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Calcium Signaling Mechanisms Across Kingdoms

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Abstract

Calcium (Ca^{2+}) is a unique mineral that serves as both a nutrient and a signal in all eukaryotes. To maintain Ca^{2+} homeostasis for both nutrition and signaling purposes, the tool kit for Ca^{2+} transport has expanded across kingdoms of eukaryotes to encode specific Ca^{2+} signals referred to as Ca^{2+} signatures. In parallel, a large array of Ca^{2+}-binding proteins has evolved as specific sensors to decode Ca^{2+} signatures. By comparing these coding and decoding mechanisms in fungi, animals, and plants, both unified and divergent themes have emerged, and the underlying complexity will challenge researchers for years to come. Considering the scale and breadth of the subject, instead of a literature survey, in this review we focus on a conceptual framework that aims to introduce readers to the principles and mechanisms of Ca^{2+} signaling. We finish with several examples of Ca^{2+}-signaling pathways, including polarized cell growth, immunity and symbiosis, and systemic signaling, to piece together specific coding and decoding mechanisms in plants versus animals.

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Contents

1. OVERVIEW: THE RISE OF A SIGNALING AGENT FROM A TOXIC ION

1.1. Why Calcium?

Cellular life is believed to have started in the oceans. Ever since the evolution of the first cell, selective permeability of the cell membrane has been the first line of defense in maintaining a biologically suitable interior milieu. Among the abundant cations in the ocean, potassium (K^+) is more compatible with biochemical reactions than is sodium (Na^+); thus, the cell is enriched in K^+ while Na is excluded. The abundant divalent cation magnesium (Mg^{2+}) functions as a popular cofactor for enzymes and a chemically suitable partner for phosphate-based compounds including ATP and other nucleotides, critical components in energy metabolism and the synthesis of the genetic materials (RNA and DNA). In contrast, Ca^{2+} becomes a toxic cation as it precipitates down inorganic phosphate at millimolar levels, hindering energy metabolism and other cellular activities (Carafoli & Krebs 2016, Jaiswal 2001). Keeping the cellular Ca^{2+} level at bay is thus essential for many aspects of cellular life. In fact, cytosolic concentrations of Ca^{2+} must be maintained in the nanomolar-to-micromolar range to prevent toxicity to cell metabolism. The large Ca^{2+} gradient across the membrane between the interior (hundreds of nanomolar) and exterior (1–10 mM) sets up a critical condition that enables rapid change in cellular Ca^{2+} beyond background or noise levels, one of the prerequisites for being easily recognized as a signaling agent. The chemical valency of Ca^{2+} also makes it readily reactive with many intracellular molecules. To prevent the toxic effect of Ca^{2+} in the context of phosphate precipitation, large molecules such as polypeptides are employed to capture Ca^{2+} and thus detoxify the cellular environment. Its flexibility in terms of the number and lengths of bonds it can form makes it an ideal partner for carboxyl or

neutral oxygen in complex molecules such as proteins to buffer Ca^{2+} concentration at low levels (Williams 2002). This unique property to bind specific proteins with multiple valency and flexibility at high affinity (nanomolar to micromolar), making it unlike any other cation, becomes a special requirement for Ca^{2+} to serve as a signaling agent. In summary, the evolutionary selection of Ca^{2+} as a signal is based on both its chemical properties and its relationship with other biologically active molecules.

1.2. Calcium Handling and Signaling in Living Cells

To precisely control cellular free Ca^{2+} levels, cells on the one hand must allow the rapid entry of Ca^{2+} for nutrient and signaling purposes and on the other hand must prevent Ca^{2+} accumulation to toxic levels by the immediate removal or chelating of Ca^{2+}. From primitive prokaryotes to multicellular eukaryotes, all cells are equipped with specific transporters and Ca^{2+}-specific binding proteins (Cyert 2001, Plattner & Verkhratsky 2015). While these proteins may be largely dedicated to detoxifying purposes in prokaryotes, they emerge as intricate signaling networks with profound regulatory functions in eukaryotes. Entry channels in particular have evolved rapidly and expanded into a large tool kit for precisely shaping Ca^{2+} fluctuations in the cell. The exclusion transporters also multiply to include those that sequester Ca^{2+} into various subcellular compartments (intracellular stores), such as the endoplasmic reticulum (ER), lysosomes or vacuoles, and mitochondria in eukaryotes (**Figure 1*a***). The Ca^{2+}-binding proteins, which originally functioned as simple chelators to buffer the Ca^{2+} level in prokaryotes (Dominguez et al. 2015), later became sensor proteins to monitor the level of Ca^{2+} for implementing changes in eukaryotes (Park et al. 2019). In multicellular organisms, Ca^{2+} not only serves as a signal for local cellular responses but also acts as a signal for orchestrating systemic responses at the whole body level (Choi et al. 2016, Südhof 2012, Tian et al. 2020) (**Figure 1*b***). The most sophisticated system for Ca^{2+}-dependent systemic signaling is synaptic transmission in the animal nervous system, in which neurotransmitters operate Ca^{2+} channels to initiate extremely rapid long-distance electrical transmission (Mateos-Aparicio & Rodríguez-Moreno 2020, Topolnik & Camiré 2019). Despite the lack of a nervous system, plants have also evolved a Ca^{2+}-based long-distance signaling mechanism that is currently being experimentally dissected (Nguyen et al. 2018, Shao et al. 2020, Toyota et al. 2018). As we delve into more details, we will see precisely how some of these signaling mechanisms have been highly conserved while some have become divergent among eukaryotic kingdoms.

1.3. The Coding and Decoding of Calcium Signals

As we have understood that Ca^{2+} signaling is a ubiquitous way to communicate between and within cells, a critical question arises: How can Ca^{2+} translate so many different stimuli into distinct responses in various cell types? To encode such specificity, each stimulus must produce a specific Ca^{2+} signal that is then decoded by specific Ca^{2+} sensors and effectors. Research in the past several decades has established that Ca^{2+} signals are encoded not only by concentration changes in the cell but also by spatial and temporal patterns (Berridge et al. 2003, Clapham 2007, Tian et al. 2020). The unique four-dimensional (including time) parameters for each Ca^{2+} signal are referred to as Ca^{2+} signatures or codes. The production of such codes (coding) is made possible by the coordinated activities of Ca^{2+} channels that mediate Ca^{2+} entry and transporters that remove Ca^{2+} from the cytoplasm. The Ca^{2+}-binding proteins act as sensors that detect and initiate the interpretation (decoding) of the Ca^{2+} signatures. Ca^{2+} binding triggers conformational changes in the Ca^{2+} sensors that in turn physically interact with and influence the activities of downstream effectors such as kinases and phosphatases (Cyert 2001, Hudmon & Schulman 2002, Tang et al. 2020), eventually leading to changes in specific cellular processes. Across the eukaryotic kingdoms

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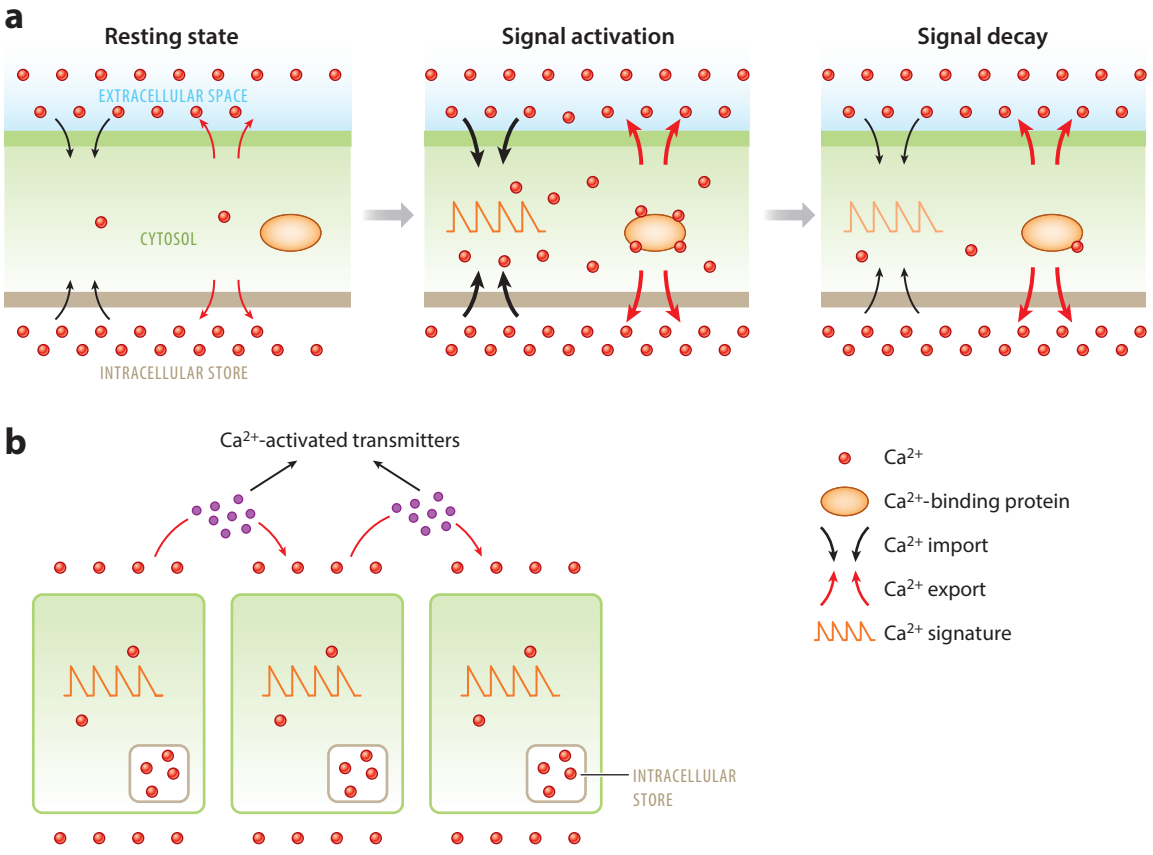

Figure 1

An overview of cytosolic Ca^{2+} signaling. (*a*) The activity of Ca^{2+} transporters for both import and export is low in the resting state of a cell. The signal-mediated activation of Ca^{2+}-permeable channels initiates rapid Ca^{2+} entry, increasing the concentration of free cytosolic Ca^{2+}. The Ca^{2+}-export transporters are activated, removing Ca^{2+} to avoid cytotoxic effects. The balance between Ca^{2+} import and export in a spatial and temporal manner orchestrates a specific pattern of Ca^{2+} change referred to as a Ca^{2+} signature. Proteins with conserved domains for high-affinity Ca^{2+} binding have evolved to function as sensors to decode these Ca^{2+} signatures, leading to the downstream activation of Ca^{2+}-dependent events. When Ca^{2+} entry is inactivated, Ca^{2+} removal continues to cause signal decay and reset the Ca^{2+} levels back to the resting state. (*b*) Systemic Ca^{2+} signaling can be activated by the local cell releasing Ca^{2+}-dependent transmitters, such as neurotransmitters in animals. The transmitters are perceived by a neighboring cell, further activating Ca^{2+} signaling and propagating the local response into a systemic response.

of fungi, animals, and plants, coding and decoding proteins can be both highly conserved and divergent, as we discuss in upcoming sections.

2. THE CODING OF CALCIUM SIGNATURES BY THE ORCHESTRATED ACTIVITIES OF CHANNELS AND PUMPS

Cells respond to different stimuli in different ways. As a second messenger for a large array of distinct signals, Ca^{2+} distinguishes each signal by presenting a unique signature. To produce such a Ca^{2+} signature, a typical series of events involves the initial perception of the stimulus by its receptor followed by the activation of Ca^{2+} channels that mediate Ca^{2+} entry into the cytoplasm through influx from the external space or release from the intracellular stores. The activation of Ca^{2+}entry must be transient to avoid overflow of Ca^{2+} and cytotoxicity, unless cell death is

the destined output. Immediately following Ca^{2+} influx, pumps and antiporters or exchangers are activated to remove Ca^{2+} from the cytoplasm against the Ca^{2+} gradient either back out of the cell or into organellar stores to restore the free cytosolic Ca^{2+} levels back to the resting state (**Figure 1*a***). The intricate regulatory mechanisms underlying activation and inactivation of these Ca^{2+} movers and removers hold the key to the coding process and, thus, to the specificity of a signaling event. Perhaps the most sophisticated mechanisms might be those in animals that have evolved the largest repertoire of channels, whereas land plants may have lost many such channels. We point readers to the summary illustrations in **Figure 2** as we briefly go through the Ca^{2+} channels and pumps in animals, yeast, and plants.

2.1. Calcium Channels

Ion channels are membrane-spanning pores formed by transmembrane (TM) proteins. Ion channels can transport up to 10^8 ions per second across membranes while at the same time selecting specific ions with greater than 99.9% accuracy (Hille 2001). The key functional features of these channels include their ionic selectivity and operation of the gate (gating). Ionic selectivity determines what ion(s) go through a particular channel so that distinct ions can be transported by different channels for specificity and control. The opening and closing of a channel directly control the activity of the channel, which is tightly regulated by intracellular and extracellular signals. Some channels are operated by membrane potential or voltage and are thus called voltage-gated channels (Lai & Jan 2006). Some are sensitive to binding of ligand molecules and are referred to as ligand-gated channels (Pankratov & Lalo 2014). In addition, some channels are sensitive to mechanical changes of the cell membrane and thus are called mechanosensitive channels (Anishkin & Kung 2005, Arnadóttir & Chalfie 2010). Ca^{2+}-permeable channels can be operated by all these mechanisms and play key roles in coding Ca^{2+} signatures.

2.1.1. Voltage-gated calcium ion channels. When examining the voltage-gated Ca^{2+} channels (CaVs) across eukaryotic kingdoms, perhaps the most interesting finding is the loss of typical CaVs among land plants. This loss likely reflects the divergent evolution in electrical signaling between animals and sessile plants.

2.1.1.1. The origin of voltage-gated calcium channels. The movement of charged ions across cell membranes produces electrical currents and membrane potential (voltage). Changes in overall transport activities alter membrane voltages that can open or close a voltage-gated channel. Typical CaVs couple the membrane voltage with Ca^{2+} signaling and regulate many physiological functions (Hille 2001). Animal CaVs feature 24-transmembrane domains (24-TMs) in a single protein subunit (Catterall 2011). The 24-TMs are organized into four subdomains, each of which contains 6-TM structural elements homologous to each other and equivalent to one subunit of homotetrameric channels, suggesting that 24-TM-type CaVs may have evolved from the fusion of single-domain CaVs in prokaryotes (Charalambous & Wallace 2011, Shimomura et al. 2020).

2.1.1.2. Voltage-gated calcium channels have expanded in the animal kingdom but were lost in land plants. Consistent with the origin of CaVs from prokaryotes, some primitive eukaryotic lineages appear to retain single-domain CaVs similar to those found in bacteria. The 24-TM, four-subdomain CaVs have evolved in some of these earlier eukaryotes. For example, in the Bikonta lineages, diatoms contain both the single-domain and four-subdomain CaVs (Helliwell et al. 2019, Verret et al. 2010). In contrast, the unicellular green alga *Chlamydomonas* has only the four-subdomain CaV (Verret et al. 2010). Surprisingly, all land plants have lost both single-domain and four-subdomain CaVs (Verret et al. 2010). In the Unikonta lineages, all fungi,

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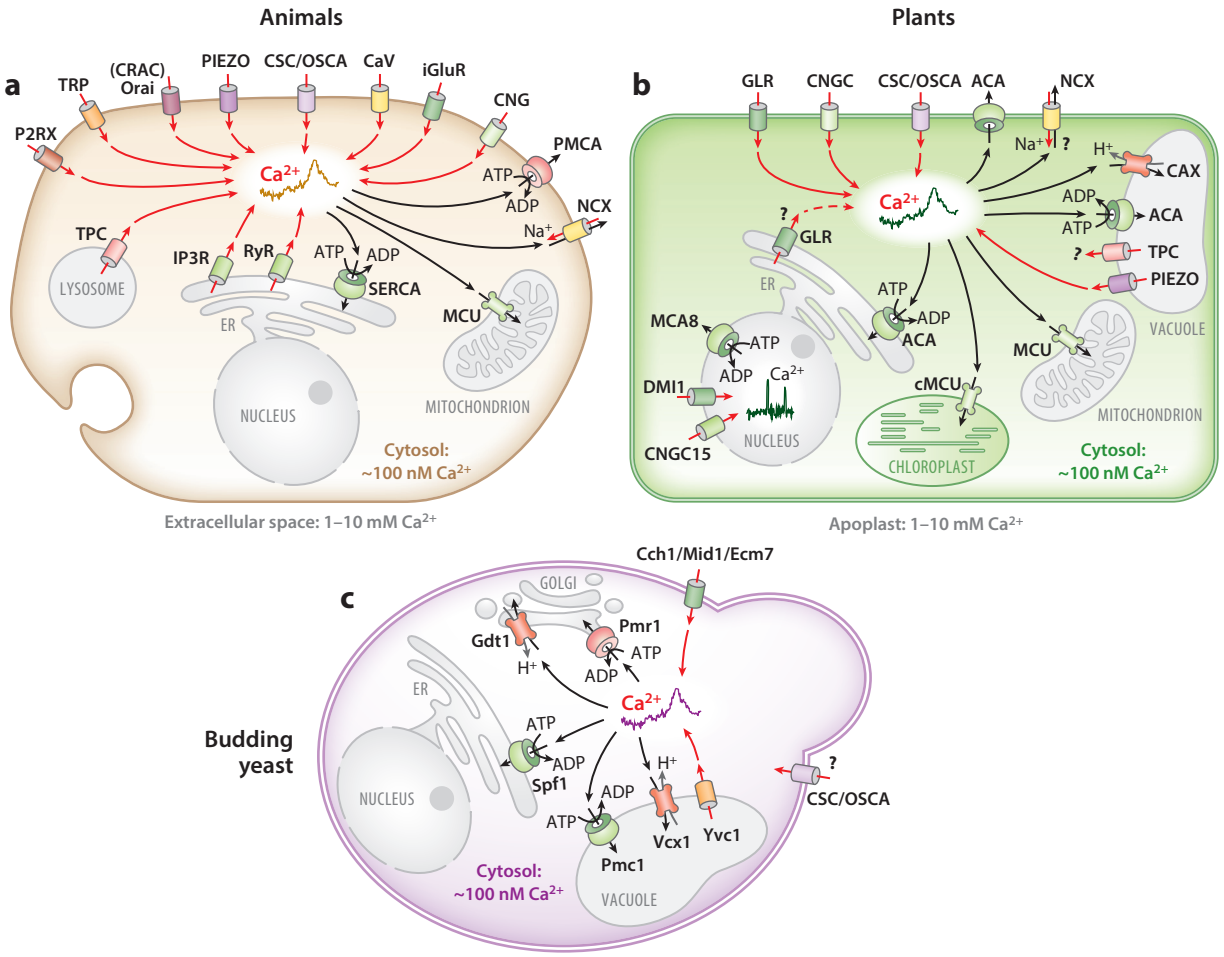

Figure 2

Ca^{2+} channels and pumps in (*a*) animals, (*b*) plants, and (*c*) budding yeast. Ca^{2+} influx relies on a variety of channels including CaVs as well as ligand-gated and mechanosensitive Ca^{2+}-permeable channels. The Ca^{2+}-ATPases, Ca^{2+}/H^{+} exchangers, and NCXs work together to remove Ca^{2+} from the cytosol. These channels and pumps or exchangers are orchestrated to produce specific Ca^{2+} signatures and maintain a low resting Ca^{2+} concentration. Note that land plants feature a considerably smaller repertoire of channels than do animals, as far as we currently know. Abbreviations: ACA, *Arabidopsis* Ca^{2+}-ATPase; CaV, voltage-gated Ca^{2+} channel; CAX, vacuolar Ca^{2+} exchanger; cMCU, chloroplast-localized mitochondrial Ca^{2+} uniporter; CNG/CNGC, cyclic nucleotide-gated channel; CRAC, Ca^{2+}-release-activated Ca^{2+} channel; ER, endoplasmic reticulum; GLR, glutamate receptor-like channel; iGluR, ionotropic glutamate receptor; IP3R, inositol 1,4,5-trisphosphate receptor; MCA8, Medicago Ca^{2+}-ATPase 8; MCU, mitochondrial Ca^{2+} uniporter; NCX, Na^{2+}/Ca^{2+} exchanger; PMCA, plasma membrane Ca^{2+}-ATPase; RyR, ryanodine receptor; SERCA, sarcoendoplasmic reticulum Ca^{2+}-ATPase; TPC, two-pore channel; TRP, transient receptor potential.

including the simplest model budding yeast, have four-subdomain CaVs but have lost the single-domain CaVs (Bonilla & Cunningham 2002). All multicellular animal lineages have acquired the four-subdomain CaVs without retaining the single-domain CaVs (Cai & Clapham 2012). In mammals, a number of four-subdomain CaVs are present and play a key role in various physiological processes, especially in the context of electrical signaling (Ertel et al. 2000). As Ca^{2+}-based fast electrical signaling mechanisms have become increasingly sophisticated and refined from protozoa to humans (Mochida 2018), similar mechanisms have gradually faded away in plants as

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they moved out of the ocean to colonize the land. Lack of movement at the organismal and cellular levels might explain why land plants have lost the CaVs. Nevertheless, long-distance signaling in plants may also use Ca^{2+}-based electrical signaling mechanisms, as discussed in Section 4.3.2.

2.1.2. Ligand-gated calcium-permeable channels. A number of Ca^{2+}-permeable channels are receptors to small molecules ranging from second messengers and hormones to amino acids. Ligand binding opens the channel, coupling receptor function to Ca^{2+} signaling. Unlike in the case of CaVs, which have faded away in land plants, several groups of ligand-gated calcium channels (LGCCs) seem to have expanded in plants beyond their numbers in animals. These groups include the cyclic nucleotide-gated channels (CNGs in animals and CNGCs in plants) and those related to the ionotropic glutamate receptors [iGluRs in animals and glutamate receptor-like channels (GLRs) in plants]. Despite their structural similarities, the regulatory mechanisms for these channels may have been altered to fit the specific physiologies of animals and plants. While these channels have been studied extensively in animals, the related counterparts in plants have yet to be understood sufficiently to provide a comparative analysis. For example, the identities of ligands for these plant channels are yet to be established, providing a fertile ground for new discoveries.

2.1.2.1. Cyclic nucleotide-gated channels in animals versus those in plants. Animal CNGs are nonselective cation channels that are opened by the direct binding of intracellular cyclic nucleotides (Yau & Baylor 1989). The native channels typically consist of multiple subunits forming tetrameric structures (James & Zagotta 2018). In addition to regulation by cyclic nucleotide (cNMP) binding, CNG channels are also regulated by Ca^{2+}-calmodulin (CaM) through a CaM-binding domain at the N-terminus of the channel protein as a negative feedback mechanism.

While the cyclic AMP (cAMP) signaling pathway mediated by protein kinase A (PKA) exists in fungi, cAMP-gated channels have not been identified in this eukaryotic kingdom (Conrad et al. 2014). Interestingly, although the cAMP-PKA module has not been found in plants, ion channels related to CNGs are abundant (DeFalco et al. 2016, Zelman et al. 2012). At least 20 members of the CNGC family are encoded in the *Arabidopsis* genome, and each member harbors one or more CaM-binding domains (CBDs) adjacent to the cNMP-binding domain (CNBD) in the C-terminal region. Available data so far suggest that CNGCs may form tetrameric structures with homo- or heteromeric compositions (Tian et al. 2020). Plant CNGCs can be either activated or inhibited by CaM, depending on their subunit composition and physiological context (Tian et al. 2020).

2.1.2.2. Ionotropic glutamate receptors in animals versus glutamate receptor-like channels in plants. Glutamate is a crucial neurotransmitter that is perceived by two types of receptors. Ionotropic GluRs (iGluRs) are ligand-gated cation channels that produce excitatory glutamate-evoked depolarization, whereas metabotropic GluRs (mGluRs) are G-protein-coupled receptors (GPCRs) that control cellular processes by G-protein-signaling cascades (Kennedy 2013, Reiner & Levitz 2018). All iGluRs are tetramers forming a nonselective cation channel (Sobolevsky 2015). Each subunit has an extracellular N-terminal domain, a ligand-binding domain (LBD), a pore-forming TM domain, and an intracellular C-terminal domain. Several full-length iGluR structures have been solved, providing insights into ligand binding and their overall architecture in different activation states and with various auxiliary proteins (Kamalova & Nakagawa 2021, Sobolevsky 2015).

With the discovery of GluR0 from *Synechocystis*, bacterial homologues of mammalian iGLuRs are believed to exist and may be the ancestors of all eukaryotic GLuRs (Arinaminpathy et al. 2003). However, GLuR0 has been shown to form a glutamate-activated K-selective channel not permeable to Ca^{2+} (Chen et al. 1999, Mayer et al. 2001). Given that fungi lack glutamate receptors, it was surprising to find that plants, while lacking a nervous system, contain a large family of

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glutamate receptors closely related to the animal iGluRs. *Arabidopsis* has 20 GLRs divided into three clades (Chiu et al. 2002). Electrophysiological analysis of the plant GLRs demonstrated that GLRs are bona fide Ca^{2+} channels (Wudick et al. 2018). Thus far, little is known about the subunit composition of native GLR channels in plants. An example of plant GLR function in systemic wound signaling is discussed in Section 4.3.2.

2.1.2.3. Other ligand-gated calcium channels that are ubiquitous in animals but not found in land plants. A number of other ligand-gated channels are permeable to Ca^{2+} and play an important role in Ca^{2+} signaling in animal systems. These include the ionotropic ATP receptors (P2XRs) gated by extracellular ATP and permeable to diverse ions including monovalent cations, Ca^{2+}, or anions (Schmid & Evans 2019, Surprenant & North 2009). Although land plants can perceive extracellular ATP, they do not appear to have P2XR-type receptors (Choi et al. 2014). In addition to the LGCCs in the plasma membrane (PM), some channels are located in the intracellular membranes that mediate Ca^{2+} release from intracellular stores. The inositol 1,4,5-trisphosphate (IP3) receptor (IP3R) and the ryanodine receptor (RyR) are major players in intracellular Ca^{2+} release in animals. IP3R is the target of the classic second messenger IP3, which is produced primarily by phospholipase C (PLC) upon activation of G-protein-coupled receptors (Santulli et al. 2017). RyR is a member of the same gene family as IP3R but has evolved specialized functions in response to different cellular stimuli. Topologically, these Ca^{2+}-release channels are members of the tetrameric cation channel superfamily (des Georges et al. 2016, Santulli et al. 2017).

Although inositol phosphates may play a role in cell signaling in plants, typical G-protein-coupled receptors that activate PLC to release IP3 have not been identified. Likewise, homologues of animal IP3Rs or RyRs are not found in land plants.

2.1.3. Calcium-permeable mechanosensitive channels. Mechanotransduction is the conversion of mechanical perturbations into electrochemical signals that eventually bring changes to the cell. The primary sensors that mediate many such rapid responses to mechanical signals are ion channels (Arnadóttir & Chalfie 2010). While mechanosensitive channels are present in all domains of life (Anishkin & Kung 2005), only a few known Ca^{2+}-permeable channels are gated by mechanical forces. The best-studied of these channels include PIEZOs and CSCs/OSCAs (Kefauver et al. 2020, Murthy et al. 2017). While PIEZO channels are found in both animals and plants, CSCs/OSCAs are present in all eukaryotes. PIEZOs are mechanosensitive, Ca^{2+}-permeable nonselective cationic channels that participate in a diverse array of mechanotransduction processes in mammals (Kefauver et al. 2020). Each PIEZO subunit is a large protein consisting of 38-TM helices and three subunits that form a trimeric channel with three-blade propeller architecture (Kefauver et al. 2020).

The CSC/OSCA/TMEM63 channels include a TM domain referred to as domain of unknown function 221 (DUF221) (Hou et al. 2014, Yuan et al. 2014). Unlike the small PIEZO family, CSC/OSCA includes 3 vertebrate members (TMEM63A/B/C) and at least 15 members in flowering plants such as *Arabidopsis*. The structures of several CSC/OSCA family members have been solved by cryogenic electron microscopy (cryo-EM), revealing them to be dimeric channels [reviewed in Kefauver et al. (2020)]. Multiple structural features have been identified that might confer mechanosensitivity on these channels, which require further experimental verification.

2.1.4. Calcium-permeable channels with mixed gating properties. Some Ca^{2+}-permeable channels are gated by multiple mechanisms, including membrane voltage, ligands, and mechanical forces. Several examples are briefly discussed here.

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2.1.4.1. The two-pore channels. Both animals and plants have two-pore channels (TPCs) that function as homodimers, with each subunit containing two homologous *Shaker*-like 6-TM repeats (Hedrich et al. 2018, Zhu et al. 2010). They belong to the voltage-gated ion channel superfamily, but their gating properties are rather complex. These channels are localized to the endolysosomal compartments in animal cells and to the vacuoles of plant cells (Peiter et al. 2005, Zhu et al. 2010). The cryo-EM structures of TPCs suggest that mammalian TPC1/2 both function as Na^+-selective channels, whereas plant TPC1 is Ca^{2+}-permeable (Guo et al. 2016; Kintzer & Stroud 2016; She et al. 2018, 2019). Unlike mammalian TPCs that are gated by phosphatidylinositol 4,5-bisphosphate (PIP2) (and by voltage for TPC1), *Arabidopsis* TPC1 activation requires both voltage and cytosolic Ca^{2+} (Hedrich et al. 2018).

2.1.4.2. The large family of transient receptor potential channels in animals is missing in land plants. The transient receptor potential (TRP) superfamily consists of at least 28 mammalian members that are typically permeable to both monovalent and divalent cations including Ca^{2+} (Clapham 2003, Julius 2013, Montell 2005). Because they serve as cellular sensors for a wide spectrum of physical and chemical stimuli, understanding the mechanisms that underlie the gating and activation of each TRP is challenging (Clapham 2003, Julius 2013). In parallel, Ca^{2+}-permeable TRP channels in the PM can mediate Ca^{2+} entry, while organellar TRP channels serve as pathways for intracellular Ca^{2+} release. Recent structural analyses have provided insights into the overall architecture and gating of different TRP subfamilies (Guo & Chen 2019). Many of the TRP channels are voltage sensitive, although the voltage sensors in S1–S4 may not be as obvious as those in typical voltage-gated cation channels (Zheng 2013).

While a single vacuolar TRP channel has been found in yeast and other fungi (Denis & Cyert 2002), typical TRP channels are missing from land plants. Such plants may use structurally different channels for sensing similar physical and chemical cues.

2.1.4.3. Store-operated calcium entry is a key pathway for interorganellar calcium influx in animals that is missing in plants. Store-operated Ca^{2+} entry (SOCE), measured as Ca^{2+}-release-activated Ca^{2+} channels (CRACs), is a major pathway for Ca^{2+} influx across the PMs of essentially all metazoans. SOCE is so named because its activity depends on the Ca^{2+} level in the ER, the major Ca^{2+} store (Lewis 2011, Putney 2017). The channel associated with SOCE consists of pore-forming Orai protein in the PM and Ca^{2+}-sensing stromal interaction molecule (STIM) in the ER membrane. STIM proteins are equipped with an N-terminal Ca^{2+}-sensing domain and a C-terminal coiled-coil domain for direct interaction with the Orai channel. In response to ER Ca^{2+} depletion, the STIM proteins undergo conformational changes, allowing them to cluster in ER-PM junctions where they trap and activate Orai channels. This process is reversible: When Ca^{2+} is pumped back into the ER, STIM dissociates from Orai, the channels close, and both proteins diffuse away from the ER-PM junctions. Recent structural studies on STIM and Orai proteins have revealed the molecular underpinnings of this interorganellar Ca^{2+}-handling mechanism (Bakowski et al. 2020, Fahrner et al. 2020).

2.2. Calcium Pumps and Exchangers

In eukaryotes, Ca^{2+} is removed by pumping either out of the cell or into intracellular stores such as the ER, mitochondria, and endolysosomal or vacuolar compartments. The remover transporters are highly conserved across eukaryotic kingdoms. The Ca^{2+} pumps and exchangers are generally believed to serve a housekeeping detoxification function that evolved in bacterial cells (Dominguez 2004, Dominguez et al. 2015) and was further expanded and became highly regulated in plants and animals. In the context of coding Ca^{2+} signatures, these pumps and exchangers play a critical role

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in shaping the spatiotemporal patterns of Ca^{2+} concentration changes in response to the initiation and termination of specific signals.

2.2.1. Plasma membrane calcium ATPases and exchangers. All Ca^{2+} pumps regardless of subcellular location belong to the P-type ATPase superfamily (Dyla et al. 2020). We describe them here based on subcellular locations so that we can clearly see how these transporters move Ca^{2+} around in the cell. The PM Ca^{2+}-ATPases (PMCAs) are the major high-affinity Ca^{2+} extrusion system used to restore the low resting levels of intracellular Ca^{2+} following Ca^{2+} elevation (Brini 2009, Strehler 2015). These PMCAs use ATP hydrolysis to drive the conformational changes and power the Ca^{2+} transport against a steep gradient between intracellular (~100 nM–10 μM) and extracellular (~2 mM) Ca^{2+}. A key regulatory property of the pumps is their Ca^{2+}-dependent activation through reversible interaction with CaM. The CaM-binding domain is located in the C-terminal cytosolic region in mammalian PMCAs and close to the N-terminus in plant pumps. The Ca^{2+}/CaM-dependent regulation of PMCA activity is an outstanding example of the autoregulatory capacity of the Ca^{2+} signal. As soon as Ca^{2+} levels reach a certain threshold, Ca^{2+}-bound CaM binds to PMCA to activate the pump, reducing the Ca^{2+} levels in the cytosol (Krebs 2017). This autoregulatory mechanism is also conserved in many members of the ACA (*Arabidopsis* Ca^{2+}-ATPase) family in plants (Geisler et al. 2000, Sze et al. 2000). Some of these ACAs are located in the PM and have equivalent functions to PMCAs in animal cells.

In addition to the PMCA primary pumps, the PM of animal cells also harbors Ca^{2+}/Na^{+} exchangers (Khananshvili 2020). The main function of NCX (Na^{2+}/Ca^{2+} exchanger) isoforms is the transport of three Na^{+} into the cell in exchange for one Ca^{2+} (Nicoll et al. 2013). Studies (Nicoll et al. 2013) have identified the Ca^{2+}-binding domains in NCXs for Ca^{2+}-dependent activation. In addition, some NCX-related transporters in plants contain EF-hand motifs that may perform a similar regulatory function. Although plant genomes encode a number of NCX-related cation/Ca^{2+} exchangers (Pittman & Hirschi 2016), the subcellular localization and function of these transporters remain underexplored.

2.2.2. The endoplasmic reticulum calcium ATPase. The ER of all eukaryotic cells contains the P-type Ca^{2+}-ATPase. The term SERCA comes from sarcoendoplasmic reticulum Ca^{2+}-ATPase in muscle cells. As a high-affinity Ca^{2+} transporter, SERCA maintains the low cytosolic Ca^{2+} level by moving Ca^{2+} from the cytosol into the ER lumen (Aguayo-Ortiz & Espinoza-Fonseca 2020, Primeau et al. 2018). Plants and fungi have SERCA-like Ca^{2+}-ATPases in their ER membranes as well. In particular, some members of the plant ER- Ca^{2+}-ATPases have CaM-binding sites and can be regulated by the CaM-dependent autoregulatory mechanism (Geisler et al. 2000, Sze et al. 2000).

2.2.3. Vacuolar calcium ATPases and exchangers. In fungal and plant cells, vacuoles serve as the major Ca^{2+} stores. The vacuolar membrane contains both primary Ca^{2+} pumps and cation/Ca^{2+} exchangers (**Figure 2**). In budding yeast, PMC1 is the major Ca^{2+} pump, whereas the model plant *Arabidopsis* has at least three ACA family members that are localized to the tonoplast (Hilleary et al. 2020, Lee et al. 2007). The vacuolar Ca^{2+} exchangers belong to the cation/Ca^{2+} exchanger superfamily that includes animal NCX (Section 2.2.1). However, vacuolar Ca^{2+} exchangers (CAXs) in fungal and plant cells are powered by the proton gradient built by the vacuolar proton (H^{+})-ATPase (Pittman & Hirschi 2016).

2.2.4. Mitochondrial calcium uniporters in all eukaryotes. In addition to the ER, mitochondria serve as another Ca^{2+} store; they take up Ca^{2+} through the mitochondrial Ca^{2+} uniporter (MCU) complex (Giorgi et al. 2018, Rizzuto et al. 2012). In mammals, the MCU complex contains

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four core components: the pore-forming MCU, the gating factors MICU1 and MICU2, and an auxiliary EMRE subunit essential for Ca^{2+} transport. The activity of the MCU is tightly regulated by the MICUs, which contain EF-hand motifs that sense the changes in cytosolic Ca^{2+} concentrations and switch the MCU on and off, reiterating the autoregulatory feature of Ca^{2+} signals. Structural analyses have defined the architecture of the mammalian MCU complex (Fan et al. 2020). Although phylogenetic analysis identified MCU-like genes in all other eukaryotic kingdoms, such as fungi and plants, the evolutionary relationships remain complex (Pittis et al. 2020). For example, the plant MCUs may have MICU subunits but may lack the EMRE subunit (Teardo et al. 2019).

3. DECODING CALCIUM SIGNALS WITH A VARIETY OF CALCIUM-BINDING PROTEINS

In response to the elevation of Ca^{2+} levels in the cell, a variety of molecules bind Ca^{2+} with high affinity. This may have been a simple detoxification mechanism in early life forms that later became a way to sense and decode Ca^{2+} signals. In this process, proteins bind Ca^{2+} and consequently experience structural changes that in turn trigger changes in activity and function. In a more sophisticated system, Ca^{2+}-binding proteins and their downstream targets can be located in a specific subcellular domain within a cell to specify a particular response by decoding a specific Ca^{2+} signal. In this section, we present the tool kits available for such decoding processes in eukaryotic cells, focusing on proteins with EF-hand motifs and examples that represent both conservation and divergence among fungi, animals, and plants.

3.1. Calmodulins and Their Targets

Calmodulin is perhaps the best-studied example of the EF-hand Ca^{2+}-binding proteins. It is one of the most conserved proteins among all eukaryotes, from budding yeast to plants and animals (Chin & Means 2000, Luan et al. 2002, McCormack et al. 2005). The four EF hands in CaM are organized into two distinct globular domains. Although each domain binds Ca^{2+} and undergoes conformational changes independently, the two domains act in concert to bind target proteins. To effectively transduce the Ca^{2+} signal, CaMs must bind Ca^{2+} selectively in the presence of high concentrations of Mg^{2+} and monovalent cations in the cell. Such cation selectivity is achieved by optimizations in the structural folds of the binding loop (Gifford et al. 2007, Nelson & Chazin 1998). Structural analysis reveals the conformational changes induced by Ca^{2+} binding, which enable target recognition (Zhang et al. 1995) (**Figure 3*a***).

3.1.1. How calmodulin interacts with and regulates downstream targets. Ca^{2+}/CaM binds and regulates the activity of a wide range of proteins that are not necessarily related in structure. This versatility has been explained by structural analyses of Ca^{2+}/CaM and target-bound Ca^{2+}/CaM (**Figure 3*a***). The two globular domains of Ca^{2+}/CaM are connected by a flexible tether that can accommodate peptides of varying sizes (Nelson et al. 2002, Zhang & Yuan 1998). Upon binding a peptide, these two domains fold toward each other to form a hydrophobic channel in which Ca^{2+}/CaM interacts with the target peptide through exposed hydrophobic domains (**Figure 3*b***). The large array of functional targets for CaMs spans a broad field of cellular functions, such as signaling proteins (kinases and phosphatases), CaM-interacting transcription factors, cytoskeleton components, transporters, and channels. Many of these are, like CaM itself, highly conserved among eukaryotes.

3.1.2. Calmodulin kinases in all eukaryotes. There are at least four types of CaM kinases (CaMKs) in animals, including CaMKI, CaMKII, CaMKIV, and CaMKK (Bhattacharyya et al. 2020, Takemoto-Kimura et al. 2017). In the resting state, these enzymes are autoinhibitory

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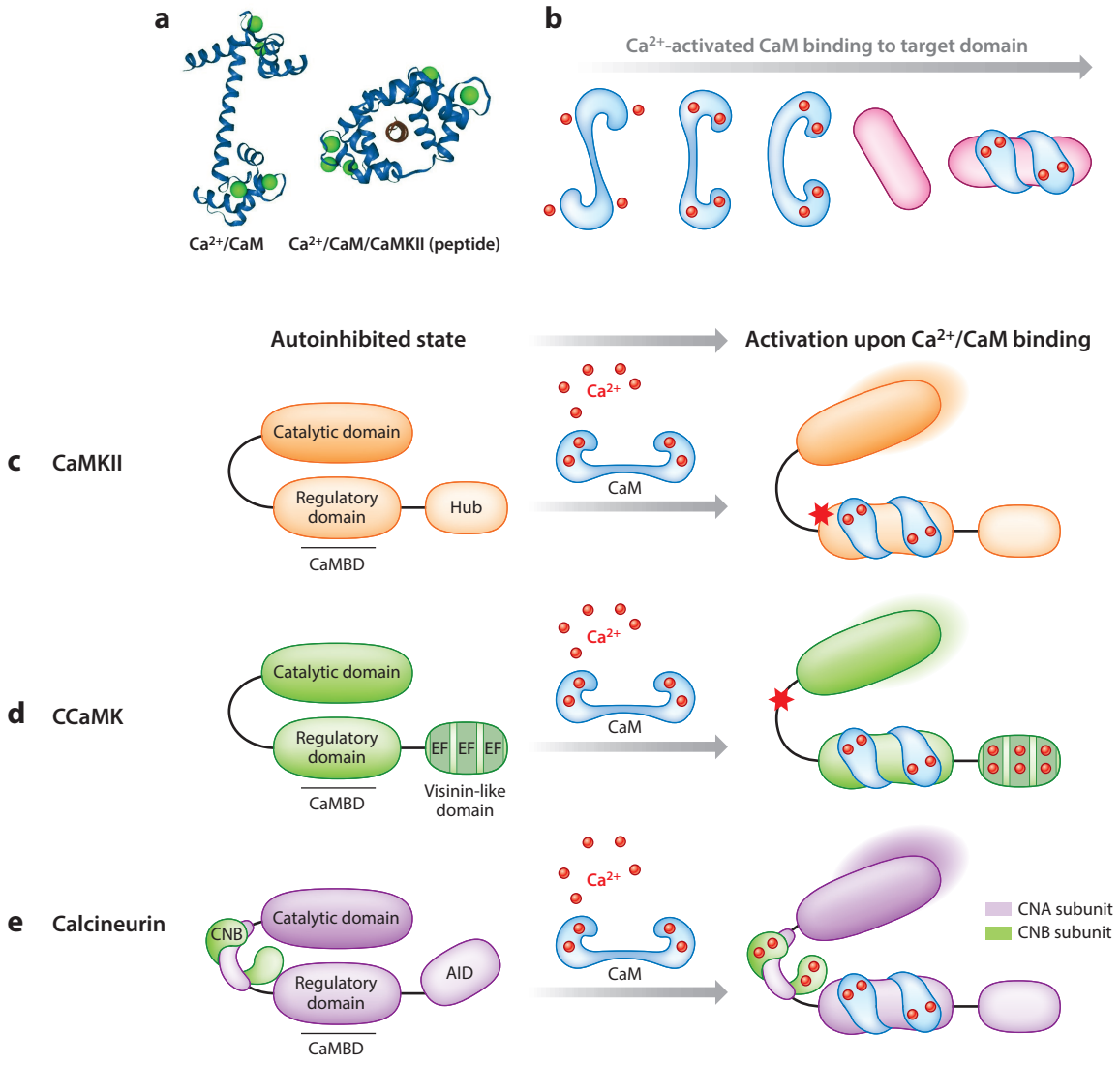

Figure 3

The decoding of Ca^{2+} signals by calmodulin (CaM). (*a*, *left*) A ribbon diagram of CaM depicting its Ca^{2+}-bound structure [Ca^{2+}/CaM, Protein Data Bank (PDB) ID: 1CLL] and (*right*) its interaction with a CaM-binding peptide from Ca^{2+}/CaM-dependent kinase II [or CaM kinase II (CaMKII)] (Ca^{2+}/CaM/CaMKII, PDB ID: 1CMI). (*b*) A schematic model depicts Ca^{2+}-bound CaM undergoing conformational changes, triggering interaction with a target domain. (*c*) CaMKII consists of an N-terminal catalytic domain, a regulatory (autoinhibitory) domain, and a C-terminal hub domain for oligomerization. CaMKII is autoinhibited in the resting state. After the Ca^{2+} level increases, Ca^{2+}/CaM associates with the CaM-binding domain (CaMBD) within the regulatory domain, promoting the autophosphorylation and activation of CaMKII. (*d*) A plant Ca^{2+}/CaM-dependent protein kinase (CCaMK) has kinase and autoinhibitory domains and three Ca^{2+}-binding EF-hand motifs in the visinin-like domain. Ca^{2+} may first bind EF-hand motifs, leading to the autophosphorylation and binding of Ca^{2+}/CaM to CaMBD. Ca^{2+}/CaM binding results in fully active CCaMK for substrate phosphorylation. In panels *c* and *d*, the stars represent phosphorylation modification. (*e*) Calcineurin is a Ca^{2+}/CaM-dependent serine/threonine phosphatase consisting of a catalytic A subunit (CNA) and a regulatory B subunit (CNB). Calcineurin A is inhibited by a C-terminal autoinhibitory domain (AID). Elevated Ca^{2+} levels enable the high-affinity binding of Ca^{2+}/CaM and a fully activated phosphatase.

complexes involving oligomeric CaMK subunits or other partner proteins. In all cases, Ca^{2+}/CaM interacts with the autoinhibitory domain to release the kinase domain and promote autophosphorylation of the kinase, leading to autonomously active states that can function without Ca^{2+}/CaM (**Figure 3*c***).

Plants also contain CaMK-like protein kinases, although the structural domains are different from those of animal CaMKs. In particular, the plant Ca^{2+}/CaM-activated kinases (CCaMKs) contain not only a CaM-binding domain but also three Ca^{2+}-binding EF-hand motifs in the C-terminal visinin-like domain (Harper & Harmon 2005, Singh & Parniske 2012). The activation mechanism entails binding of both Ca^{2+} and CaM to these regulatory domains, with Ca^{2+} binding to the visinin-like domain before CaM interaction (Singh & Parniske 2012, Takezawa et al. 1996) (**Figure 3*d***).

3.1.3. Calmodulin-regulated protein phosphatase (calcineurin) in fungi and animals. Calcineurin (or PP2B) is a Ca^{2+}/CaM-dependent serine/threonine phosphatase that is highly conserved in fungi and animals (Aramburu et al. 2000, Cyert 2001) but missing in plants. Calcineurin is a heterodimer composed of a catalytic A subunit (CNA) and a regulatory B subunit (CNB) with four EF hands. Under resting Ca^{2+} levels, the CNA and CNB subunits are associated but the enzyme is inactive due to an autoinhibitory domain at the C-terminus of the A subunit. The elevation of Ca^{2+} levels produces Ca^{2+}-bound CaM that binds to the CNA subunit and releases the autoinhibition, thus activating the phosphatase (Klee et al. 1998) (**Figure 3*e***).

3.1.4. Calmodulin-regulated calcium channels and pumps: a mechanism to couple calcium decoding to the coding process. A number of Ca^{2+} channels and pumps contain CaM-binding domains and thus serve as targets for CaM, providing a mechanism for Ca^{2+} sensing to modify the Ca^{2+}-coding activities. A classic example is the feedback regulation of CaVs by CaM in Ca^{2+}-dependent inactivation (CDI) (Ben-Johny & Yue 2014). Similar regulation is also found in CNG-type channels from animals and CNGCs from plants. While the CaM-mediated regulation of animal CNGs, like that of CaVs, largely entails CDI that inhibits the channels (Trudeau & Zagotta 2003) (**Figure 4*a***), plant CNGCs can be regulated both negatively and positively depending on their subunit compositions and physiological context (Pan et al. 2019, Tian et al. 2019, Zeb et al. 2020).

Ca^{2+} sensors such as CaM not only target channels that elevate cytosolic Ca^{2+} levels but also regulate pumps that remove Ca^{2+} from the cytosol. In all cases, Ca^{2+} pumps that contain the CaM-binding domain (CaMBD) are activated by Ca^{2+}/CaM (Section 2.2.1). In other words, Ca^{2+} elevation immediately activates the pumps to restore the low resting level (Krebs 2017, Strehler 2015) (**Figure 4*b***). Interestingly, while all CaM-activated Ca^{2+} pumps are located in the PM in animal cells, such pumps are broadly distributed in the PM and the ER and vacuolar membranes in plant cells (Geisler et al. 2000, Lee et al. 2007). A bacterial H^+/Ca^{2+} antiporter (and possibly other related antiporters in eukaryotes) may be activated by a direct Ca^{2+}-sensing mechanism within the exchanger protein (Lu et al. 2020). Together, these findings present a coupling mechanism for the cell to respond to Ca^{2+} elevation by immediately removing free Ca^{2+} to prevent overload. Such a mechanism is likely well conserved throughout evolution (**Figure 4**).

3.2. Expansion and Evolution of Novel Calcium Sensors in Land Plants

Comparing Ca^{2+} signaling tool kits among eukaryotes, a significant finding is that land plants have evolved a large number of Ca^{2+}-binding EF-hand proteins, more than those in fungi and animals. This situation is in sharp contrast to the smaller repertoire of Ca^{2+} channels in plants described in Section 2.1.

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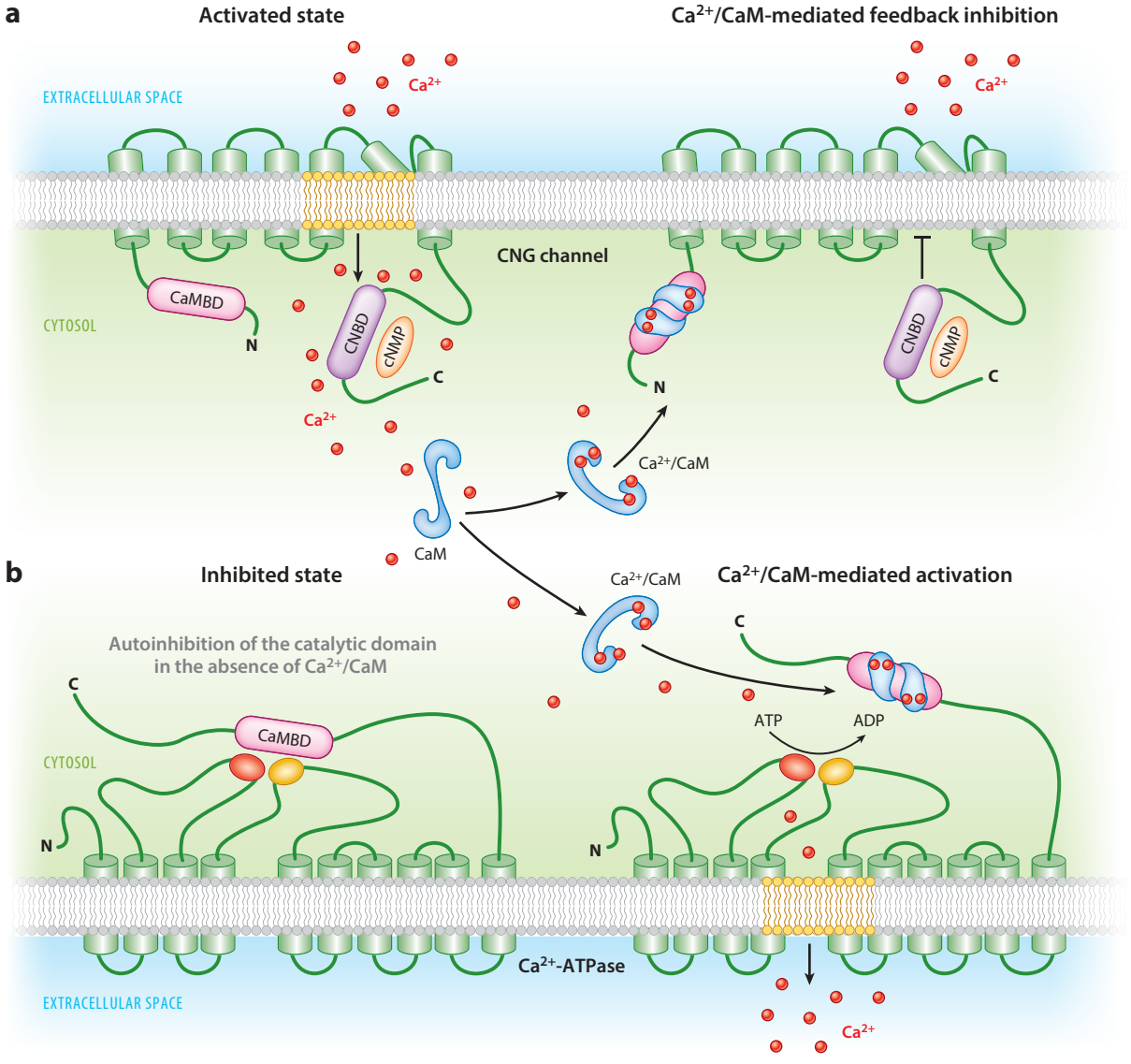

Figure 4

Ca^{2+}-dependent regulation of cyclic nucleotide-gated channels (CNGs) and Ca^{2+}-ATPase. (*a*) The process of feedback inactivation of an animal CNG. The CNG harbors a cyclic nucleotide (cNMP)-binding domain (CNBD) at the C-terminus and a calmodulin (CaM)-binding domain (CaMBD) at the N-terminus. Binding of cNMPs causes a rearrangement in the CNBD and promotes the opening of the channel pore via an allosteric mechanism. Activated CNGs mediate Ca^{2+} influx into the cytosol. Elevated Ca^{2+} levels facilitate Ca^{2+}/CaM binding to the CaMBD and cause the inhibition of channel activity. (*b*) The Ca^{2+}-dependent activation of animal Ca^{2+}-ATPase located in the plasma membrane. In the resting state, Ca^{2+}-ATPase is autoinhibited by the association of CaMBD with the catalytic region. Upon the elevation of Ca^{2+} levels, Ca^{2+}/CaM binds to the CaMBD, releasing the autoinhibition of the catalytic domain. ATP hydrolysis drives conformational changes and powers Ca^{2+} transport to shape the specific Ca^{2+} signature and reset the resting state.

3.2.1. The calmodulin-like proteins. While CaM is a ubiquitous Ca^{2+} sensor in all eukaryotes (Section 3.1), plants have acquired a remarkable variety of CaM-like proteins (CMLs). CMLs remain poorly characterized at both the structural and functional levels despite the fact that they may be the largest class of Ca^{2+} sensors in plants (about 50 in *Arabidopsis*) (McCormack et al. 2005). CMLs contain a variable number of EF hands (from one to six), some of which have degenerated, possibly contributing to the functional diversity of CMLs (La Verde et al. 2018). Like CaM, this large family of CMLs must function by interacting with and regulating the activity of their targets, some of which may be shared with CaM (La Verde et al. 2018).

3.2.2. Calcium-dependent protein kinases. Plants have evolved new types of Ca^{2+} sensors with both Ca^{2+}-binding EF-hand motifs and catalytic kinase domains. Such kinases include the plant CCaMK discussed earlier (Section 3.1.1) and a large family of Ca^{2+}-dependent protein kinases (CDPKs) that contain a CaM-like domain with four typical EF hands but do not have the CaMBD in CCaMK (Harper et al. 2004). A typical CDPK has a serine/threonine kinase domain followed by an autoinhibitory domain and ending with the CaM-like domain. The resting state features an inactive enzyme with the kinase domain covered by the autoinhibitory domain. Activation occurs upon Ca^{2+} binding to the EF-hand motifs, causing a conformational change that disengages the autoinhibitor–kinase domain interaction (Harper & Harmon 2005, Harper et al. 2004).

3.2.3. The CBL-CIPK network. In searching for plant homologues of calcineurin, a calcineurin B-like protein (CBL) was identified in *Arabidopsis* (Kudla et al. 1999). Although the CBL protein is most related to CNBs in yeast and animals, its partner proteins are not CNA-type protein phosphatases but a large family of protein kinases called CBL-interacting protein kinases (CIPKs) that are not found in fungi or animals (Shi et al. 1999). This represents a shift of paradigm in Ca^{2+} decoding from fungi and animals to plants (Luan 2009). The CIPKs belong to the superfamily of SNF1-related kinases (SnRKs) in plants (Hrabak et al. 2003). There are 10 CBLs and 26 CIPKs in *Arabidopsis*, and interactions between the Ca^{2+}-sensor subunits (CBLs) and CIPKs form an intricate signaling network for decoding Ca^{2+} signals in plants (Tang et al. 2020).

4. EXAMPLES OF CALCIUM-SIGNALING PATHWAYS

After comparing the tool kits available to encode and decode Ca^{2+} signatures in various organisms, we now turn to several example pathways to illustrate how plants and animals use their tool kits in various Ca^{2+}-signaling processes. We show that plants and animals not only have different tool kits but the way they put the tool kits to use can also differ. Conceptually they share the same basic principles: Signal-receptor pairs first activate channels to induce an elevation in a specific spatiotemporal pattern (the signature), followed by the activation of the decoding components (sensors and effectors), ultimately leading to changes in gene expression and/or other cellular processes.

4.1. Calcium Signaling for Polarized Growth: Axon Guidance and Pollen Tube Elongation

A hallmark for cell growth and development is the polarity that guides the differential distribution of structural elements in different domains of an individual cell. The process of tip growth is an extreme form of polarized growth of living cells that results in an elongated cylindrical cell morphology with a rounded tip (growth cone) at which growth takes place. Tip growth occurs in fungi (hyphae) and plants (e.g., root hairs and pollen tubes) as well as animals (axons of neurons). In all these processes, Ca^{2+} signaling plays a key role in remodeling the cytoskeletal organization and membrane trafficking that drive the rapid extension of the growing tip.

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4.1.1. Calcium signaling in axon pathfinding. Neurons form precise connections to support the development and function of the nervous system. Axon pathfinding is a process in which growth cones drive axons to connect with their synaptic partners to form functional circuits (McCormick & Gupton 2020, Stoeckli 2018). A central theme in the axon guidance field is that Ca^{2+} signals control growth cone behaviors such as extension, turning, and pausing by remodeling the growth cone cytoskeleton (Gasperini et al. 2017, Sutherland et al. 2014). Axon pathfinding begins with the guidance cues that direct growth cone activity. A number of guidance cues have been identified, including both chemical and mechanical factors. With the growing repertoire of guidance cues, receptors, and cell adhesion molecules, signaling pathways interact to form a complex network (McCormick & Gupton 2020, Sutherland et al. 2014). In response to a range of guidance cues, CaVs and TRP channels are often activated to facilitate the Ca^{2+} influx required for growth cone motility. In response to mechanical cues, adhesion receptors as well as mechanosensitive ion channels, such as PIEZO or TRP channels, coordinate to produce precise Ca^{2+} signatures for modulating outgrowth (Sutherland et al. 2014). Following the elevation of Ca^{2+} levels, Ca^{2+} decoders such as CaMKII and calcineurin (CaN) are largely responsible for the Ca^{2+}-cytoskeleton nexus in the growth cone. A general principle of Ca^{2+} decoding has been learned by studying axon guidance, namely, that different frequencies and amplitudes of Ca^{2+} spiking can be recognized by CaMKII but not by CaN. In other words, some decoders are more fine-tuned than others. The targets of CaMKII and CaN include some cytoskeleton-regulating proteins that facilitate growth cone turning and/or extension (Kerstein et al. 2017).

Dynamic motility of the growth cones requires remodeling of the PM together with its cytoskeletal scaffolds. While exocytosis drives growth cone attraction, endocytosis facilitates growth cone repulsion. Ca^{2+}-dependent signaling events in the cytosol, through the decoding components CaMKII and CaN, drive a balance between membrane protrusion and retraction through the balancing of exocytosis and endocytosis activity (Gasperini et al. 2017).

4.1.2. Calcium signaling in pollen tube tip growth in plants. Plant reproduction starts with pollen grain germination on the stigma of the pistil. The pollen tubes grow through the female tissues and navigate precisely to reach the ovule where fertilization occurs. Pollen tubes elongate by tip growth and find the ovule in response to guidance cues that are mainly peptides perceived by receptor-like kinases (Li et al. 2018, Zhong & Qu 2019, Zhou & Dresselhaus 2019). Ca^{2+} signaling plays a central role in pollen tube tip growth and guidance (Hepler et al. 2012, Konrad et al. 2011, Tian et al. 2020). Several Ca^{2+}-coding components are expressed in pollen tubes and play a critical role in pollen tube growth (Tian et al. 2020). These include CNGCs, GLR channels, and Ca^{2+}-ATPases, illustrating the importance of a delicate balance between Ca^{2+} influx and removal in building the specific Ca^{2+} signal for pollen tube tip growth (Tian et al. 2020). The Ca^{2+} signals are decoded by Ca^{2+}-sensor proteins, including CaMs, CMLs, CDPKs, and CBL-CIPK pairs (Steinhorst et al. 2015; Yip Delormel & Boudsocq 2019; Zhou et al. 2014, 2015). Like tip growth in axon guidance, Ca^{2+} signaling is connected to cytoskeleton (and cell wall) dynamics and membrane trafficking in the pollen tube (Gu & Nielsen 2013, Guo & Yang 2020). However, a few gaps between guidance cues, Ca^{2+} signaling, and cytoskeleton/cell wall/membrane dynamics remain to be resolved in future research.

4.2. Calcium Signaling in Host-Microbe Interactions

Both plants and animals coexist and coevolve with microbes in their environments to form either mutually beneficial (symbiotic) or competitive (pathogenic) relationships. In both types of interactions, Ca^{2+} has emerged as a critical signaling agent.

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4.2.1. Immune responses in mammals present classic pathways for calcium signaling. Animals have evolved both adaptive and innate immune response mechanisms that involve different cell types and yet often work together to defend against invading pathogens. Adaptive immunity is performed by B and T lymphocytes that produce antibody- or cell-based immunity against specific foreign antigens. A classic Ca^{2+}-signaling pathway has been established by research on the T cell activation process. Antigen binding to the T cell receptor (TCR) initiates the PLC-mediated production of IP3, leading to Ca^{2+} release from the ER through the IP3 receptor, which in turn activates store-operated channels to further boost Ca^{2+} levels in the cell (Hogan 2017, Trebak & Kinet 2019, Vaeth et al. 2020). Other Ca^{2+} channels of CaV and P2X types may also contribute to the specific signatures in response to various antigens (Badou et al. 2013, Trebak & Kinet 2019). Following the elevation of Ca^{2+} levels in helper T cells, CaN serves as a major Ca^{2+}-decoding machine that dephosphorylates NFAT (nuclear factor of activated T cells), enabling the nuclear translocation of NFAT to activate the transcription of genes, including those encoding cytokines (Hogan et al. 2003) (**Figure 5*a***).

Innate immunity in animals involves a variety of different cell types, especially macrophages, neutrophils, dendritic cells, and other leukocytes (Riera Romo et al. 2016, Sokol & Luster 2015). Macrophages and dendritic cells are best known for their role in innate immunity and in connection with adaptive immunity, using pattern recognition receptors (PRRs) to perceive both pathogen invasion and danger signals released from damaged host cells. Although Ca^{2+}-based signaling is well recognized in innate immunity (Feske et al. 2015), the detailed mechanistic processes are less understood than are those in T lymphocytes. Further challenges are associated with the large variety of cell types involved in innate immune responses and the fact that each cell type may have a different tool kit for Ca^{2+} signaling (Feske et al. 2015). For example, the activation of multiple receptors at the surface of a macrophage (Fitzgerald & Kagan 2020, Sokol & Luster 2015) often initiates PLC-IP3-IP3R-mediated Ca^{2+} release from the ER and the opening of Orai channels (Feske et al. 2015). Other Ca^{2+} channels of TRP and P2X types may also contribute to innate immunity in macrophages (Feske et al. 2015). Following the elevation of Ca^{2+} levels, a calcineurin-NFAT nexus activates the transcription of genes for cytokines such as interleukin 2 (Fric et al. 2012) (**Figure 5*b***). Several isoforms of NFATs function in various cell types, all leading to the production of cytokines to further enhance the immune response by activating both innate and adaptive immunity.

4.2.2. Plant hosts respond to pathogenic and symbiotic microbes with different calcium-signaling mechanisms. Although, unlike animals, plants do not have specific immune cells for adaptive immunity, they are capable of developing innate immunity against all types of pathogens (Jones et al. 2016). In response to bacterial pathogens, plant cells, like animal cells, use specialized cell surface receptors (PRRs) to recognize pathogen-associated molecular patterns (PAMPs) and mount a defense program called PAMP-triggered immunity (PTI) (Yu et al. 2017, Zhang et al. 2020, Zipfel & Oldroyd 2017). The perception of PAMPs triggers a Ca^{2+} spike that varies in peak time, amplitude, and duration in response to different types and dosages of PAMPs (Yuan et al. 2017). Several CNGC-type Ca^{2+} channels are associated with PAMP-triggered Ca^{2+} spikes in plant cells (Moeder et al. 2019, Tian et al. 2020). Some studies have also linked the PAMP-receptor interaction to the activation of the Ca^{2+} channels (Thor et al. 2020, Tian et al. 2019, Wang et al. 2019). Following the PAMP-induced Ca^{2+} spike in the cytoplasm, several proteins including CDPKs serve as Ca^{2+} sensors to boost reactive oxygen species production and gene expression, leading to optimized immune output (Moeder et al. 2019, Yuan et al. 2017) (**Figure 5*c***).

While many microorganisms are pathogenic, some are beneficial to plant hosts. Arbuscular mycorrhizal fungi (AMF) are ancient obligate biotrophs that colonize a majority (>80%) of land

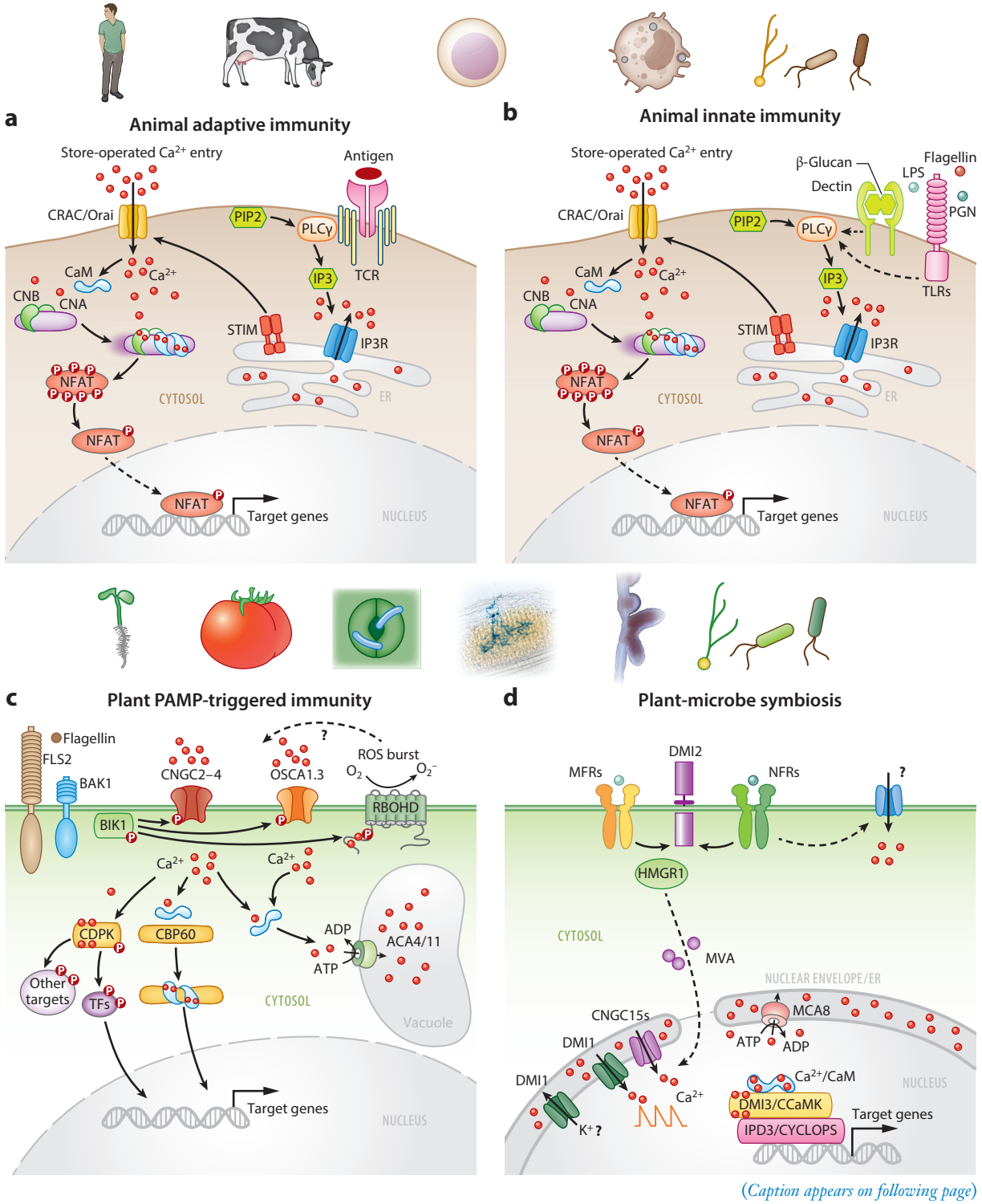

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Figure 5 (*Figure appears on preceding page*)

Ca^{2+}-signaling networks in host-microbe interactions. (*a*,*b*) In animal adaptive and innate immunity, cells employ cell surface receptors to recognize signals of both host and pathogenic origin and to activate Ca^{2+} signaling. In a T cell, as shown in panel *a*, a TCR perceives a foreign antigen presented by other immune cells, whereas in innate immune cells, as shown in panel *b*, a variety of surface receptors, including Dectin-1/2 receptors and TLRs, recognize pathogenic patterns (e.g., β-glucan, flagellin, LPSs, or PGN). In both adaptive and innate immunity, receptor activation initiates the PLC-dependent hydrolysis of PIP2 to produce IP3. IP3, acting as a second messenger, binds to and activates the IP3R located in the ER membrane, releasing Ca^{2+} from the ER. The resultant ER Ca^{2+} depletion causes conformational changes in STIM proteins (in the ER membrane) that in turn physically interact with and activate the CRAC/Orai proteins in the plasma membrane, further boosting the cytosolic Ca^{2+} level. CaM binds Ca^{2+} and activates calcineurin (see **Figure 3*e*** for details), which in turn dephosphorylates multiple sites of the NFAT. The dephosphorylated NFAT is then translocated to the nucleus and regulates target gene expression. The diagrams displayed in panels *a* and *b* are (*left* to *right*) human, cow, T cell, macrophage, and pathogenic microbes. (*c*) Ca^{2+} signaling in PTI in *Arabidopsis* plants. PAMPs such as bacterial flagellin are recognized by the FLS2/BAK1 receptor complex, which in turn phosphorylates and activates a receptor-like cytosolic kinase BIK1. Activated BIK1 phosphorylates and activates the CNGC2–4 and OSCA1.3 Ca^{2+} channels, producing Ca^{2+} spikes in the cytosol. Elevated Ca^{2+} levels may activate vacuolar ACA4/11 to remove the cytosolic Ca^{2+}. BIK1 and Ca^{2+} work together to activate NADPH/RBOHD, enhancing the production of ROS that may further activate Ca^{2+} channel activity via a ROS receptor or other unknown mechanisms. The PAMP-initiated Ca^{2+} signature can be recognized by proteins carrying Ca^{2+}- or CaM-binding domains, such as CDPKs and CBP60, and eventually regulates defensive gene expression. (*d*) In rhizobial and mycorrhizal symbioses, the symbiosis receptor kinase MtDMI2 is activated following symbiotic signal perception by corresponding receptors (NFRs and MFRs). DMI2 interacts with HMGR1 to trigger the production of a chemical messenger for activating Ca^{2+} channels (CNGC15 and DMI1) and, together with a Ca^{2+}-ATPase (MCA8), produce nuclear Ca^{2+} oscillations. A CCaMK (MtDMI3/LjCCaMK) subsequently decodes the Ca^{2+} signals, leading to the phosphorylation of the transcription factor MtIPD2/LjCYCLOPS and the activation of symbiotic genes. The diagrams above panels *c* and *d* are (*left* to *right*) *Arabidopsis* seedling, tomato, bacterial entry through stoma, rhizobial symbiotic infection, legume root nodule, and pathogenic/symbiotic microbes. Question marks indicate currently unknown activities or mechanisms. Abbreviations: ACA, Ca^{2+}-ATPase; BAK1, BRASSINOSTEROID INSENSITIVE 1; CaM, calmodulin; CBP60, CaM-binding protein 60; CCaMK, Ca^{2+}/CaM-dependent protein kinase; CDPK, Ca^{2+}-dependent protein kinase; CNA, catalytic A subunit of Ca^{2+}/CaM-dependent serine/threonine phosphatase; CNB, catalytic B subunit of Ca^{2+}/CaM-dependent serine/threonine phosphatase; CNGC, cyclic nucleotide-gated Ca^{2+} channel complex; CRAC, Ca^{2+}-release-activated Ca^{2+} channel; ER, endoplasmic reticulum; FLS2, FLAGELLIN SENSITIVE 2; HMGR1, 3-hydroxy-3-methylglutaryl-CoA reductase; IP3, inositol trisphosphate; IP3R, inositol trisphosphate receptor; LPS, lipopolysaccharide; MCA8, Medicago Ca^{2+}-ATPase 8; MFR, Myc-factor receptor; MVA, mevalonic acid; NFAT, nuclear factor of activated T cell; NFR, Nod-factor receptor; P, phosphorylation; PAMP, pathogen-associated molecular pattern; PGN, peptidoglycan; PIP2, phosphatidylinositol 4,5-bisphosphate; PLC, phospholipase C; PTI, PAMP-triggered innate immunity; RBOHD, respiratory burst oxidase protein D; ROS, reactive oxygen species; STIM, stromal interaction molecule; TCR, T cell receptor; TF, transcription factor; TLR, Toll-like receptor.

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plants (Harrison 2005, Parniske 2008). AMF symbiosis facilitates plant access to soil nutrients (such as phosphate) and water. Root nodule symbiosis (RNS), which is more recently evolved between rhizobia and legumes, enables plants to acquire nitrogen (Oldroyd 2013, Zipfel & Oldroyd 2017). Studies in model legumes have revealed a conserved symbiosis signaling pathway in which the coding and decoding of sustained nuclear Ca^{2+} oscillations play a central role in both RNS and AMF symbiosis (Tian et al. 2020, Yuan et al. 2017, Zipfel & Oldroyd 2017). During the initial phase of symbiosis, Nod factors (from rhizobia) and Myc factors (from AMF) bind to their respective receptors and activate the leucine-rich repeat receptor (LRR) kinase. These LRR kinases activate the production of chemical messengers that in turn open the Ca^{2+} channels to produce the nuclear Ca^{2+} signature. DMI1, a nuclear envelope protein, is essential for Nod factor– or Myc factor–induced Ca^{2+} spiking and has been shown to function as a tetrameric Ca^{2+}-regulated Ca^{2+} channel (Kim et al. 2019). In addition, a study (Charpentier et al. 2016) linked CNGC-type channels to Nod factor–induced Ca^{2+} spiking and nodulation. The Ca^{2+} signature is decoded by a CCaMK (Gleason et al. 2006, Lévy et al. 2004) that phosphorylates and activates a transcription activator to induce the expression of core genes in RNS and AMF symbiosis (Pimprikar et al. 2016, Singh et al. 2014, Yano et al. 2008) (**Figure 5*d***). Further work is warranted to understand how DMI1, CNGC, and Ca^{2+} pumps (e.g., MCA8) work together to produce symbiosis-specific nuclear Ca^{2+} oscillations.

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4.3. Long-Range Systemic Calcium Signaling: Glutamate Receptors in Synaptic Transmission in Animals and Wound-Induced Calcium Waves in Plants

For multicellular organisms, the intercellular and interorgan communications that are referred to as systemic signaling transmit signals from local to distal regions so that the organism responds and functions as a whole. The nerve system in animals is the best known and most sophisticated systemic signaling platform in which cells (neurons) are interconnected through synapses that relay signals from one cell (or organ) to another at lightning speed. Even in sessile organisms such as plants, systemic signaling mechanisms exist, albeit at lower speed and specificity. In both animals and plants, Ca^{2+} serves as a critical agent in the systemic signaling networks.

4.3.1. Calcium signaling in synaptic transmission. Ca^{2+} is arguably the most important second messenger in the brain because of its pivotal roles in presynaptic neurotransmitter release, postsynaptic responses, and plasticity induction. Synaptic transmission relies on both electrical and chemical mechanisms that often intertwine in conducting systemic signaling throughout the body (**Figure 6*a*,*b***). While action potentials can rapidly propagate through electrical synapses, they lack the specificity and precise regulation that are conferred by chemical synaptic transmission. The role of Ca^{2+} is best described in chemical synapses involving numerous neurotransmitters. For brevity and comparison with plants, we focus on glutamate-mediated synaptic transmission in mammals to illustrate how Ca^{2+} works as a signaling agent for systemic neuronal transmission. As details on this subject are well documented in a number of expert review articles (Mateos-Aparicio & Rodríguez-Moreno 2020, Mochida 2018, Topolnik & Camiré 2019), here we simply want to extract a conceptual framework that readers in an emerging area of plant research may refer to.

At the presynaptic terminal, a neuronal action potential (firing) induces depolarization that activates CaVs (**Figure 6*c***). The resulting elevation in Ca^{2+} concentration is perceived by the effector proteins, including the synaptotagmins that function as Ca^{2+}-sensing SNAP receptors (SNAREs), and triggers the release of neurotransmitters such as glutamate through the synchronized exocytosis of synaptic vesicles (Südhof 2012). In the case of glutamate-mediated synapses, glutamate released from the presynaptic terminal into the synaptic cleft binds to both metabotropic- and ionotropic-type receptors in the postsynaptic cell membrane and triggers Ca^{2+} signaling via different mechanisms. In the case of ionotropic receptors (iGluRs), as discussed in Section 2.1.2.2, Ca^{2+} can enter the cell directly through these ligand-gated channels. For the metabotropic-type receptors (mGluRs), they typically induce the activation of the PLC-IP3 pathway to release Ca^{2+} from the intracellular ER store via activation of IP3Rs (Reiner & Levitz 2018). Initial Ca^{2+} elevation can be followed by the activation of CRACs to further increase the level of Ca^{2+}. Ca^{2+} sensors and effectors such as CaM and its targets, e.g., CaMKII and CaN, have been shown to play a critical role in relaying the Ca^{2+} signals and modulating synaptic plasticity (**Figure 6*c***). There are numerous Ca^{2+}/CaM-stimulated enzymes that can modulate the sensitivity and plasticity of a synapse as well (Kennedy 2013).

4.3.2. Glutamate-dependent systemic calcium signaling in plants. Although plants lack a nervous system, they are capable of transmitting local signals throughout the entire plant. This long-distance signaling allows the perception of local stresses to be translated into whole plant responses (Choi et al. 2016, Takahashi et al. 2020). In addition to hormones and small RNAs that can be translocated system-wide through the vasculature (Takahashi et al. 2020), recent studies (Farmer et al. 2020, Grenzi et al. 2020, Hilleary & Gilroy 2018, Tian et al. 2020) have identified electrical and Ca^{2+} waves as rapid long-distance signaling carriers. We focus here on wounding-induced systemic Ca^{2+} waves and possible channels involved in transmitting such Ca^{2+} signals from local to distal organs (**Figure 6*d–f***). In *Arabidopsis*, following wounding of a local leaf,

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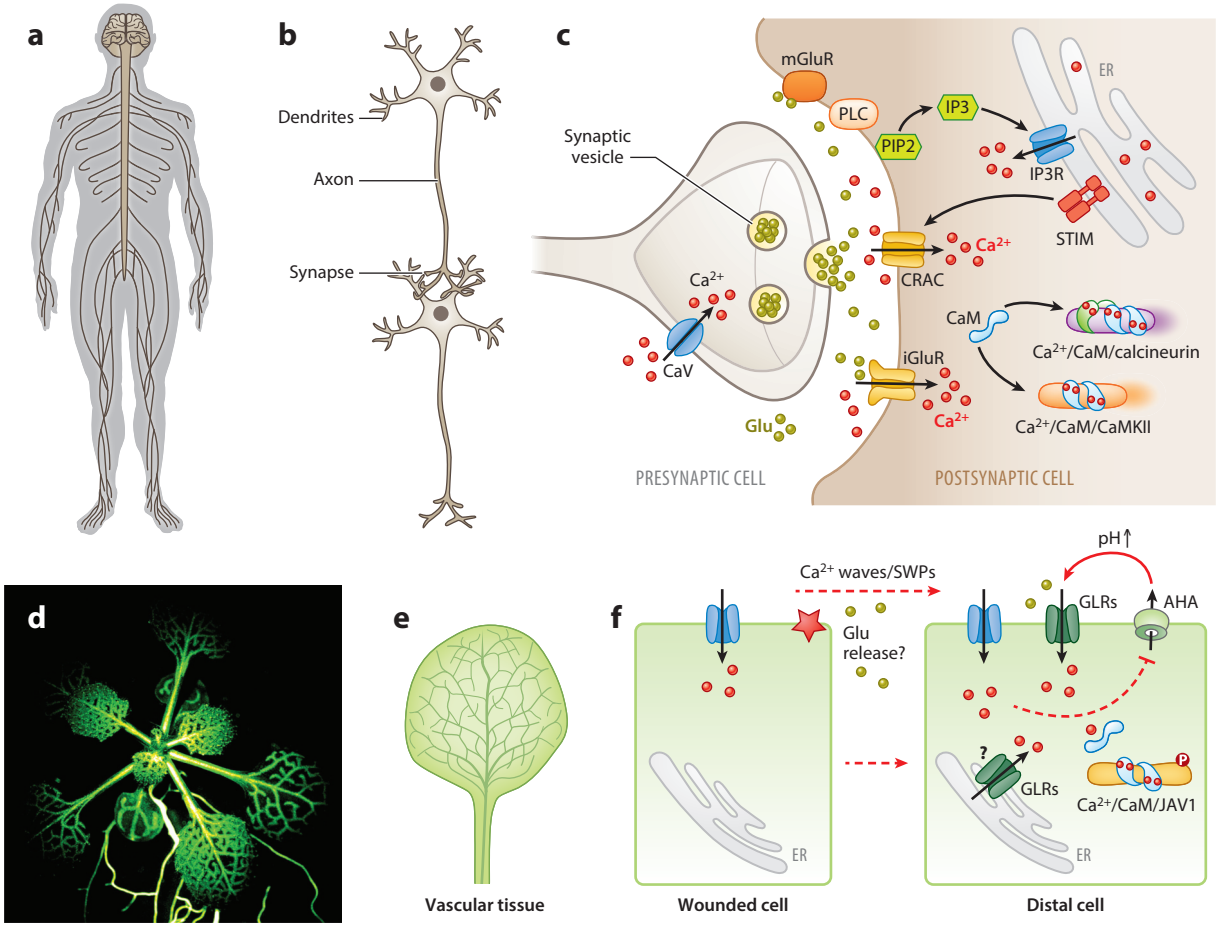

Figure 6

Long-range systemic Ca^{2+} signaling in animals and plants. (*a*) Schematic of the human nerve system. (*b*) Two neurons interconnect through synapses. (*c*) Ca^{2+} signaling in synaptic transmission. In the presynaptic cell, a neuronal action potential induces depolarization that activates CaVs, resulting in elevated Ca^{2+} levels and the exocytosis of synaptic vesicles, releasing neurotransmitters such as Glu into the synaptic cleft. Glu can be recognized by either iGluRs that directly mediate Ca^{2+} entry or mGluRs that activate a PLC-IP3 pathway to release Ca^{2+} from the ER, which in turn activates the CRAC/Orai proteins. The Ca^{2+} signals are perceived by Ca^{2+}/CaM, leading to the activation of calcineurin and CaMKII in the postsynaptic cell, which leads in turn to subsequent modifications of cellular activities and plasticity in neuronal transmission. (*d*) An *Arabidopsis* plant showing systemic Ca^{2+} elevation in all leaves after wounding of its roots. The leaf vasculature shows fluorescence from the genetically encoded Ca^{2+} reporter GCaMP6s. (*e*) A diagram of typical *Arabidopsis* leaf vasculature. (*f*) Upon wounding (*star*), the wounded cell may release Glu and inhibit AHA1. The resultant extracellular pH increase may provide an optimized subdomain environment in which Glu activates GLR3.3 and GLR3.6. Although GLRs may appear in the ER, a small portion of these GLRs may be targeted to the plasma membrane to mediate Glu-induced Ca^{2+} entry. Elevated Ca^{2+} binds CaM, which interacts with and destabilizes the jasmonic acid–associated JAV1, followed by the activation of jasmonic acid biosynthesis genes. Accompanying the Ca^{2+} waves are electrical signals in the form of SWPs that are also involved in systemic signaling. Abbreviations: AHA, H^+-ATPase; CaM, calmodulin; CaMKII, calmodulin kinase II; CaV, voltage-gated Ca^{2+} channel; CRAC, Ca^{2+}-release-activated Ca^{2+} channel; ER, endoplasmic reticulum; GLR, glutamate receptor-like channel; Glu, glutamate; iGluR, ionotropic glutamate receptor; IP3, inositol 1,4,5-trisphosphate; IP3R, inositol 1,4,5-trisphosphate receptor; mGluR, metabotropic glutamate receptor; PIP2, phosphatidylinositol 4,5-bisphosphate; PLC, phospholipase C; STIM, stromal interaction molecule; SWP, slow-wave potential.

cytosolic Ca^{2+} elevation takes place within seconds at the site of wounding. The cytosolic Ca^{2+} elevation in local cells propagates to distal leaves through the vasculature (in what is termed a Ca^{2+} wave) at rates of ~1 mm s^{-1}, which is faster than the speed of mass flow (Toyota et al. 2018). Importantly, this systemic Ca^{2+} wave is followed by a systemic defense response in the form of an accumulation of the wound-induced hormone jasmonic acid (JA). In searching for the molecular components essential for wound-induced Ca^{2+} waves, a study (Toyota et al. 2018) identified GLR-type channels as essential for propagating the systemic Ca^{2+} waves. Accompanying the Ca^{2+} waves is an electrical signal in the form of slow-wave potentials (SWPs) that also require GLR3-type proteins (Mousavi et al. 2013, Nguyen et al. 2018). Therefore, Ca^{2+} waves may be the carrier of the electrical signals, as Ca^{2+} entry induces depolarization of the PM, a critical component of the SWPs. The *Arabidopsis* H^+-ATPase 1 (AHA1) proton pump also plays a key role in shaping the SWPs and thus the systemic wound response (Farmer et al. 2020). In support of GLRs functioning in the process, glutamate application at the wounded site triggers a long-distance Ca^{2+} wave typically induced by wounding (Toyota et al. 2018), indicating that glutamate may serve as a chemical trigger of long-distance wound signaling. Furthermore, glutamate applied to the wounded site in the root not only is sufficient to trigger a Ca^{2+} wave in the leaf but also elicits a systemic SWP measured on the leaf (Shao et al. 2020). Both the Ca^{2+} waves and SWPs are abolished in mutant plants disrupted in *GLR3.3* and *GLR3.6* genes, thus connecting these glutamate receptors, Ca^{2+} waves, and electrical signals (Shao et al. 2020). Single-cell Ca^{2+} imaging and patch-clamp analysis link the GLRs and AHA1 in that GLR3.3 and GLR3.6 both display Ca^{2+}-permeable channel activities gated by not only glutamate but also extracellular pH (Shao et al. 2020). Together, these findings support the hypothesis that, following wounding, AHA1 may be inhibited, initiating apoplastic alkalization that together with wound-released glutamate activates GLRs, resulting in the depolarization of the PM in the form of SWPs and the elevation of cytosolic Ca^{2+} levels to propagate into the systemic Ca^{2+} waves. Following Ca^{2+} elevation, a Ca^{2+}- and CaM-dependent regulation mechanism appears to be critical for the JA biosynthesis pathway (Yan et al. 2018) (**Figure 6*f***). Further work should solve the detailed mechanisms underlying signal generation at local sites and propagation into systemic waves at the whole plant level.

5. CONCLUDING REMARKS AND QUESTIONS FOR FUTURE RESEARCH

Emerging as a signaling agent from a toxic ion, Ca^{2+} plays a critical role in all aspects of cell physiology across eukaryotic kingdoms. The Ca^{2+} signature concept answers a key question on the specificity of Ca^{2+} signaling pathways, indicating that every signal produces a unique Ca^{2+} change in the cell in the form of spatiotemporal patterns. To produce such a signature, numerous Ca^{2+} channels and transporters work together in the coding process to specify an individual signal. To interpret the signature, a variety of Ca^{2+} sensors and effectors orchestrate a decoding process to translate a specific Ca^{2+} code into a distinct cellular response. Research activities in the field have been directed to identifying the components of both the coding and decoding mechanisms in specific signaling contexts.

Examining a large repertoire of Ca^{2+} signaling tool kits across fungi, animals, and plants, we now know that some components are highly conserved throughout evolution and others have evolved more recently in specific kingdoms. Comparing flowering plants and mammals, we see significant divergence in both coding and decoding tool kits. In the coding sector, a large expansion of Ca^{2+} channels is observed in mammals while degeneration may have occurred in flowering plants. Yet the decoding sector witnesses the opposite trend: Many more Ca^{2+} sensors have evolved in flowering plants than in mammals. How do such differences correlate with the

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organization (structure) and functional processes intrinsic to each kingdom? Structurally animals and plants differ by organizational specificity: Each cell type and organ is more strictly differentiated in animals than it is in plants, thanks to highly specified genetic programming during development. Functionally, animals respond by rapid behavioral changes and plants respond largely by slow developmental programs. Possibly as a result of these different speeds of response, voltage-gated Ca^{2+} channels that are dedicated to rapid electrical signaling in animals are not found in plants. If plants need fewer coding components, why do they require more decoders than animals? This is one of the many questions that remain to be answered by future research. Others include

- how channels (movers) and pumps (removers) couple their actions to shape the exact signature,
- how decoders recognize specific spatiotemporal patterns of Ca^{2+} changes,
- how Ca^{2+}-signaling modules connect to other components in the pathway, and
- how Ca^{2+}-signaling pathways cross talk with each other and to other Ca^{2+}-independent pathways to form a complex signaling network.

All these questions must be answered in the specific physiological and cellular contexts of a given organism, which will engage researchers in the field for many years to come and will lead to a more complete understanding of Ca^{2+}-signaling mechanisms in eukaryotic systems.

NOTE ADDED IN PROOF

At the proof stage of this review, new information has come to light. First, structural analysis of the *Arabidopsis* GLR3.4 revealed that plant GLRs are tetrameric Ca^{2+} channels with both common and divergent features compared to the animal homologs (Green et al. 2021).

Second, PIEZO orthologs in moss were reported to be tonoplast localized and to play a role in modulating vacuole morphology and tip growth (Radin et al. 2021). Together with other studies in *Arabidopsis* (Fang et al. 2021, Mousavi et al. 2021), these reports suggest that plant PIEZO channels may have unique cellular functions in the plant kingdom (**Figure 2**).

Finally, in addition to PTI, both plants and animals have effector-triggered immunity (ETI) featuring the effector-recognizing intracellular receptors dominated by the nucleotide-binding LRR (NLR) proteins. A plant coiled-coil NLR as well as some so-called helper NLR proteins were reported to function as PM Ca^{2+}-permeable channels essential for immune signaling and cell death, highlighting the central role of Ca^{2+} signaling in both PTI and ETI in plants (Bi et al. 2021, Jacob et al. 2021).

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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Contents

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