immune-inhibitory CaM-binding transcription factor (CAMTA2).[158] Additionally, calcium sensor proteins localized in chloroplasts can also be manipulated. The effectors SsITL from *Sclerotinia sclerotiorum* and HopAU1 from *P. syringae* both target the chloroplast-localized calcium sensor CAS, disrupting SA signaling to promote infection.[159,160] The fungal effector PdCDIE1 disrupts the Ca^{2+}-dependent interaction between CaM and its target Hsp70, leading to excessive ROS accumulation and cell death. This demonstrates a direct link between calcium signaling and ROS homeostasis in effector-triggered susceptibility in citrus.[161]

Collectively, these findings demonstrate that calcium signaling components are prominent and vulnerable targets of pathogen effectors. By manipulating calcium influx, signal relay, or downstream transcriptional responses, pathogens effectively reprogram plant immunity to promote infection (Figure 1).

5 | CHALLENGES AND FUTURE PERSPECTIVES

Despite significant advances in understanding the role of calcium signaling in plant immunity, many fundamental questions remain. One major challenge is the precise decoding of calcium signatures. Although spatiotemporal patterns of calcium transients are believed to encode stimulus-specific information, it remains unclear

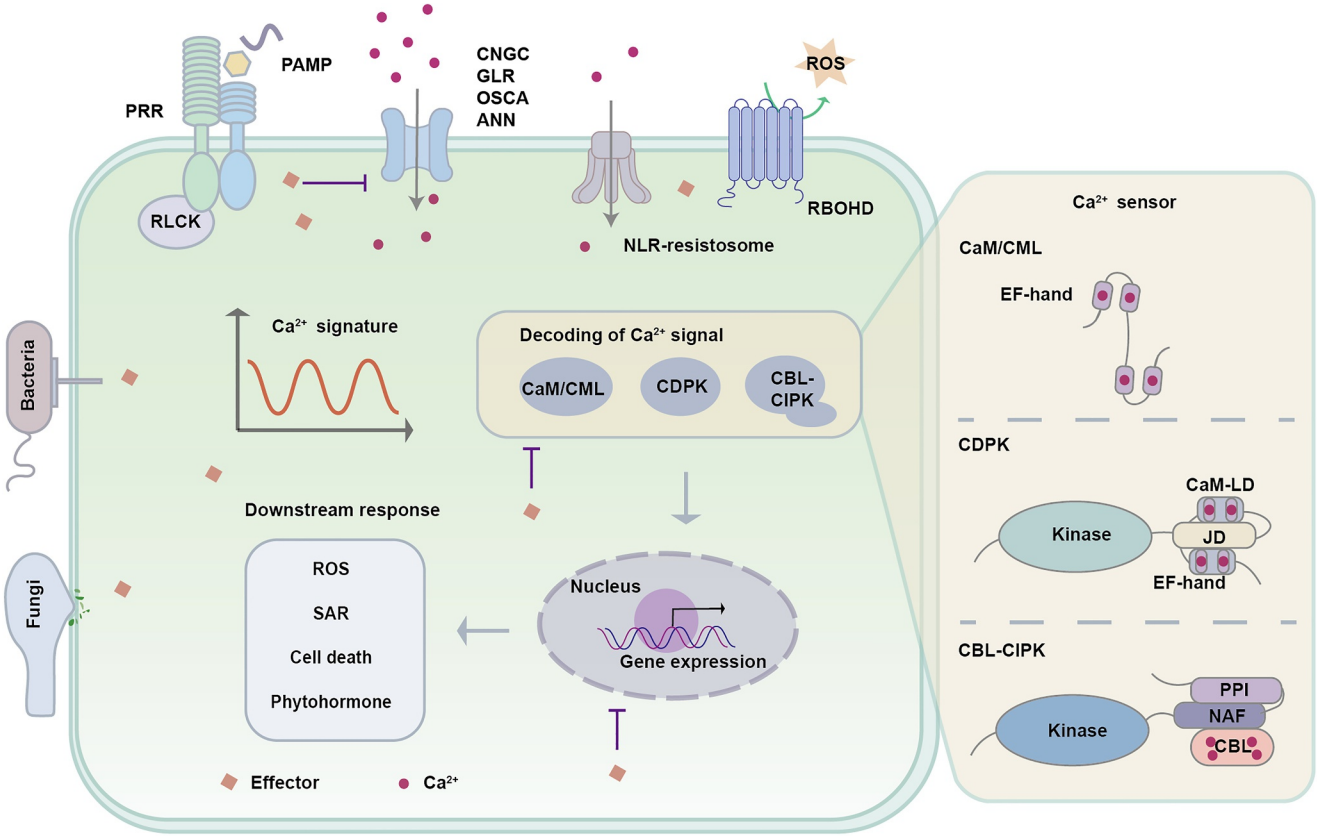

FIGURE 1 A model of calcium signaling-mediated immune regulation in plants. Pathogen recognition by PRRs activates diverse calcium-permeable channels, such as CNGCs, GLRs, OSCAs, ANNs, TPCs, and Ca^{2+}-permeable pores, driving a rapid cytosolic Ca^{2+} influx. These elevated Ca^{2+} levels are decoded by calcium-binding proteins such as CaMs/CMLs, CDPKs, and CBLs-CIPKs. These sensors in turn activate downstream immune responses such as ROS production, MAPK activation, phytohormone modulation, and transcriptional reprogramming. Collectively, these signaling events culminate in the expression of defense-related genes, HR, SAR, and the establishment of comprehensive immune responses. ANN, annexin; CaM/CML, calmodulin and calmodulin-like protein; CaM-LD, CaM-like domain; CBL, calcineurin B-like protein; CDPK, calcium-dependent protein kinase; CIPK, CBL-interacting protein kinase; CNGC, cyclic nucleotide-gated channel; GLR, glutamate receptor-like channel; HR, hypersensitive response; JD, junction domain; MAPK, mitogen-activated protein kinase; NAF, Asn-Ala-Phe; OSCA, hyperosmolality-gated calcium-permeable channel; PAMP, pathogen-associated molecular pattern; PPI, protein-phosphatase interaction; PRR, pattern recognition receptor; RBOHD, respiratory burst oxidase homolog D; RLCK, receptor-like cytoplasmic kinase; ROS, reactive oxygen species; SAR, systemic acquired resistance; TPC, two-pore channel.

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how different calcium sensors discern subtle differences in calcium oscillation frequency, amplitude, and duration. Recent studies in *Arabidopsis* have revealed a synergistic interaction between CPK5 and TCH3 in decoding immune-related calcium signals, offering insights into signal specificity.[119] However, the landscape remains complex due to functional redundancy and overlap among sensor proteins. Understanding how sensor families integrate, compensate, or specialize under different immune contexts remains a critical area for future investigation. While several calcium-permeable channels have been identified, their roles in in vivo regulation and pathogen-specific responses remain poorly characterized. Similarly, the physiological significance of calcium stores in the ER and vacuole demands further investigation. Another unresolved question is how calcium signaling is spatiotemporally integrated with other cellular signaling networks. Understanding these interconnections will be essential for understanding immune specificity and robustness.

Calcium signaling operates within a broader signaling matrix, including MAPK cascades, ROS generation, and hormonal pathways.[31] For example, some CPKs and MAPKs co-regulate WRKY transcription factors, thereby modulating the expression of defense genes. Calcium signals are also involved in balancing growth and immunity, a trade-off critical for plant fitness. Growth hormones like auxins and gibberellins often suppress immune responses, whereas stress-induced calcium fluxes may inhibit growth-promoting pathways. Future research will explore how plants prioritize immunity under stress without compromising development or yield. Moreover, epigenetic mechanisms, such as histone modifications and DNA methylation, have emerged as regulators of calcium-responsive genes.

Calcium signaling plays a central role in plant immune regulation, acting as both an early warning system and a fine-tuning mechanism for downstream defense activation. Despite considerable progress, much remains to be uncovered. Future research may focus on deciphering the calcium code, identifying novel components of the calcium signaling network, and integrating this knowledge into broader signaling frameworks. Technological advances in imaging, bioinformatics, and synthetic biology will continue to expand our understanding of calcium signaling dynamics. Applying this knowledge to crops offers exciting prospects for developing next-generation plants with improved resistance and resilience. Leveraging current understanding of calcium signaling can inform strategies to enhance crop disease resistance. Key Ca^{2+} channels, sensors, and downstream immune components can serve as targets for genome editing to optimize defense responses. Synthetic biology approaches may enable engineered Ca^{2+} sensors or inducible modules to trigger timely immunity without impairing growth. Integrating these tools with high-throughput phenotyping and multi-omics will accelerate the development of crops exhibiting durable broad-spectrum resistance.

AUTHOR CONTRIBUTIONS

Lifan Sun: Writing—review and editing; funding acquisition. **Yu Wang**: Resources. **Jie Zhang**: Funding acquisition; project administration.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

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