



# Ca<sup>2+</sup> channels and Ca<sup>2+</sup> signals involved in abiotic stress responses in plant cells: recent advances

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## Abstract

Calcium (Ca<sup>2+</sup>) signals are essential transducers and regulators in many adaptive and developmental processes in plants. Protective responses of plants to a variety of environmental stress factors are mediated by transient changes of Ca<sup>2+</sup> concentration in plant cells. Ca<sup>2+</sup> ions are quickly transported by channel proteins present on the plasma membrane. During responses to external stimuli, various signal molecules are transported directly from extracellular to intracellular compartments via Ca<sup>2+</sup> channel proteins. Three types of Ca<sup>2+</sup> channels have been identified in plant cell membranes: voltage-dependent Ca<sup>2+</sup>-permeable channels (VDCCs), which is sorted to depolarization-activated Ca<sup>2+</sup>-permeable channels (DACCs) and hyperpolarization-activated Ca<sup>2+</sup>-permeable channels (HACCs), voltage-independent Ca<sup>2+</sup>-permeable channels (VICCs). They make functions in the abiotic stress such as TPCs, CNGCs, MS channels, annexins which distribute in the organelles, plasma membrane, mitochondria, cytosol, intracellular membrane. This review summarizes recent advances in our knowledge of many types of Ca<sup>2+</sup> channels and Ca<sup>2+</sup> signals involved in abiotic stress resistance and responses in plant cells.

**Keywords** Plant cells · Ca<sup>2+</sup> channels · Abiotic stress · Signal transduction

## Introduction

Plants are subject to numerous abiotic stress factors (including drought, salinity, high or low temperature, and hypo-osmotic conditions) that suppress growth and may even cause death. Accordingly, plants have evolved a variety of physiological mechanisms (collectively termed “environmental adaptability”) to resist abiotic stress factors (Gilroy and Trewavas 2001).

Calcium (Ca<sup>2+</sup>) functions as a second messenger in many biotic activities. Signals are transmitted through Ca<sup>2+</sup> conducting channels, and are able to sense and respond to internal and environmental stimuli (Jammes et al. 2011). In plants, these are essential mechanisms, and Ca<sup>2+</sup> plays an important role in resisting abiotic stress (Hepler 2005).

Intracellular Ca<sup>2+</sup> is significant in signal transduction for gene expression and cell cycle control (Berridge et al. 2003), and is involved a variety of plant biological processes such as light signaling (Harada et al. 2003), hormone responses (Munemasa et al. 2007), cell growth (Frietsch et al. 2007), stress and plant-pathogen interactions (Qi et al. 2010).

Two general categories of transfer systems for Ca<sup>2+</sup> transport are found in plants: influx and efflux via channels and carriers. Ca<sup>2+</sup> channels are a type of transmembrane channel protein present on the surface of plant cells or organs that transmit Ca<sup>2+</sup> quickly and specifically. Ca<sup>2+</sup> channels are thus essential in transfer and regulation of Ca<sup>2+</sup>, which is involved in all responses to abiotic stress. This review describes recent research advances on Ca<sup>2+</sup> channels and their roles in abiotic stress response mechanisms.

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## Generation of Ca<sup>2+</sup> signals

Plants have strong adaptive abilities to sense changes in their surrounding environment and to regulate their growth and development through appropriate responses to stimuli. To induce expression of related genes, stress signals originating outside the cell must cross the cell wall and reach the cell

interior. Under environmental stresses (e.g., drought, low temperature, salinity), osmotic pressure at the cell membrane increases (Boudsocq and Lauriere 2005), and this increase is transmitted to membrane signal receptors. Activation of  $\text{Ca}^{2+}$  channels by a series of phosphorylation reactions results in  $\text{Ca}^{2+}$  influx, and increasing  $\text{Ca}^{2+}$  concentration induces  $\text{Ca}^{2+}$  signals (Chinnusamy et al. 2004). The source of quickly increasing  $\text{Ca}^{2+}$  is release from intracellular  $\text{Ca}^{2+}$  storage sites such as endoplasmic reticulum (ER) and vacuoles.  $\text{Ca}^{2+}$  signals are essentially a type of chemical code, and decoding is performed by  $\text{Ca}^{2+}$  sensors or decoders that recognize changes in  $\text{Ca}^{2+}$  signals and are transferred into the nucleus where genes are involved in transcription activity (Swarbreck et al. 2013).  $\text{Ca}^{2+}$  signals may also be generated automatically in plant cell nuclei. Nuclear  $\text{Ca}^{2+}$  signals are linked to a variety of extranuclear signals, and provide the best model for studies of symbiotic nuclear  $\text{Ca}^{2+}$  signals (Charpentier and Oldroyd 2013).

After the plant perceives the stimulus,  $\text{Ca}^{2+}$  transporters regulate intracellular  $\text{Ca}^{2+}$  concentration and produce related  $\text{Ca}^{2+}$  signals. Intracellular  $\text{Ca}^{2+}$  concentration plays essential roles in several aspects of plant growth, including cell division and organ formation (Zhang et al. 2014). One classification system recognizes two types of  $\text{Ca}^{2+}$  channel based on location:  $\text{Ca}^{2+}$  influx channels in plasma membrane, and  $\text{Ca}^{2+}$  releasing channels in intracellular membranes. An alternative system recognizes (i) voltage-dependent  $\text{Ca}^{2+}$ -permeable channels (VDCCs), which are subdivided into depolarization-activated  $\text{Ca}^{2+}$ -permeable channels (DACCs) and hyperpolarization-activated  $\text{Ca}^{2+}$ -permeable channels (HACCs), and (ii) voltage-independent  $\text{Ca}^{2+}$ -permeable channels (VICCs).  $\text{H}^{+}/\text{Ca}^{2+}$  enzyme and  $\text{Ca}^{2+}$ -ATP enzyme are the major components of  $\text{Ca}^{2+}$  transporters and  $\text{Ca}^{2+}$  pumps, which form transporting systems for intracellular  $\text{Ca}^{2+}$  and maintain  $\text{Ca}^{2+}$  stability.

### Influx $\text{Ca}^{2+}$ -permeable channels in plasma membrane

Elevated levels of intracellular or extracellular  $\text{Ca}^{2+}$  are maintained by plasma membrane  $\text{Ca}^{2+}$ -permeable channels (Munaron et al. 2004). These influx channels are classified into VDCCs and VICCs as described above. Intracellular  $\text{Ca}^{2+}$  may be accumulated by  $\text{Ca}^{2+}$  influx channels in plasma membrane.

### Voltage-dependent $\text{Ca}^{2+}$ -permeable channels (VDCCs)

VDCCs are subdivided into DACCs and HACCs as described above, and in more detail below. Activation of VDCCs is one mechanism whereby voltage pulses in plasma membrane cause elevation of cytosolic  $\text{Ca}^{2+}$  level.

### Depolarization-activated $\text{Ca}^{2+}$ -permeable channels (DACCs)

The first VDCCs discovered in plasma membrane were DACCs (Thuleau et al. 1994). Depolarization on plasma membrane is due to cation influx. Cell depolarization is induced by low-temperature stress (White 2009). DACCs, which open in response to low but above-freezing temperatures, are apparently present in plasma membranes of root cells in all types of plants.

The existence of DACCs in carrot cell suspension was demonstrated using patch-clamp technology (Thuleau et al. 1994). DACCs were activated when plasma membrane was depolarized to  $-135$  mV, and they showed high permeability to  $\text{Mg}^{2+}$ ,  $\text{Sr}^{2+}$  and  $\text{Ba}^{2+}$ . This was the first direct demonstration of VDCCs on plasma membrane in higher plants. Similar VDCCs were subsequently found in protoplasts of leaves, mesophyll, and roots of *A. thaliana* (thale cress) (Piñeros and Tester 2011).

Two types of VDCCs were found in wheat: root  $\text{Ca}^{2+}$  channel (RCA channel) and Maxi-Cation channel (Piñeros and Tester 1995). RCA channels are usually closed in dormant or normal wheat root cells. When cells are depolarized, RCA channels are activated, resulting in  $\text{Ca}^{2+}$  influx. RCA channels were later shown to be sensitive under certain conditions to 1,4-dihydropyridines (DHPs) such as nifedipine, with increased opening rate of channels (Piñeros and Tester 2011). Maxi-Cation channels are permselective to monatomic and divalent cations (e.g.,  $\text{K}^{+}$ ,  $\text{Na}^{2+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Ba}^{2+}$ ), and therefore have useful applications in pharmacology. Cationic influx channels are inhibited by ruthenium red, while efflux channels are inhibited by ruthenium red, diltiazem, verapamil, quinine (Weiger and Hermann 2014). Maxi-Cation channels are inhibited by polyamines. Effects of  $\text{Ca}^{2+}/\text{H}^{+}$  transport under polyamine treatment in pea roots were studied by microelectrode technique, and  $\text{Ca}^{2+}$  activity was found to be coupled with  $\text{H}^{+}$  pump.  $\text{H}^{+}$  pump may inhibit accumulation of intracellular  $\text{Ca}^{2+}$  (Pottosin et al. 2014). Many other types of cation channels can be suppressed by polyamines, resulting in plasma membrane depolarization. In contrast, reduction of polyamine level leads to increased cation channel activation and hyperpolarization. A cooperative mechanism between  $\text{Ca}^{2+}$ -dependent protein kinase 32 (CPK32)

and cyclic nucleotide-gated channel 18 (CNGC18) was responsible for increased depolarization of pollen tubes and regulation of their growth (Zhou et al. 2014).

### Hyperpolarization-activated $\text{Ca}^{2+}$ -permeable channels (HACCs)

Hyperpolarization (the opposite of depolarization) refers to an increase in potential difference (PD) relative to normal transmembrane potential. Voltage PD across plasma membrane in plants is generally between  $-120$  and  $-180$  mV.

Hyperpolarization of plasma membrane may be caused by  $\text{H}^+$  pump. HACCs are activated when PD falls below  $-120$  mV, and the degree of activation depends on voltage strength and duration. VDCCs activated by hyperpolarization were discovered in a sequential manner. Miedema et al. (2008) showed that  $\text{Ca}^{2+}$  channel conductance is activated by hyperpolarization in root cells of *A. thaliana*. On plasma membrane of epidermal cells in onions, such channels are involved in mechanical protection (Pickard and Ding 1993), and enables depolarization of plasma membrane to prevent water loss by initiating closure of stomata in guard cells (Cosgrove and Hedrich 1991). HACCs is also a key component of the phytohormone abscisic acid (ABA) in guard cells (Jiao et al. 2013).

Annexins, a type of binding protein consisting of  $\text{Ca}^{2+}$ , phospholipids, and cytoskeleton, can also induce  $\text{Ca}^{2+}$  mobilization in HACCs. Annexins were first discovered in higher plants (Boustead et al. 1989), and shown to affect cell growth, development, adaptation, and responses to abiotic stress. They are widely distributed in plants, and localized in cytosol, plasma membrane, intracellular membranes, and certain organelles. They play functional roles in exocytosis and  $\text{Ca}^{2+}$  metabolism. Pharmacological experiments have shown that annexins help regulate activities of non-selective cation channels and  $\text{Ca}^{2+}$  influx channels. Annexin affected transmembrane  $\text{Ca}^{2+}$  current in synthetic membrane only under appropriate pH, and such current was highly sensitive to  $\text{Ca}^{2+}$  inhibitor and  $\text{Gd}^{3+}$  (Laohavisit et al. 2009).

### Voltage-independent $\text{Ca}^{2+}$ -permeable channels (VICCs)

Phytohormones affect the permeability of  $\text{Ca}^{2+}$  channels. Under drought stress, ABA acts synergistically with  $\text{Ca}^{2+}$  to prevent stomatal opening and reduce water evaporation (Jiao et al. 2013). ABA also helps regulate iron channel activation in plasma membrane,  $\text{H}_2\text{O}_2$  production, and  $\text{Ca}^{2+}$  influx (Siegel et al. 2009).  $\text{Ca}^{2+}$  permeability of plasma membrane in coleoptile vesicular cells of corn was enhanced by the phytohormone auxin, and appeared to be regulated by auxin-binding protein 1 (ABP1) (Kirpichnikova et al. 2014).

Cyclic nucleotide-gated channels (CNGCs) associated with  $\text{Ca}^{2+}$  signaling play roles in plant physiological processes such as plant growth, thermotolerance, and in responses to biotic and abiotic stress factors (Gao et al. 2012). The genome of *A. thaliana* includes  $\sim 20$  CNGC-encoding genes (Jha et al. 2016). Because of difficulty in isolating CNGC mutants, it remains unclear which CNGCs are involved in which processes (Table 1).

The 20 CNGCs can be divided into five subfamilies. CNGCs 1, 2, 7, 8, 10, 11, 12, 16, and 18 are involved mainly in plant growth (Frietsch et al. 2007). CNGCs 1, 2, 3, 10, 19, and 20 are involved in stress responses (Kugler et al. 2009). CNGCs 1, 2 mainly influence the metal toxicity and the others are mainly related to the salt stress. CNGCs 2, 4, 11, and 12 are involved in immunity (Dietrich et al. 2010). The *AtCNGC2* mutant *dnd1* (*defense no death*) belongs to immune phenotype, and the *A. thaliana* mutant *rdd1* (*repressor of defense no death 1*) inhibited most *dnd1* phenotypes. Genetic analysis revealed involvement of *rdd1* in *AtCNGC4* signal transduction, and bimolecular fluorescence complementation analysis showed the presence of *AtCNGC2* and *AtCNGC4* in the same pathway (Chin et al. 2013). The existence of non-selective  $\text{Ca}^{2+}$  channels encoded by *CNGC5* and *CNGC6* in *A. thaliana* guard cells was demonstrated by overexpression experiments. Guard cells of *CNGC5* and *CNGC6* mutants displayed harmful effects on electricity activated by cGMP and show synergistically with ABA (Wang et al. 2013). *CNGC6* is discovered to be mediated heat-induced  $\text{Ca}^{2+}$  influx and related to the heat shock (*HSP*) genes in *A. thaliana*. Gao (2012) showed the activation of the  $\text{Ca}^{2+}$  channel could increase the concentration of cytosolic cAMP and then downstream expression of the *HSP* gene to the heat shock response. CNGC12 interacts with the  $\text{Ca}^{2+}$  sensor calmodulin (CaM) via combination of an IQ-motif channel with the CaM C-terminus. At the N-terminal binding site of CNGC12,  $\text{Ca}^{2+}$ /CaM plays a regulatory role through negative feedback (Defalco et al. 2016a, b). Shih (2015) found that CNGC14 played a role in the auxin-induced  $\text{Ca}^{2+}$  signaling pathway controlled by gravitropism in roots. Charpentier et al. (2016) showed that  $\text{Ca}^{2+}$  spiking in *Medicago truncatula* was controlled by three CNGC15 homologs (Mt-CNGC15a, -b, -c) acting as channels in nuclear membrane, and  $\text{Ca}^{2+}$  could not cross the membrane when these homologs were knocked down.  $\text{K}^+$  is maintained by CNGC15 through its interaction with  $\text{K}^+$  channel during  $\text{Ca}^{2+}$  spiking in the membrane (Capoen et al. 2011). By quantitative PCR analysis of pollen, Tune-Ozdemir (2013) showed expression of heat-resistance genes in a *CNGC16* mutant. Pollen feasibility analysis indicated that the mutant pollen was highly sensitive to  $\text{Ca}^{2+}$ , and that thermotolerance was enhanced by the pollen through cyclic nucleotide signals,  $\text{Ca}^{2+}$

**Table 1** Main cyclic nucleotide-gated channels distribution in *A. thaliana*

Types	Permeable ions	Distribution	Flow direction	Functions	References
CNGC 1	Ca <sup>2+</sup> , Na <sup>+</sup> , K <sup>+</sup>	Plasma membrane	Na <sup>+</sup> influx K <sup>+</sup> efflux	Conferred Pb <sup>2+</sup> tolerance; affect the growth of root	Sunkar et al. (2000), Ma et al. (2006)
CNGC 2	Ca <sup>2+</sup> , K <sup>+</sup>	Plasma membrane	Ca <sup>2+</sup> influx K <sup>+</sup> efflux	Ca <sup>2+</sup> signaling; plant growth; stress responses; immunity	Finka et al. (2012), Frietsch et al. (2007), Kugler et al. (2009), Dietrich et al. (2010)
CNGC 3	Na <sup>+</sup> , K <sup>+</sup>	Plasma membrane	Na <sup>+</sup> influx K <sup>+</sup> efflux	Affect seed germination and distribution of monovalent cations	Gobert et al. (2006)
CNGC 4	Ca <sup>2+</sup> , K <sup>+</sup>	Plasma membrane	Ca <sup>2+</sup> influx K <sup>+</sup> efflux	Displayed an alteration in flowering transition; pathogen defense	Fortuna et al. (2015), Chin et al. (2013)
CNGC 5	Ca <sup>2+</sup>	Plasma membrane	Ca <sup>2+</sup> influx	Be required for a cyclic GMP (cGMP)-activated nonselective Ca <sup>2+</sup> channel in guard cells	Wang et al. (2013)
CNGC 6	Ca <sup>2+</sup>	Plasma membrane	Ca <sup>2+</sup> influx	Heat-activated involved in HSRs	Gao et al. (2012)
CNGC 7	–	Plasma membrane	–	Provide an essential function at the initiation of pollen tube tip growth	Tuncozdemir et al. (2013)
CNGC 8	–	–	–		
CNGC 10	Na <sup>+</sup> , K <sup>+</sup>	Plasma membrane	Na <sup>+</sup> influx K <sup>+</sup> efflux	Sensitive to salt stress	Guo et al. (2008)
CNGC 12	Ca <sup>2+</sup> , K <sup>+</sup>	Plasma membrane	Ca <sup>2+</sup> influx K <sup>+</sup> efflux	Programed cell death, immunity	Dietrich et al. (2010), Defalco et al. (2016a, b)
CNGC 14	Ca <sup>2+</sup>	Plasma membrane	Ca <sup>2+</sup> influx	Cell expansion	Shih et al. (2015)
CNGC 16	–	Pollen	–	Be critical for heat stress tolerance	Tuncozdemir et al. (2013)
CNGC 17	Ca <sup>2+</sup>	Plasma membrane	Ca <sup>2+</sup> influx	Cell expansion	Ladwig et al. (2015)
CNGC 18	Ca <sup>2+</sup>	Plasma membrane	Ca <sup>2+</sup> influx	Pollen tube guidance	Gao et al. (2016), Zhou et al. (2014), Frietsch et al. (2007)
CNGC 19	Ca <sup>2+</sup>	Vacuole	Ca <sup>2+</sup> efflux	–	Kugler et al. (2009)
CNGC -	Ca <sup>2+</sup>	Endoplasmic Reticulum	Ca <sup>2+</sup> efflux	–	Defalco et al. (2016a, b)

channels, and a thermotolerance-activating signal network. CNGC17 forms compounds with the leucine-rich repeat receptor-like protein kinase co-receptor BAK1, members of the *A. thaliana* H<sup>+</sup>-ATPase family of proton pumps, and the phytosulfokine receptor PSKR1 (Ladwig et al. 2015). CNGC18 is one of the isoforms related to Ca<sup>2+</sup> channels; it helps regulate pollen tube guidance and interacts with calcium-dependent protein kinase (CPK32) (Zhou et al. 2014). In *Xenopus* oocytes, CNGC18 was activated following co-expression of CPK32 (Zhou et al. 2014), indicating that CNGCs are involved in Ca<sup>2+</sup> channel function (Gao et al. 2016). However, the mechanisms of CNGC distribution remain unclear. A proposal that CNGCs are distributed only on plasma membrane was shown to be incorrect. Mt-CNGC15a/b/c is distributed in the nucleus, and controls Ca<sup>2+</sup> store flux in the nuclear envelope lumen and to ER (Yuen and Christopher 2013). Many CNGCs have putative nuclear localization signal (NLS) sequences, including isoforms located in plasma membrane (Charpentier et al. 2016; Fischer et al. 2013). Among the 21 CNGCs in *M. truncatula*, 14 types in DMI1 (Capoen et al. 2011) and CASTOR (Charpentier et al. 2008) are predicted to contain NLS motifs. It remains to be determined whether

CNGC distribution is dynamic in the face of differing cellular stimuli.

Besides *A. thaliana*, CNGCs are also distributed in other kinds of species which are discovered by the bioinformatics analyses. There are total 16 CNGCs genes in *Oryza sativa* L. expanded through chromosomal segmentation. The family of *OsCNGCs* could be divided into four major groups and two sub-groups (Nawaz et al. 2014); *Physcomitrella* contains eight CNGC homologues, four of which are clustered with the AtCNGCs including AtCNGC2, AtCNGC4 and AtCNGC19, indicating that there may be a conserved function between mosses and angio-sperms (Verret et al. 2010). In the important crop tomato, *Solanum lycopersicum* L., there are 18 CNGC genes. SICNGC genes make sense in the disease resistance and Ca<sup>2+</sup> signaling. They silenced these SICNGCs genes and found the changes in the expression of the Ca<sup>2+</sup> signaling genes. Thus they made a conclusion that the regulation of the resistance may be related to the affecting of the Ca<sup>2+</sup> signaling (Saand et al. 2015). In pear (*Pyrus bretschneideri* Rehd.), there are 21 CNGC genes which could be divided into five groups. Group 1 has the most motifs in all CNGCs groups including 26 motifs. Among all kinds of motifs, there are 8 motifs existing all kinds of group



indicating the conservative part of the CNGC family (Chen et al. 2015).

Reactive oxygen species (ROS) present in the surrounding environment are the basis of an important index that reflects damage and defensive responses in plants under stress. ROS are related to levels of polyamines and ABA (Alcazar et al. 2010), which produce nitric oxide (NO) and regulate opening and equilibrium of  $\text{Ca}^{2+}$  channels. NO and  $\text{Ca}^{2+}$  are essential parts of signal cascades related to aging in plants, but interaction between these two components during the aging process remains unclear (Ma et al. 2010). Associations between ROS and  $\text{Ca}^{2+}$  are involved in cell–cell communication and long-distance delivery (Steinhorst and Kudla 2013). ROS function as a second messenger to activate anion channels during sensing and guard cells signaling. Anion channels distributed on plasma membrane are activated by anion fluxes via voltage-gated  $\text{K}^+$  transport channels (Murata et al. 2015), ABA (Roelfsema et al. 2012), and NADPH (Letierrier et al. 2016). Damage by ROS can be reduced by antioxidant enzymes through inhibition of phospholipase C (PLC) activity and blocking of  $\text{Ca}^{2+}$  signaling pathways in cells (Domijan et al. 2014). PLC is also involved in responses to lipopolysaccharide stress. Treatment of cultured plant cells with 20  $\mu\text{M}$  U73122 (a PLC inhibitor) inhibited stress response and greatly increased  $\text{Ca}^{2+}$  signals relative to negative control. Ranf et al. (2015) recently discovered lectin S-domain receptor kinase, characterized as a receptor in lipopolysaccharide stress response.

## **$\text{Ca}^{2+}$ releasing channels in intracellular membranes**

### **$\text{Ca}^{2+}$ channels located in chloroplasts**

Chloroplasts have a bilayer structure and contain chlorophyll used for photosynthesis. The chloroplast stroma includes numerous thylakoids comprised of a membranous capsule and containing DNA. Pottosin and Schönknecht (1996) studied  $\text{Ca}^{2+}$  currents generated by opening of VDCCs. Such  $\text{Ca}^{2+}$  channels had electrical conductivity higher than that of monovalent cation channels, but showed greater selectivity for divalent than for monovalent cations. Opening of the channels was enhanced when chloroplasts had greater positive charge in the stroma than inside the thylakoids. This type of channel controls exchanges between thylakoids and chloroplast, but its involvement in signal transduction is unclear. Chloroplasts produce immune signaling molecules such as salicylic acid and jasmonic acid, and are thus involved in plant immune responses. The molecular mechanisms of nuclear immune signaling to chloroplasts and mitochondria are unknown. Specific  $\text{Ca}^{2+}$  signals may be triggered by chloroplasts or mitochondria in response to biotic

or abiotic stress (Nomura and Shiina 2014).  $\text{Ca}^{2+}$  absorbance can be inhibited by light stimulation and by ruthenium red. Recognition of  $\text{Ca}^{2+}$  transporters and the presence of signals indicate that  $\text{Ca}^{2+}$  functions not only in the cell interior, but also in plant immune responses and responses to external stress factors.

Proteins such as calcium-sensing receptor (CAS) are present in chloroplasts and can be transferred to the stroma to reduce specific  $\text{Ca}^{2+}$  signals via the pathogen-associated molecular pattern (PAMP) pathway. This pathway is involved in  $\text{Ca}^{2+}$  transfer and in death of sensitive cells mediated by R genes (Nomura et al. 2013). CAS also makes functions in the photoacclimation in *Chlamydomonas* proved by the knockdown species (Petroutsos et al. 2011). AtCAS makes sense in the stomatal closure related to the concentration of  $\text{Ca}^{2+}$  (Han et al. 2003).

### **$\text{Ca}^{2+}$ channels located in tonoplasts**

The vacuole occupies > 90% of the space in a plant cell, and contains the major  $\text{Ca}^{2+}$  store and source of  $\text{Ca}^{2+}$  for cell signaling (Pottosin and Schönknecht 2007). The electrochemical gradient of  $\text{Ca}^{2+}$  across the tonoplast (membrane that surrounds the vacuole) is very large. Channels that react to  $\text{Ca}^{2+}$  stimulating factors are distributed in tonoplast.  $\text{Ca}^{2+}$  concentration is regulated through release or uptake of  $\text{Ca}^{2+}$  stimulated by low temperature. Slow vacuolar (SV) channels, encoded by two-pore channel 1 (*TPC1*), were detected by fura-2 fluorescence measurements and patch-clamp technique (Peiter et al. 2005) in carrot root vacuoles (Gradogna et al. 2009). AtTPC1 make in sense in homeostasis more than signalling to stress (Stael et al. 2012).

Certain types of  $\text{Ca}^{2+}$  channels coexist in tonoplasts. DACCs and VDCCs such as SV channels are selective for divalent cations, but their physiological functions remain unclear. The SV channel encoded by *TPC1* is characterized by slow inactivation and activation, and its function is controversial because of its complicated mechanism and low cation selectivity (Peiter 2011). In the cytoplasm of guard cells of *Vicia faba* (fava bean), increase of  $\text{Ca}^{2+}$  concentration activates an SV channel present in tonoplast and results in  $\text{Ca}^{2+}$  efflux, a depolarizing reaction that leads to further opening of the SV channel. This phenomenon was proposed to be a positive feedback mechanism resulting from  $\text{Ca}^{2+}$  oscillation and “calcium-induced calcium release” (Laver et al. 2013).

$\text{Ca}^{2+}$  DACCs in tonoplasts of suspension-cultured tobacco cells were described in the 1990s. Such channels were blocked by  $\text{Cd}^{2+}$  at various concentrations, but were not sensitive to  $\text{Ni}^{2+}$ ,  $\text{La}^{3+}$ ,  $\text{Gd}^{3+}$ , verapamil, or nifedipine at the same concentrations for which sensitivity to  $\text{Ba}^{2+}$ ,  $\text{Sr}^{2+}$ ,  $\text{Ca}^{2+}$ , or  $\text{Mg}^{2+}$  was observed (Ping et al. 1992). Electrical

conductivity was 19 pS under 50 mmol/L  $\text{Ca}^{2+}$ , and 30 pS under 50 mmol/L  $\text{Ba}^{2+}$ .

DACCs may be involved in signaling pathways that are selective for divalent cations and promote  $\text{Ca}^{2+}$  influx into cytoplasm. Several  $\text{Ca}^{2+}$  channels present in tonoplast are activated by second messengers such as  $\text{IP}_3$  and cyclic ADP ribose (cADPR).  $\text{Ca}^{2+}$  release is promoted by  $\text{IP}_3$  in vacuoles of *Beta vulgaris* (beet), indicating the presence of  $\text{Ca}^{2+}$  channels (Schönknecht 2013).

### **$\text{Ca}^{2+}$ channels located in lysosomes**

Mucolipin transient receptor potential (TRP) channels (termed TRPML1, -2, -3) are the basic  $\text{Ca}^{2+}$  channels in lysosomes. TRPML1 is a key regulator of most lysosomal trafficking processes (Li et al. 2013; Cheng et al. 2010), which are localized in late endosome or lysosome (Venkatachalam et al. 2015). Regulation of TRPML1 by  $\text{PI}(3,5)\text{P}_2$  is an example of compartment-specific regulation of organellar channels.

Two-pore channels (TPCs) are found only in acidic organelles and lysosomes that have protective functions (Morgan and Galione 2014). Induction of  $\text{Ca}^{2+}$  release by nicotinic acid adenine dinucleotide phosphate (NAADP) is partially based on overexpression of TPCs (Parrington and Tunn 2014; Calcraft et al. 2009), though a specific relationship between TPCs and NAADP has not been conclusively demonstrated. TPC1 is activated by the dimerization of the predicted helix within the carboxyl-terminus (CTH), this indicates the TPC1 depends on the C-terminal dimerization (Larisch et al. 2016).

### **$\text{Ca}^{2+}$ channels located in ER**

$\text{Ca}^{2+}$  channels distributed in ER are also present (but less well known) in various plant species. *Bryonia* calcium channel 1 (BCC1) was described in ER of tendril tissues in *Bryonia dioica* (a climbing vine). Opening of BCC1 is controlled by  $\text{Ca}^{2+}$  concentration, which is regulated by  $\text{Ca}^{2+}$ -ATPase in ER. BCC1 may play a key role in  $\text{Ca}^{2+}$  signal delivery via sensing/signaling pathways in higher plants (Klusener et al. 1995) belonging to voltage-gated rectifier channel. LCC1 (*Lepidium* calcium channel 1) is a  $\text{Ca}^{2+}$  channel which is voltage gated and strongly rectifying existing in the ER of root cells discovered by the technology of planar lipid bilayer in *Lepidium sativum* (garden cress; a cruciferous plant). BCC1 and LCC1 are highly selective and voltage-dependent  $\text{Ca}^{2+}$  channels whose activity is promoted by  $\text{Ba}^{2+}$ ,  $\text{Sr}^{2+}$ , and  $\text{Mg}^{2+}$ , and inhibited by  $\text{La}^{3+}$  and  $\text{Gd}^{3+}$  (Klusener and Weiler 1999).  $\text{Ca}^{2+}$  flux from ER is closely related to cell signaling.  $\text{Ca}^{2+}$  release appears to be associated with ER levels of cADPR, NAADP, and  $\text{IP}_3$ , but direct evidence for such association is needed.

### **$\text{Ca}^{2+}$ channels located in mitochondria**

$\text{Ca}^{2+}$  efflux is mediated by  $\text{Na}^{+}$ -dependent (mitoNCX) and  $\text{Na}^{+}$ -independent  $\text{Ca}^{2+}$  transporters. In an *A. thaliana* model, six *MCU* genes with low homology to the human, are conserved and have been identified as putative MCU channel proteins. They and their human MCU homologs share a pore-loop domain, transmembrane domains, and conserved DVME (Asp-Val-Met-Glu) signature sequence (Stael et al. 2012). AtMCU1 activity is sensitive to the MCU inhibitors ruthenium red and  $\text{Gd}^{3+}$ , and to *A. thaliana* protein MICU, a regulatory MCUC component. AtMCU1 is expressed mainly in root cells and is localized in mitochondria. Its absence results in moderate changes in  $\text{Ca}^{2+}$  dynamics, as assessed by in vivo measurements in root tips. Under restrictive growth conditions, knockdown or overexpression of AtMCU1 results in altered ultrastructure of root mitochondria and shortening of primary roots (Teardo et al. 2016).

### **$\text{Ca}^{2+}$ channels related to abiotic stress resistance**

Changes in  $\text{Ca}^{2+}$  concentration and in forms of protein phosphorylation including mitogen-activated protein kinase (MAPK) cascades in plant cells may result from biotic and abiotic stress signals. Cytoplasmic  $\text{Ca}^{2+}$  concentration is the first to respond to all types of stress stimuli, and changes are quickly mediated via  $\text{Ca}^{2+}$  channels and other media to reach sensory elements in cells and thereby extend the stress signals (Kudla et al. 2010).  $\text{Ca}^{2+}$ -dependent protein kinases (CDPKs) are involved in the signal transduction under the stress. Among all CDPK genes, the expression of *VaCPK21* is significantly up-regulated in *Vitis amurensis* which is probably to be acted as a positive regulator under the salt and high temperature stress (Dubrovina et al. 2016). VaCPK1 and VaCPK21 are also related to the stilbene synthesis contributing to the plant biotic stress resistance (Aleynova et al. 2017).  $\text{Ca}^{2+}$  concentration was monitored by fluorescence signals in cells of *A. thaliana*, which have an aequorin expressing system; signals were emitted by germinating seedlings within 5 s after exposure to exogenous NaCl or mannitol, reaching a maximal level within 10 s (Knight et al. 1997). The appearance of these fluorescence signals in such a short time illustrates the ability of  $\text{Ca}^{2+}$ -channel proteins distributed on the cell membrane to respond very quickly to stress, resulting in  $\text{Ca}^{2+}$  influx and transduction of a series of signals. In *Populus euphratica*, heat shock (HS) could induce an early influx of  $\text{Ca}^{2+}$  and  $\text{K}^{+}$ .  $\text{GdCl}_3$  acts as an inhibitor to decrease the  $\text{H}_2\text{O}_2$ , indicating that the *P. euphratica* probably resists the HS through the enhancement of the antioxidant system (Yu et al. 2016). Discovery and functional characterization of stress-related  $\text{Ca}^{2+}$  channels

**Table 2** Main  $\text{Ca}^{2+}$  channels distribution in plants under the abiotic stress

Types	Sub-types	Species	Distribution	Affiliation	Functions	References
TPC	OsTPC	Rice	Vacuole	Voltage-gated ion channels (VGICs)	Hypersensitive cell death; synthesis of phytoalexin	Hamada et al. (2012)
	AtTPC	<i>A. thaliana</i>			Tolerance of stress; anionic channel opening; stomatal closure	Hashimoto et al. (2004), Choi et al. (2014)
CNGCs	TaTPC	Wheat	Plasma membrane	Voltage-independent $\text{Ca}^{2+}$ -permeable channel (VICCs)	Response to stress	(Wang et al. 2005)
	CNGC2	<i>A. thaliana</i>			stress responses	Finka et al. (2012), Frietsch et al. (2007), Kugler et al. (2009), Dietrich et al. (2010)
	CNGC10 CNGC16				Sensitive to salt stress Be critical for heat stress tolerance	Guo et al. (2008) Tuncozdemir et al. (2013)
MSL	MSL1-3	<i>A. thaliana</i>	Mitochondria; chloroplast	Nonselective channel	Sense mechanical stimuli	Wilson et al. (2011)
	MSL4-10	<i>A. thaliana</i>	mitochondria		Sense mechanical stimuli	Nakayama et al. (2012)
Annexins	AtANN1	<i>A. thaliana</i>	Cytosol; plasma membrane; intracellular membrane; certain organelles	Hyperpolarization-activated (HACC)	Drought stress tolerance	Clark et al. (2012); Szalonek et al. (2015)
	ANNBJ1	<i>Brassica juncea</i>				
	NNANN1	<i>Nelumbo nucifera</i>				
	GHANN1	<i>Gossypium hirsutum</i>				
	STANN1	<i>Solanum tuberosum</i>				

has lagged behind that of  $\text{K}^+$  channels (Lan et al. 2011; Very and; Sentenac 2002; Hirsch et al. 1998) which have been cloned and more intensively studied (Table 2).

ABA, ethylene, auxin, and  $\text{IP}_3$  are known to regulate plant growth and signaling in response to environmental stresses through complex signal transduction and metabolic processes. However, relationships between abiotic stress factors and resulting plant signals are unclear in many cases.

### Role of two-pore channels (TPCs) in abiotic stress resistance

Two-pore channels comprise a subfamily of the eukaryotic voltage-gated ion channels (VGICs) superfamily that are mainly expressed in acidic stores in plants (Sandra et al. 2017), which comprise a large family of intracellular cation channels that are expressed only in acid organelles and vacuoles. The names applied to TPCs differ depending on the species of plant. OsTPC1, AtTPC1, and TaTPC1 are typical TPCs described in rice, guard cells, and wheat.

OsTPC1, a voltage-gated  $\text{Ca}^{2+}$  channel found in rice, has a function similar to that of its homolog AtTPC1. Hamada et al. (2012) showed that OsTPC1 plays an essential role in hypersensitive cell death induced by TvX. Persistent increase of  $\text{Ca}^{2+}$  induced by TvX is mediated by OsTPC1

as  $\text{Ca}^{2+}$  channel. OsTPC1 is also involved in synthesis of phytoalexins, a type of antimicrobial substance.

In some cases, a particular signal transduction pathway may be involved in responses to multiple types of stress, which are difficult to distinguish because resistance to them depends on the same action. AtTPC1 is the most studied (to date) protein that functions in response to multiple stress factors. AtTPC1 is an SV  $\text{Ca}^{2+}$  TPC involved in stomatal closure in guard cells. AtTPC1 can compensate for *cchl* mutation in yeast, and restores  $\text{Ca}^{2+}$  function to enhance tolerance of sugar stress (Hashimoto et al. 2004). In studies of AtTPC1 mutant *attpc 1–2*, exogenous  $\text{Ca}^{2+}$  treatment did not induce stomatal closure nor activate anionic channels to produce current. AtTPC1 existing in guard cell stomata evidently responds to exogenous  $\text{Ca}^{2+}$  signals and participates in both anionic channel opening and stomatal closure, but is not regulated by ABA or methyl jasmonate (Islam et al. 2010). Transmission systems based on fast  $\text{Ca}^{2+}$  waves can resist stress, and  $\text{Ca}^{2+}$  speed may reach  $420 \mu\text{m/s}$  (Choi et al. 2014). In *A. thaliana* root tissue subjected to salinity stress,  $\text{Ca}^{2+}$  spreads through AtTPC1, a  $\text{Ca}^{2+}$  channel, existing in the cortex and endodermis. Waves in the  $\text{Ca}^{2+}$ /TPC1 system may involve specific molecular reactions induced by salinity stress (Choi et al. 2014).

TaTPC1, a  $\text{Ca}^{2+}$  channel found in wheat, is induced by high salinity, polyethylene glycol, low temperature, or ABA

(Wang et al. 2005). In complementation experiments, a yeast *cch1* mutant survived under  $\text{Li}^+$  ion stress when *TaTPC1* was expressed. Stomatal closure ability was higher in *TaTPC1*-overexpressing plants (Wang et al. 2005). The above findings all indicate the involvement of  $\text{Ca}^{2+}$  in responses to environmental changes.

### Role of cyclic nucleotide-gated channels (CNGCs) in abiotic stress resistance

The CNGCs are ligand-gated cation channels localized mostly in the plasma membrane belonging to the VICCs. Members of the CNGC family in *A. thaliana* are involved in ion signal transduction through  $\text{Ca}^{2+}$  flow, and in responses to biotic and abiotic stress factors.

Tune-Ozdemir (2013) demonstrated expression of heat-resistance genes in a *CNGC16* mutant of *A. thaliana* by quantitative PCR analysis. Pollen feasibility analysis showed that pollen of the mutant was highly sensitive to  $\text{Ca}^{2+}$ , and that thermotolerance was induced by pollen through cyclic nucleotide signals,  $\text{Ca}^{2+}$  channels, and a signal network. *CNGC16* was responsive to high temperature and drought, whereas a *cgnc16* mutant was sensitive to exogenous  $\text{CaCl}_2$  (Tune-Ozdemir et al. 2013). In rice, a single-nucleotide polymorphism in *COLD1* (a G protein) enhanced cold tolerance through rapid  $\text{Ca}^{2+}$  flow, suggesting that CNGCs may be complexed with *COLD1* (Ma et al. 2015). In *A. thaliana* pollen and leaf cells, high temperature stress results in a sharp rise of cGMP concentration and greatly reduced expression of heat stress response genes, including those encoding heat shock transcription factors such as *HsfA2* and *HsfB1*. Thus, *CNGC16* appears to be a permeability channel involved in cyclic nucleotide signaling responses to high temperature and drought.

*CNGC19* and *CNGC20* play a role in responses to salinity stress (Kugler et al. 2009). Expression of these two genes is upregulated in response to increased salinity stress, but is unaffected by mannitol stress. Under various durations (6–72 h) of salinity stress, there was a strong response by *CNGC19* in buds, but no response by *CNGC19* in roots. *CNGC20* expression increased greatly after 1 h of salinity stress.

### Role of $\text{Ca}^{2+}$ -permeable mechanosensitive (MS) channels in abiotic stress resistance

$\text{Ca}^{2+}$ -permeable MS channels are able to sense mechanical stimuli. In *Escherichia coli*, hypo-osmotic shock is an activator for increase of cytoplasmic  $\text{Ca}^{2+}$  concentration, mainly by  $\text{Ca}^{2+}$  influx through plasma membrane (Nakagawa et al. 2007; Kurusu et al. 2012). *MscS*, one of three types of MS channels, helps prevent rupturing of cells under hypo-osmotic stress (Hurst et al. 2008). *MscS*-like

channels (MSLs), a kind of nonselective channel, are present in plants and algae, which can be divided into two types: class I (localized in mitochondria and having plastids with target sequences) and class II (lacking plastids). The *A. thaliana* genome includes ten *MSL* genes: *MSL1-3* (class I) and *MSL4-10* (class II). The eukaryotic *MscS* members, especially *MSL2* and *MSL3* existing in the chloroplast make a great significant in the various physiological functions such as chloroplast division, plastid size, shape (Wilson et al. 2011; Haswell and Meyerowitz 2006). They contain a C-terminal cytoplasmic conserved domain (Jensen and Haswell 2012), which is necessary for the proper channel functions and subcellular localization. Class II such as *MSL10*, is distinguished with 6 TM regions with large soluble N- and C-termini, also has a large cytoplasmic loop between TM helix 4 and 5 (Haswell 2007; Nakayama et al. 2012), which is the basic of specific functions in the eukaryote such as controlling and sensing the  $\text{Ca}^{2+}$  influx including hypoosmotic stress (Nakayama et al. 2012).

### Role of annexins in abiotic stress resistance

Annexins are a type of  $\text{Ca}^{2+}$  channel belonging to HACCs involved in drought stress tolerance in plants. *AtANN1* is an annexin found in *A. thaliana*. In a study by Konopka-Postupolska et al. (2009), *A. thaliana* was treated by short photoperiod for 4 weeks, and then by drought stress until complete dehydration. An *atann1* deletion mutant died by day 5, whereas wild-type and an *AtANN1*-overexpressing mutant remained green, illustrating the role of annexins in drought stress resistance.

### Future prospects

The environment of plants contains a variety of physical and chemical stimuli, and the associated signal transduction pathways involve many types of  $\text{Ca}^{2+}$  channels. Research on plant  $\text{Ca}^{2+}$  channels has undergone important, sequential advances during the past decade. Continued development of patch-clamp technology, calcium imaging systems, and related methods will lead to discovery and elucidation of more  $\text{Ca}^{2+}$  channels.

$\text{Ca}^{2+}$  concentrations resulting from various plant cell stimuli display differences in range, duration, and spatial distribution that are associated with specific reactions.  $\text{Ca}^{2+}$  signals are one of the most important signal types that regulate plant homeostasis and growth. Research on  $\text{Ca}^{2+}$  channels and  $\text{Ca}^{2+}$  signals is essential to clarify the mechanisms of plant tolerance/resistance to all types of abiotic and biotic stress, and is becoming increasingly popular in our field. Studies on stress-related physiological modifications are well advanced, but the associated molecular



modifications remain poorly known. There is an exciting future for studies on identification of stress-related proteins and use of transgenesis techniques to enhance stress resistance in plants.

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## Compliance with ethical standards

**Conflict of interest** No conflict of interest exists in the submission of this manuscript, and manuscript is approved by all authors for publication. I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

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