



Calcium-Regulated Phosphorylation Systems Controlling Uptake and Balance of Plant Nutrients

Shunya Saito* and Nobuyuki Uozumi*

Department of Biomolecular Engineering, Graduate School of Engineering, Tohoku University, Sendai, Japan

OPEN ACCESS

Edited by:

Francisco Rubio,
Spanish National Research Council,
Spain

Reviewed by:

Isabelle Chérel,
Institut National de la Recherche
Agronomique (INRA), France
Ingo Dreyer,
University of Talca, Chile

*Correspondence:

Shunya Saito
shunya.saito@tohoku.ac.jp
Nobuyuki Uozumi
uozumi@tohoku.ac.jp

Specialty section:

This article was submitted to
Plant Nutrition,
a section of the journal
Frontiers in Plant Science

Received: 05 November 2019

Accepted: 14 January 2020

Published: 11 February 2020

Citation:

Saito S and Uozumi N (2020) Calcium-Regulated Phosphorylation Systems Controlling Uptake and Balance of Plant Nutrients.
Front. Plant Sci. 11:44.
doi: 10.3389/fpls.2020.00044

Essential elements taken up from the soil and distributed throughout the whole plant play diverse roles in different tissues. Cations and anions contribute to maintenance of intracellular osmolarity and the formation of membrane potential, while nitrate, ammonium, and sulfate are incorporated into amino acids and other organic compounds. In contrast to these ion species, calcium concentrations are usually kept low in the cytosol and calcium displays unique behavior as a cytosolic signaling molecule. Various environmental stresses stimulate increases in the cytosolic calcium concentration, leading to activation of calcium-regulated protein kinases and downstream signaling pathways. In this review, we summarize the stress responsive regulation of nutrient uptake and balancing by two types of calcium-regulated phosphorylation systems: CPK and CBL-CIPK. CPK is a family of protein kinases activated by calcium. CBL is a group of calcium sensor proteins that interact with CIPK kinases, which phosphorylate their downstream targets. In *Arabidopsis*, quite a few ion transport systems are regulated by CPKs or CBL-CIPK complexes, including channels/transporters that mediate transport of potassium (KAT1, KAT2, GORK, AKT1, AKT2, HAK5, SPIK), sodium (SOS1), ammonium (AMT1;1, AMT1;2), nitrate and chloride (SLAC1, SLAH2, SLAH3, NRT1.1, NRT2.4, NRT2.5), and proton (AHA2, V-ATPase). CPKs and CBL-CIPKs also play a role in C/N nutrient response and in acquisition of magnesium and iron. This functional regulation by calcium-dependent phosphorylation systems ensures the growth of plants and enables them to acquire tolerance against various environmental stresses. Calcium serves as the key factor for the regulation of membrane transport systems.

Keywords: nutrition, calcium, membrane transport, *Arabidopsis thaliana*, ion homeostasis

INTRODUCTION

Plants require various ions as essential nutrients, which are taken up from the soil and distributed throughout the whole plant (Welch, 1995; Merchant, 2010; Grusak et al., 2016). Each of these nutrients, once they are transferred to their destination within plant tissues *via* corresponding transporters/ion channels, plays diverse and critical roles in maintaining plant growth. Potassium, nitrate, and chloride contribute to maintenance of intracellular osmolarity, enabling control of cell turgor pressure which is crucial for cell expansion, stomatal movement, and pollen tube growth (Kroeger et al., 2011; Saito and Uozumi, 2019). Nitrate, ammonium, sulfate, and phosphorus are

metabolized to produce various proteins and organic compounds (Leustek and Saito, 1999; López-Arredondo et al., 2013; López-Arredondo et al., 2014). Metal ions such as iron (Balk and Schaedler, 2014), manganese (Schmidt et al., 2016; Schmidt and Husted, 2019), magnesium (Gerendás and Führes, 2013), zinc (Broadley et al., 2007) and molybdenum (Mendel, 2013) work as essential cofactors for enzyme activity.

Among these essential nutrient ions, calcium exhibits some unique behaviors. In contrast to other macronutrient ions, such as potassium, for which the cellular concentration is normally in the range of 80 to 100 mM, calcium concentrations are usually relatively low and kept around 0.1 μ M in the cytosol (Bush, 1995; Walker et al., 1996; Sanders et al., 1999; Hepler, 2005). However, when plants are exposed to environmental stresses such as drought, saline soil, pathogens, wounding, or nutrient deficiency, a rapid increase of the cytosolic calcium concentration occurs, either as a result of Ca^{2+} import *via* plasma membrane ion channels or Ca^{2+} release from intracellular calcium stores (Steinhorst and Kudla, 2013b; Zhu, 2016; Manishankar et al., 2018; Toyota et al., 2018). This leads to activation of calcium-regulated protein kinases, initiation of downstream phosphorylation signaling, and finally, achievement of stress resistance resulting from an activation of stress responsive genes or adjustment of ion channel activity. Ca^{2+} -regulated proteins which play a key role in this phosphorylation process can be divided into three major groups: Calcium dependent protein kinases (CPK), CPK-related protein kinases (CRK), and Calcineurin-B like proteins (CBL). CPK is a family of Ser/Thr kinases containing a calcium binding site (EF hand) in their C-terminal region. Binding of Ca^{2+} to the EF hand stimulates a conformational change, thus allowing autophosphorylation of the kinase (Hashimoto and Kudla, 2011; Schulz et al., 2013). There are 34 CPK members in the *Arabidopsis* genome, and over half of these have been functionally characterized (Kudla et al., 2010; Boudsocq and Sheen, 2013; Shi et al., 2018; Saito and Uozumi, 2019). CRKs, on the other hand, were recently shown to be able to phosphorylate Tyr residues (Nemoto et al., 2015). The function of only two of eight CRK members in *Arabidopsis* has been analyzed so far (Rigó et al., 2013; Baba et al., 2018). CBL differs from the other two groups with regard to CBL itself being a Ca^{2+} sensor protein but not a kinase. Ca^{2+} -bound and activated CBL interacts with another group of kinases called CBL-interacting protein kinases (CIPK), thereby enhancing CIPK autophosphorylation and recruitment to their target proteins (Batistic et al., 2008; Batistič and Kudla, 2009; Mao et al., 2016). Ten members of CBL and 26 members of CIPK exist in the *Arabidopsis* genome, each has a unique expression and subcellular localization profile. Together they form a specific interaction network, allowing regulation of genes and ion channels in various locations (Mahajan et al., 2006; Steinhorst and Kudla, 2013b; Manik et al., 2015; Manishankar et al., 2018; Saito and Uozumi, 2019). In this review, we focus on the stress responsive regulation of nutrient uptake and balancing by CPK and CBL-CIPK.

Calcium-Dependent Import of Potassium and Anions—Regulator of Intracellular Osmolarity

Potassium (K^+) is the most abundant ion in plant cells. As a soluble ion, it plays a critical role in adjusting cellular osmolarity, membrane electric potential, or intracellular pH (Almeida et al., 2017; Ragel et al., 2019). These processes are important for the regulation of cell expansion, which is a prerequisite for plant growth and stomatal movement. Other ion species that contribute to this regulation are nitrate (NO_3^-) and chloride (Cl^-). These anions work synergistically with K^+ in the regulation of guard cell turgor pressure, and ultimately the control of stomatal aperture. K^+ , NO_3^- , and Cl^- fluxes across the plasma membrane of pollen tubes are also essential for its growth (Mouline et al., 2002; Wu et al., 2011; Gutermuth et al., 2013; Liu et al., 2016).

Early studies proposed a correlation between cytosolic calcium and the uptake of potassium in a variety of plant species (Hirata and Mitsui, 1965; Johansen et al., 1968; Rains and Floyd, 1970). Indeed, it has been reported that K^+ deficiency induces rapid Ca^{2+} increase in *Arabidopsis* roots (Behera et al., 2016). In *Arabidopsis* root cells, K^+ uptake from the soil and export to the xylem are orchestrated by several types of transporters. Main contributors to root K^+ uptake are the Shaker-type K^+ channel AKT1 and the KT/KUP/HAK type transporter HAK5 (Pyo et al., 2010; Rubio et al., 2010; Alemán et al., 2011). The activity of these two K^+ transport systems depends on CBL1 (or CBL9) and CIPK23 (Xu et al., 2006; Lee et al., 2007; Ragel et al., 2015). When cytosolic Ca^{2+} increases, activated CBL1/9 interacts with and recruits CIPK23 to the plasma membrane, enabling it to activate AKT1 and HAK5. Another CBL member, CBL10, is capable of CIPK-independent negative regulation of AKT1 activity, suggesting a role in maintaining balance of K^+ uptake (Ren et al., 2013). CIPK9, most likely paired with CBL2 or CBL3, also regulates K^+ homeostasis under low K^+ conditions *via* phosphorylation of a yet unknown target (Pandey et al., 2007a; Liu et al., 2012b; Singh et al., 2018). In addition, members of the cyclic-nucleotide gated channel family CNGC3, CNGC10, and CNGC13 (Kaplan et al., 2007; Caballero et al., 2012; Ragel et al., 2019), and the cation-proton antiporter CHX13 (Zhao et al., 2008) have also been reported to mediate K^+ flux into root cell. Activity of these CNGCs might be regulated by Ca^{2+} -activated calmodulin binding and resulting blocking of the cyclic-nucleotide binding domain (Kaplan et al., 2007; DeFalco et al., 2016; Pan et al., 2019). K^+ uptake by AKT1 and HAK5 is also conserved in rice, although systems corresponding to CNGCs and CHX remain to be identified in rice (Ragel et al., 2019). Increase of the K^+ concentration in root stellar cell enables drive of K^+ into the xylem mediated by the Shaker-type K^+ efflux channel SKOR, followed by translocation of K^+ to the shoot (Liu et al., 2006; Ragel et al., 2019).

In contrast to its role connected to potassium, the role of calcium as a second messenger for the nitrate response was only recently discovered (Riveras et al., 2015). Nitrate uptake and distribution throughout the plant is mainly mediated by members of the nitrate transporter (NRT) or nitrate transporter 1/peptide transporter (NPF) family (Léran et al., 2014). In *Arabidopsis* roots, NRT2.1/2.2/2.4/2.5 and NPF2.3/4.6/6.3 are responsible for NO_3^- uptake and translocation (Taochy et al., 2015; Nogueru and Lacombe, 2016; Xuan et al., 2017; Zhao et al., 2018a). Among these transporters, NPF6.3, also known as NRT1.1 or CHL1, is well studied and considered a major contributor to NO_3^- transport (Léran et al., 2013; Leran et al., 2015; Undurraga et al., 2017). NPF6.3 is characterized as a dual affinity bidirectional NO_3^- transporter. This unique transporter switches its affinity from low-affinity to high-affinity mode by dimerization, which is controlled by phosphorylation of Thr101 by CBL1/9-CIPK23 (Liu and Tsay, 2003; Ho et al., 2009; Parker and Newstead, 2014; Sun et al., 2014). Two other members of CBL-CIPK are also involved in regulation of NRT/NPF. CIPK8 plays a role in the nitrate response by influencing the expression level of several nitrate-responsive genes including NPF6.3 and NRT2.1 (Hu et al., 2009). CBL7, on the other hand, was shown to regulate the expression levels of NRT2.4 and NRT2.5 (Ma et al., 2015). Other than NRT/NPF, two homologues of the guard cell S-type anion channel SLAC1, SLAH2 and SLAH3, are also suggested to mediate xylem loading of NO_3^- (Maierhofer et al., 2014a; Maierhofer et al., 2014b). Activation of these two SLAHs is also dependent on CBL1/9-CIPK23, and in addition, several members of the CPK family, such as CPK21 (Maierhofer et al., 2014a; Maierhofer et al., 2014b; Yao et al., 2017). Some members of the NRT/NPF or SLAH family are capable of transporting other ion species as well. NRT1.5/NPF7.3 can mediate K^+ and NO_3^- loading into the xylem, working synergistically with SKOR to maintain K^+/NO_3^- balance in root and shoot (Lin et al., 2008; Drechsler et al., 2015; Li et al., 2017b). Another NPF member, NPF2.4, is responsible for Cl^- loading into the xylem (Li et al., 2016). SLAH1, a silent channel subunit expressed together with SLAH3 in xylem-pole pericycle cells, mediates root to shoot Cl^- translocation by forming a heteromer with SLAH3 (Cubero-Font et al., 2016; Qiu et al., 2016).

Once imported into the xylem, K^+ travels long-distance from root to shoot to be exported into appropriate aerial tissues. In addition, K^+ can be transported from green cells into the phloem to be returned back to the roots. Detailed mechanism of this root-shoot translocation of K^+ still remains ambiguous, although transporters which affect the shoot/root ratio of K^+ might contribute, such as KUP7 (Han et al., 2016) and OsHAK16 from rice (Feng et al., 2019). Likewise, the identity of the transporters responsible for the retrieval of anions from the xylem remains unclear too, albeit several transporters such as NRT1.8/NPF7.2 (Li et al., 2010; Fan et al., 2017; Zhang et al., 2018) and Cation/Chloride Cotransporters (CCCs) (Li et al., 2017a) have been suggested.

Regulation of Cell Expansion and Movement

One of the key roles of K^+ , NO_3^- , and Cl^- in aerial parts of plants is regulation of stomatal aperture. Stomatal movement occurs through change of osmolarity concomitantly with ion flow (mainly K^+) across the guard cell membrane. A number of guard cell-expressed transporters contribute to this regulation; KAT1, KAT2, AKT1, AKT2, NPF6.3, and H^+ -ATPases such as AHA2 for stomatal opening (Szyroki et al., 2001; Guo et al., 2003; Saito and Uozumi, 2019), and SLAC1, SLAH3, GORK, and ALMT12 for stomatal closing (Hosy et al., 2003; Vahisalu et al., 2008; Meyer et al., 2010; Geiger et al., 2011; Saito and Uozumi, 2019). Stomata, being the site of water loss *via* transpiration and entrance of pathogens, are regulated by specific signal transduction pathways that ensure rapid closure in response to drought or pathogen attack. This signaling is mediated by an increase in guard cell cytosolic Ca^{2+} concentration and the resulting regulation of transporters by activated CPKs or CBL-CIPKs (Pandey et al., 2007b; Munemasa et al., 2015; Saito and Uozumi, 2019). Ca^{2+} -activated CPK3, CPK6, CPK21, CPK23 (Geiger et al., 2010; Geiger et al., 2011; Scherzer et al., 2012), and CBL1/9-CIPK23 (Maierhofer et al., 2014a) are capable of eliciting anion efflux through SLAC1 and SLAH3. In addition, CBL5-CIPK11 can also activate SLAC1 (Saito et al., 2018). Following this anion efflux, K^+ is driven out from guard cells *via* the Shaker K^+ efflux channel GORK, causing turgor pressure decrease and cell shrinkage, leading to stomatal closure. Moreover, GORK itself, either directly or indirectly, is activated by CPK21 (van Kleeff et al., 2018), CPK33 (Corratgé-Faillie et al., 2017), and CBL1-CIPK5 (Förster et al., 2019). In addition, Ca^{2+} also triggers attenuation of stomatal opening. CIPK11 (although its interacting CBL remains undetermined) has been reported to inhibit AHA2 activity (Fuglsang et al., 2007; Yang et al., 2010), and CPK13 reduces K^+ influx mediated by the Shaker K^+ channels KAT1 and KAT2 (Ronzier et al., 2014). Additionally, CBL2/3 and CIPK9/17 were reported to regulate stomatal movement *via* control of vacuolar morphology (Song et al., 2018), possibly achieved by phosphorylation of the vacuolar localized transporters like K^+/H^+ antiporter NHX (Barragán et al., 2012; Andres et al., 2014), two pore K^+ channel TPK1 (Gobert et al., 2007) and V-ATPase (Ratajczak, 2000; Eisenach and De Angeli, 2017). It is noteworthy that *cbl2 cbl3* double mutation in *Arabidopsis* results in reduced activity of V-ATPase (Tang et al., 2012).

Calcium is also well recognized as a predominant regulator of pollen germination and pollen tube elongation in a wide range of plant species (Steinhorst and Kudla, 2013a; Zheng et al., 2019). Control of cell volume through Ca^{2+} -dependent regulation of ion channels plays a crucial role in pollen tube growth. So far, CPKs and CBL-CIPKs reported to function in pollen tubes are CPK2/11/17/20/24/34, CBL1/2/3/9, and CIPK12/19 (Myers et al., 2009; Mähls et al., 2013; Zhou et al., 2015). CPK11, together with CPK24, modulates the activity of the pollen-expressed plasma membrane K^+ influx channel SPIK, which is required for pollen germination (Mouline et al., 2002; Zhao et al., 2013). Pollen tubes

TABLE 1 | Summary of ion channels/transporters and other Ca²⁺-regulated proteins reviewed in this article.

Name	Activator	Deactivator	Type of transport	Expressed in	Role
AKT1	CBL1/9-CIPK23	CBL10	K ⁺ influx	Root, guard cell	K ⁺ uptake, stomatal opening
HAK5	CBL1/9-CIPK23		K ⁺ influx	Root	K ⁺ uptake
Unknown	CBL2/3-CIPK9				K ⁺ homeostasis
CNGC3	Calmodulin?		K ⁺ influx	Root	K ⁺ uptake
CNGC10	Calmodulin?		K ⁺ influx	Root	K ⁺ uptake
CNGC13	Calmodulin?		K ⁺ influx	Root	K ⁺ uptake
CHX13			K ⁺ influx	Root	K ⁺ uptake
SKOR			K ⁺ efflux	Root xylem pericycle	Xylem loading of K ⁺
NRT2.1	CIPK8		NO ₃ ⁻ influx	Root	NO ₃ ⁻ uptake
NRT2.2			NO ₃ ⁻ influx	Root	NO ₃ ⁻ uptake
NRT2.4	CBL7		NO ₃ ⁻ influx	Root	NO ₃ ⁻ uptake
NRT2.5	CBL7		NO ₃ ⁻ influx	Root	NO ₃ ⁻ uptake
NPF2.3			NO ₃ ⁻ influx	Root	NO ₃ ⁻ uptake
NPF4.6			NO ₃ ⁻ influx	Root	NO ₃ ⁻ uptake
NPF6.3	CIPK8, CPK10/30/32 (via NLP7 phosphorylation)	CBL1/9-CIPK23(via conversion of NO ₃ ⁻ affinity mode)	NO ₃ ⁻ influx	Root, guard cell	NO ₃ ⁻ uptake, stomatal opening
NRT1.5			K ⁺ /H ⁺ antiport, NO ₃ ⁻ efflux	Root xylem pericycle	Xylem loading of K ⁺ and NO ₃ ⁻
NPF2.4			Cl ⁻ efflux	Root xylem pericycle	Xylem loading of Cl ⁻
SLAH2	CBL1/9-CIPK23		NO ₃ ⁻ efflux	Root stele	Xylem loading of NO ₃ ⁻
SLAH3	CBL1/9-CIPK23, CPK3/6/21/23, CPK2/20		NO ₃ ⁻ efflux, Cl ⁻ efflux (when forming heteromer with SLAH1)	Root xylem pericycle, guard cell, pollen tube	Xylem loading of NO ₃ ⁻ and Cl ⁻ , stomatal closure, pollen tube elongation
AKT2	CBL4-CIPK6		Weak/non-rectified K ⁺ transport (switched by phosphorylation)	Phloem, guard cell	Phloem membrane repolarization
KAT1		CPK13	K ⁺ influx	Guard cell	Stomatal opening
KAT2		CPK13	K ⁺ influx	Guard cell	Stomatal opening
AHA2		CIPK11	H ⁺ efflux	Guard cell	Stomatal opening
GORK	CPK21/33, CBL1-CIPK5 (via inhibition of ABI2)		K ⁺ efflux	Root, guard cell	Restoring root Ca ²⁺ homeostasis, stomatal closure
SLAC1	CBL1/9-CIPK23, CPK3/6/21/23, CBL5-CIPK11		Cl ⁻ efflux	Guard cell	Stomatal closure
ALMT12			Malate efflux	Guard cell	Stomatal closure
Unknown	CBL2/3-CIPK9/17			Guard cell tonoplast	Control of guard cell vacuolar morphology?
V-ATPase	CBL2/3-unidentified CIPK		H ⁺ influx	Guard cell tonoplast	Vacuolar pH homeostasis
SPIK	CPK11 and CPK24 together		K ⁺ influx	Pollen tube	Pollen tube growth
SOS1	CBL1/4-CIPK24		Na ⁺ /H ⁺ antiport	Root	Removal of Na ⁺ from root cell

(Continued)

TABLE 1 | Continued

Name	Activator	Deactivator	Type of transport	Expressed in	Role
Unknown	CBL10-CIPK24		Na ⁺ /H ⁺ antiport	Root vacuole	Na ⁺ compartment into vacuole
Unknown	Na ⁺ bound GIPC		Ca ²⁺ influx	Root	Initiation of cytosolic Ca ²⁺ increase
AMT1;1		CBL1/9-CIPK23	NH ₄ ⁺ influx	Root	NH ₄ ⁺ uptake
AMT1;2		CBL1/9-CIPK23	NH ₄ ⁺ influx	Root	NH ₄ ⁺ uptake
Unknown	CBL1, CIPK14		Glucose?		Glucose response
ATL31 (ubiquitin ligase)	CIPK7/12/14	–	–	Ubiquitous	Regulation of C/N-nutrient response
FROs (ferric chelate reductase)	CBL1/9-CIPK23	–	–	Varies	Iron acquisition
Unknown	CBL2/3-CIPK3/9/23			Tonoplast	Mg ²⁺ storage
NIP1;1	CPK31		As ³⁺ influx	Root	As ³⁺ uptake

(Loqué and Von Wirén, 2004; Straub et al., 2017). Thus, it is likely that CBL1-CIPK23 plays a key role in maintaining ion homeostasis in root cells and in preventing the toxic effects of NH₄⁺ (Britto and Kronzucker, 2002; Zheng et al., 2015). Another element that controls the NO₃⁻/NH₄⁺ balance is the transcription factor NLP7, which was recently shown to induce up-regulation of NPF6.3 transcripts in the presence of NH₄⁺ (Zhao et al., 2018b). NLP7 is phosphoregulated by CPK10/30/32, which are activated by NO₃⁻-dependent elevation of intracellular Ca²⁺ (Liu et al., 2017).

Possible Role of Calcium in Balancing of Energy Source

Essential nutrients translocated through vascular tissues are not only limited to ions but also include organic compounds such as amino acids and sugars (Fischer et al., 1998; Liu et al., 2012a). Sugars are transported through phloem in the form of sucrose and distributed throughout the plant (Liu et al., 2012a). Loading of sucrose from the phloem to the apoplast requires activity of the shaker K⁺ channel AKT2 (Shabala, 2003; Dreyer et al., 2017; Ragel et al., 2019). AKT2, usually weakly-rectified, can be converted into a non-rectifying K⁺ channel *via* phosphorylation, thereby enabling K⁺ efflux and phloem membrane repolarization and the consequent retrieval of sucrose (Deeken et al., 2002; Michard et al., 2005a; Michard et al., 2005b; Gajdanowicz et al., 2011; Sandmann et al., 2011; Saito et al., 2017). Though the kinase responsible for this phosphorylation remains to be identified, it must be noted that AKT2 activity can be enhanced by the CBL4-CIPK6 complex in a Ca²⁺-dependent but phosphorylation-independent manner (Held et al., 2011).

The efficiency of cellular energy use is optimized by carbon/nitrogen (C/N) balance, and therefore its maintenance is of great significance for growth and development of plants (Coruzzi and

Bush, 2001; Zheng, 2009; Maekawa et al., 2014). In a recent study, three members of CIPK, CIPK7/12/14, were identified as key regulators of the C/N-nutrient response, achieved through their phosphorylation of ubiquitin ligase ATL31 (Yasuda et al., 2014; Yasuda et al., 2017).

Additionally, although most of the carbon compounds are derived from photosynthesis, plants respond to externally supplied sugars as well. These exogenous sugars, in addition to their use as energy source, show hormone-like behavior, working in parallel with some of the ABA-responsive genes (Rolland and Sheen, 2005; Yamada et al., 2011; Singh et al., 2014; Williams et al., 2014; Yuan et al., 2014). Among the calcium-regulated phosphorylation modules, CBL1 (Li et al., 2013) and CIPK14 (Yan et al., 2014) were found to positively regulate the response to glucose by an yet unidentified mechanism.

Uptake Regulation of Metal Ions and Toxins

Metal ions such as magnesium (Mg²⁺), iron (Fe), zinc (Zn²⁺), and manganese (Mn²⁺) work as cofactors of numerous enzymes and are therefore indispensable for plant growth. Several Ca²⁺-regulated phosphorylation components also participate in maintaining homeostasis of these ions. Iron deficiency was reported to elicit an increase of Ca²⁺ in *Arabidopsis* roots. This induces CBL1/9-CIPK23 to enhance Ferric chelate reductase (FRO) activity, which is required for converting Fe³⁺ in the soil into the transported form, Fe²⁺, thereby substantially regulating iron acquisition (Tian et al., 2016). CIPK23 alongside with CBL2/3 and CIPK3/9, is also required for modulation of plant growth under high Mg²⁺ condition, likely mediated by Mg²⁺ compartmentalization to the vacuole (Mogami et al., 2015; Tang et al., 2015). Additionally, Zn²⁺ and Mn²⁺ levels were found to be reduced in *cipk23* mutant plants, suggesting some unidentified regulatory system of metal acquisition involving CIPK23 (Tian et al., 2016). On the other hand, some CPKs and

CBL-CIPKs are involved in uptake of toxic ions. For instance, CPK31 was reported to regulate uptake of non-essential and toxic arsenite (As^{3+}) (Ji et al., 2017), and in rice, several members of the CPK family exhibited increased phosphorylation in response to cadmium (Cd^{2+}) application (Zhong et al., 2017).

CONCLUSIONS

In this minireview we have summarized the Ca^{2+} -regulated uptake, storage, and translocation of nutrient ions, and possible role of Ca^{2+} in energy source balancing (Figure 1, Table 1). Most of these regulatory mechanisms are initiated by a rise of the cytosolic Ca^{2+} level in response to stress or nutrient depletion, and ultimately lead to resistance against unfavorable conditions. Thus, full understanding of the Ca^{2+} -dependent phosphorylation machinery would be a vital step for optimizing plant growth and reproduction.

REFERENCES

- Alemán, F., Nieves-Cordones, M., Martínez, V., and Rubio, F. (2011). Root K^+ acquisition in plants: the *Arabidopsis thaliana* model. *Plant Cell Physiol.* 52, 1603–1612. doi: 10.1093/pcp/pcr096
- Almeida, D. M., Margarida Oliveira, M., and Saibo, N. J. M. (2017). Regulation of Na^+ and K^+ homeostasis in plants: towards improved salt stress tolerance in crop plants. *Genet. Mol. Biol.* 40, 326–345. doi: 10.1590/1678-4685-gmb-2016-0106
- Andres, Z., Perez-Hormaeche, J., Leidi, E. O., Schlucking, K., Steinhorst, L., McLachlan, D. H., et al. (2014). Control of vacuolar dynamics and regulation of stomatal aperture by tonoplast potassium uptake. *Proc. Natl. Acad. Sci.* 111, E1806–E1814. doi: 10.1073/pnas.1320421111
- Baba, A. I., Rigó, G., Ayaydin, F., Rehman, A. U., András, N., Zsigmond, L., et al. (2018). Functional analysis of the *Arabidopsis thaliana* CDPK-related kinase family: AtCRK1 regulates responses to continuous light. *Int. J. Mol. Sci.* 19, 1–21. doi: 10.3390/ijms19051282
- Balk, J., and Schaedler, T. A. (2014). Iron cofactor assembly in plants. *Annu. Rev. Plant Biol.* 65, 125–153. doi: 10.1146/annurev-arplant-050213-035759
- Barragán, V., Leidi, E. O., Andrés, Z., Rubio, L., de Luca, A., Fernández, J. A., et al. (2012). Ion exchangers NHX1 and NHX2 mediate active potassium uptake into vacuoles to regulate cell turgor and stomatal function in *Arabidopsis*. *Plant Cell* 24, 1127–1142. doi: 10.1105/tpc.111.095273
- Batistič, O., and Kudla, J. (2009). Plant calcineurin B-like proteins and their interacting protein kinases. *Biochim. Biophys. Acta Mol. Cell Res.* 1793, 985–992. doi: 10.1016/j.bbamcr.2008.10.006
- Batistic, O., Sorek, N., Schültke, S., Yalovsky, S., and Kudla, J. (2008). Dual fatty acyl modification determines the localization and plasma membrane targeting of CBL/CIPK Ca^{2+} signaling complexes in *Arabidopsis*. *Plant Cell* 20, 1346–1362. doi: 10.1105/tpc.108.058123
- Behera, S., Long, Y., Schmitz-Thom, I., Wang, X.-P., Zhang, C., Li, H., et al. (2016). Two spatially and temporally distinct Ca^{2+} signals convey *Arabidopsis thaliana* responses to K^+ deficiency. *New Phytol.* 213, 739–750. doi: 10.1111/nph.14145
- Benito, B., Haro, R., Amtmann, A., Cuin, T. A., and Dreyer, I. (2014). The twins K^+ and Na^+ in plants. *J. Plant Physiol.* 171, 723–731. doi: 10.1016/j.jplph.2013.10.014
- Boudsocq, M., and Sheen, J. (2013). CDPKs in immune and stress signaling. *Trends Plant Sci.* 18, 30–40. doi: 10.1016/j.tplants.2012.08.008
- Britto, D. T., and Kronzucker, H. J. (2002). NH_4^+ toxicity in higher plants: a critical review. *J. Plant Physiol.* 159, 567–584. doi: 10.1078/0176-1617-0774
- Broadley, M. R., White, P. J., Hammond, J. P., Zelko, I., and Lux, A. (2007). Zinc in plants: Tansley review. *New Phytol.* 173, 677–702. doi: 10.1111/j.1469-8137.2007.01996.x

AUTHOR CONTRIBUTIONS

Conceptualization, original draft preparation, review, and editing were done by SS, and NU contributed to the article by funding acquisition.

FUNDING

This work was supported by JSPS KAKENHI Grant Number (16H06558, 18H03762, 19H02880, 19K21140, and 19K22264).

ACKNOWLEDGMENTS

We thank Anke Reinders for critical reading of the manuscript.

- Bush, D. S. (1995). Calcium regulation in plant cells and its role in signaling. *Annu. Rev. Plant Physiol. Plant Mol. Biol.* 46, 95–122. doi: 10.1146/annurev.pp.46.060195.000523
- Caballero, F., Botella, M. A., Rubio, L., Fernández, J. A., Martínez, V., and Rubio, F. (2012). A Ca^{2+} -sensitive system mediates low-affinity K^+ uptake in the absence of AKT1 in *Arabidopsis* plants. *Plant Cell Physiol.* 53, 2047–2059. doi: 10.1093/pcp/pcs140
- Corratgé-Faillie, C., Ronzier, E., Sanchez, F., Prado, K., Kim, J.-H., Lanciano, S., et al. (2017). The *Arabidopsis* guard cell outward potassium channel GORK is regulated by CPK33. *FEBS Lett.*, 591, 1982–1992. doi: 10.1002/1873-3468.12687
- Coruzzi, G., and Bush, D. R. (2001). Nitrogen and carbon nutrient and metabolite signaling in plants. *Plant Physiol.* 125, 61–64. doi: 10.1104/pp.125.1.61
- Cubero-Font, P., Maierhofer, T., Jaslan, J., Rosales, M. A., Espartero, J., Díaz-Rueda, P., et al. (2016). Silent S-type anion channel subunit SLAH1 gates SLAH3 open for chloride root-to-shoot translocation. *Curr. Biol.*, 26, 1–8. doi: 10.1016/j.cub.2016.06.045
- Deeken, R., Geiger, D., Fromm, J., Koroleva, O., Ache, P., Langenfeld-Heyser, R., et al. (2002). Loss of the AKT2/3 potassium channel affects sugar loading into the phloem of *Arabidopsis*. *Planta* 216, 334–344. doi: 10.1007/s00425-002-0895-1
- DeFalco, T. A., Marshall, C. B., Munro, K., Kang, H. G., Moeder, W., Ikura, M., et al. (2016). Multiple calmodulin-binding sites positively and negatively regulate *Arabidopsis* CYCLIC NUCLEOTIDE-GATED CHANNEL12. *Plant Cell* 28, 1738–1751. doi: 10.1105/tpc.15.00870
- Demidchik, V., and Tester, M. (2002). Sodium fluxes through nonselective cation channels in the plasma membrane of protoplasts from *Arabidopsis* roots. *Plant Physiol.* 128, 379–387. doi: 10.1104/pp.010524
- Drechsler, N., Zheng, Y., Bohner, A., Nobmann, B., von Wirén, N., Kunze, R., et al. (2015). Nitrate-dependent control of shoot K^+ homeostasis by NPF7.3/NRT1.5 and SKOR in *Arabidopsis*. *Plant Physiol.* 169, 01152.2015. doi: 10.1104/pp.15.01152
- Dreyer, I., Gomez-porras, J. L., and Riedelsberger, J. (2017). The potassium battery: a mobile energy source for transport processes in plant vascular tissues. *New Phytol.* 216, 1049–1053. doi: 10.1111/nph.14667
- Eisenach, C., and De Angeli, A. (2017). Ion transport at the vacuole during stomatal movements. *Plant Physiol.* 174, 520–530. doi: 10.1104/pp.17.00130
- Fan, X., Naz, M., Fan, X., Xuan, W., Miller, A. J., and Xu, G. (2017). Plant nitrate transporters: from gene function to application. *J. Exp. Bot.* 68, 2463–2475. doi: 10.1093/jxb/erx011
- Feng, H., Tang, Q., Cai, J., Xu, B., Xu, G., and Yu, L. (2019). Rice OsHAK16 functions in potassium uptake and translocation in shoot, maintaining potassium homeostasis and salt tolerance. *Planta* 250, 549–561. doi: 10.1007/s00425-019-03194-3

- Fischer, W. N., André, B., Rentsch, D., Krolkiewicz, S., Tegeder, M., Breikreuz, K., et al. (1998). Amino acid transport in plants. *Trends Plant Sci.* 3, 188–195. doi: 10.1016/S1360-1385(98)01231-X
- Förster, S., Schmidt, L. K., Kopic, E., Anschutz, U., Huang, S., Schlücking, K., et al. (2019). Wounding-induced stomatal closure requires jasmonate-mediated activation of GORK K⁺ channels by a Ca²⁺ sensor-kinase CBL1-CIPK5 complex. *Dev. Cell* 48, 87–99.e6. doi: 10.1016/j.devcel.2018.11.014
- Fuglsang, A. T., Guo, Y., Cui, T. A., Qiu, Q., Song, C., Kristiansen, K. A., et al. (2007). *Arabidopsis* protein kinase PKS5 inhibits the plasma membrane H⁺-ATPase by preventing interaction with 14-3-3 protein. *Plant Cell* 19, 1617–1634. doi: 10.1105/tpc.105.035626
- Gajdanowicz, P., Michard, E., Sandmann, M., Rocha, M., Corrêa, L. G. G., Ramírez-Aguilar, S. J., et al. (2011). Potassium K⁺ gradients serve as a mobile energy source in plant vascular tissues. *Proc. Natl. Acad. Sci. U. S. A.* 108, 864–869. doi: 10.1073/pnas.1009777108
- Geiger, D., Scherzer, S., Mumm, P., Marten, I., Ache, P., Matschi, S., et al. (2010). Guard cell anion channel SLAC1 is regulated by CDPK protein kinases with distinct Ca²⁺ affinities. *Proc. Natl. Acad. Sci. U. S. A.* 107, 8023–8028. doi: 10.1073/pnas.0912030107
- Geiger, D., Maierhofer, T., Al-Rasheid, K. A. S., Scherzer, S., Mumm, P., Liese, A., et al. (2011). Stomatal closure by fast abscisic acid signaling is mediated by the guard cell anion channel SLAH3 and the receptor RCAR1. *Sci. Signal.* 4, ra32. doi: 10.1126/scisignal.2001346
- Gerendás, J., and Führs, H. (2013). The significance of magnesium for crop quality. *Plant Soil* 368, 101–128. doi: 10.1007/s11104-012-1555-2
- Gobert, A., Isayenkov, S., Voelker, C., Czempinski, K., and Maathuis, F. J. M. (2007). The two-pore channel TPK1 gene encodes the vacuolar K⁺ conductance and plays a role in K⁺ homeostasis. *Proc. Natl. Acad. Sci.* 104, 10726–10731. doi: 10.1073/pnas.0702595104
- Grusak, M. A., Broadley, M. R., and White, P. J. (2016). Plant macro- and micronutrient minerals. *eLS*, 1–6. doi: 10.1002/9780470015902.a0001306.pub2
- Guo, F.-Q., Young, J., and Crawford, N. M. (2003). The nitrate transporter AtNRT1.1 (CHL1) functions in stomatal opening and contributes to drought susceptibility in *Arabidopsis*. *Plant Cell* 15, 107–117. doi: 10.1105/tpc.006312
- Gutermuth, T., Lassig, R., Portes, M., Maierhofer, T., Romeis, T., Borst, J., et al. (2013). Pollen tube growth regulation by free anions depends on the interaction between the anion channel SLAH3 and calcium-dependent protein kinases CPK2 and CPK20. *Plant Cell* 25, 4525–4543. doi: 10.1105/tpc.113.118463
- Han, M., Wu, W., Wu, W. H., and Wang, Y. (2016). Potassium transporter KUP7 is involved in K⁺ acquisition and translocation in *Arabidopsis* root under K⁺-limited conditions. *Mol. Plant* 9, 437–446. doi: 10.1016/j.molp.2016.01.012
- Hashimoto, K., and Kudla, J. (2011). Calcium decoding mechanisms in plants. *Biochimie* 93, 2054–2059. doi: 10.1016/j.biochi.2011.05.019
- Held, K., Pascaud, F., Eckert, C., Gajdanowicz, P., Hashimoto, K., Corratgé-Faillie, C., et al. (2011). Calcium-dependent modulation and plasma membrane targeting of the AKT2 potassium channel by the CBL4/CIPK6 calcium sensor/protein kinase complex. *Cell Res.* 21, 1116–1130. doi: 10.1038/cr.2011.50
- Hepler, P. K. (2005). Calcium: a central regulator of plant growth and development. *Plant Cell* 17, 2142–2155. doi: 10.1105/tpc.105.032508
- Hirata, H., and Mitsui, S. (1965). Role of calcium in potassium uptake by plant roots. *Plant Cell Physiol.* 6, 699–709. doi: 10.1093/oxfordjournals.pcp.a079142
- Ho, C. H., Lin, S. H., Hu, H. C., and Tsay, Y. F. (2009). CHL1 functions as a nitrate sensor in plants. *Cell* 138, 1184–1194. doi: 10.1016/j.cell.2009.07.004
- Hosy, E., Vavasseur, A., Moulène, K., Dreyer, I., Gaymard, F., Porée, F., et al. (2003). The *Arabidopsis* outward K⁺ channel GORK is involved in regulation of stomatal movements and plant transpiration. *Proc. Natl. Acad. Sci. U. S. A.* 100, 5549–5554. doi: 10.1073/pnas.0733970100
- Hu, H. C., Wang, Y. Y., and Tsay, Y. F. (2009). AtCIPK8, a CBL-interacting protein kinase, regulates the low-affinity phase of the primary nitrate response. *Plant J.* 57, 264–278. doi: 10.1111/j.1365-313X.2008.03685.x
- Ji, R., Zhou, L., Liu, J., Wang, Y., Yang, L., Zheng, Q., et al. (2017). Calcium-dependent protein kinase CPK31 interacts with arsenic transporter AtNIP1;1 and regulates arsenite uptake in *Arabidopsis thaliana*. *PLoS One* 12, 1–20. doi: 10.1371/journal.pone.0173681
- Jiang, Z., Zhou, X., Tao, M., Yuan, F., Liu, L., Wu, F., et al. (2019). Plant cell-surface GIPC sphingolipids sense salt to trigger Ca²⁺ influx. *Nature* 572, 341–346. doi: 10.1038/s41586-019-1449-z
- Johansen, C., Edwards, D. G., and Loneragan, J. F. (1968). Interaction between potassium and calcium in their absorption by intact barley plants. *Plant Physiol.* 43, 1722–1726. doi: 10.1104/pp.43.10.1722
- Kaplan, B., Sherman, T., and Fromm, H. (2007). Cyclic nucleotide-gated channels in plants. *FEBS Lett.* 581, 2237–2246. doi: 10.1016/j.febslet.2007.02.017
- Keisham, M., Mukherjee, S., and Bhatla, S. C. (2018). Mechanisms of sodium transport in plants—progresses and challenges. *Int. J. Mol. Sci.* 19, e647. doi: 10.3390/ijms19030647
- Kim, B. G., Waadt, R., Cheong, Y. H., Pandey, G. K., Dominguez-Solis, J. R., Schültke, S., et al. (2007). The calcium sensor CBL10 mediates salt tolerance by regulating ion homeostasis in *Arabidopsis*. *Plant J.* 52, 473–484. doi: 10.1111/j.1365-313X.2007.03249.x
- Kolkisaoglu, U. (2004). Calcium sensors and their interacting protein kinases: genomics of the *Arabidopsis* and rice CBL-CIPK signaling networks. *Plant Physiol.* 134, 43–58. doi: 10.1104/pp.103.033068
- Köster, P., Wallrad, L., Edel, K. H., Faisal, M., Alatar, A. A., and Kudla, J. (2018). The battle of two ions: Ca²⁺ signalling against Na⁺ stress. *Plant Biol.* 1, 39–48. doi: 10.1111/plb.12704
- Kroeger, J. H., Zerkour, R., and Geitmann, A. (2011). Regulator or driving force? The role of turgor pressure in oscillatory plant cell growth. *PLoS One* 6, e18549. doi: 10.1371/journal.pone.0018549
- Kudla, J., Batistic, O., and Hashimoto, K. (2010). Calcium signals: the lead currency of plant information processing. *Plant Cell* 22, 541–563. doi: 10.1105/tpc.109.072686
- Lee, S. C., Lan, W.-Z., Kim, B.-G., Li, L., Cheong, Y. H., Pandey, G. K., et al. (2007). A protein phosphorylation/dephosphorylation network regulates a plant potassium channel. *Proc. Natl. Acad. Sci. U. S. A.* 104, 15959–15964. doi: 10.1073/pnas.0707912104
- Leran, S., Edel, K. H., Pervent, M., Hashimoto, K., Corratgé-Faillie, C., Offenborn, J. N., et al. (2015). Nitrate sensing and uptake in *Arabidopsis* are enhanced by ABI2, a phosphatase inactivated by the stress hormone abscisic acid. *Sci. Signal.* 8, ra43. doi: 10.1126/scisignal.aaa4829
- Léran, S., Muñoz, S., Brachet, C., Tillard, P., Gojon, A., and Lacombe, B. (2013). *Arabidopsis* NRT1.1 is a bidirectional transporter involved in root-to-shoot nitrate translocation. *Mol. Plant* 6, 1984–1987. doi: 10.1093/mp/sst068
- Léran, S., Varala, K., Boyer, J. C., Chiurazzi, M., Crawford, N., Daniel-Vedele, F., et al. (2014). A unified nomenclature of nitrate transporter 1/peptide transporter family members in plants. *Trends Plant Sci.* 19, 5–9. doi: 10.1016/j.tplants.2013.08.008
- Leustek, T., and Saito, K. (1999). Sulfate transport and assimilation in plants. *Plant Physiol.* 120, 637–643. doi: 10.1104/pp.120.3.637
- López-Arredondo, D. L., Leyva-González, M. A., Alatorre-Cobos, F., and Herrera-Estrella, L. (2013). Biotechnology of nutrient uptake and assimilation in plants. *Int. J. Dev. Biol.* 57, 595–610. doi: 10.1387/ijdb.130268lh
- López-Arredondo, D. L., Leyva-González, M. A., González-Morales, S. I., López-Bucio, J., and Herrera-Estrella, L. (2014). Phosphate nutrition: improving low-phosphate tolerance in crops. *Annu. Rev. Plant Biol.* 65, 95–123. doi: 10.1146/annurev-arplant-050213-035949
- Li, J. Y., Fu, Y. L., Pike, S. M., Bao, J., Tian, W., Zhang, Y., et al. (2010). The *Arabidopsis* nitrate transporter NRT1.8 functions in nitrate removal from the xylem sap and mediates cadmium tolerance. *Plant Cell* 22, 1633–1646. doi: 10.1105/tpc.110.075242
- Li, Z. Y., Xu, Z. S., Chen, Y., He, G. Y., Yang, G. X., Chen, M., et al. (2013). A novel role for *Arabidopsis* CBL1 in affecting plant responses to glucose and gibberellin during germination and seedling development. *PLoS One* 8. doi: 10.1371/journal.pone.0056412
- Li, B., Byrt, C., Qiu, J., Baumann, U., Hrmova, M., Evrard, A., et al. (2016). Identification of a stelar-localized transport protein that facilitates root-to-shoot transfer of chloride in *Arabidopsis*. *Plant Physiol.* 170, 1014–1029. doi: 10.1104/pp.15.01163
- Li, B., Tester, M., and Gilliam, M. (2017a). Chloride on the move. *Trends Plant Sci.* 22, 236–248. doi: 10.1016/j.tplants.2016.12.004
- Li, H., Yu, M., Du, X.-Q., Wang, Z.-F., Wu, W.-H., Quintero, F. J., et al. (2017b). NRT1.5/NPF7.3 functions as a proton-coupled H⁺/K⁺ antiporter for K⁺

- loading into the xylem in *Arabidopsis*. *Plant Cell* 29, tpc.00972.2016. doi: 10.1105/tpc.16.00972
- Lin, S.-H., Kuo, H.-F., Canivenc, G., Lin, C.-S., Lepetit, M., Hsu, P.-K., et al. (2008). Mutation of the *Arabidopsis* NRT1.5 nitrate transporter causes defective root-to-shoot nitrate transport. *Plant Cell Online* 20, 2514–2528. doi: 10.1105/tpc.108.060244
- Liu, K. H., and Tsay, Y. F. (2003). Switching between the two action modes of the dual-affinity nitrate transporter CHL1 by phosphorylation. *EMBO J.* 22, 1005–1013. doi: 10.1093/emboj/cdg118
- Liu, K., Li, L., and Luan, S. (2006). Intracellular K⁺ sensing of SKOR, a Shaker-type K⁺ channel from *Arabidopsis*. *Plant J.* 46, 260–268. doi: 10.1111/j.1365-313X.2006.02689.x
- Liu, D. D., Chao, W. M., and Turgeon, R. (2012a). Transport of sucrose, not hexose, in the phloem. *J. Exp. Bot.* 63, 4315–4320. doi: 10.1093/jxb/ers127
- Liu, L.-L., Ren, H.-M., Chen, L.-Q., Wang, Y., and Wu, W.-H. (2012b). A protein kinase CIPK9 interacts with calcium sensor CBL3 and regulates K⁺ homeostasis under low-K⁺ stress in *Arabidopsis*. *Plant Physiol.* 161, 266–277. doi: 10.1104/pp.112.206896
- Liu, L., Zheng, C., Kuang, B., Wei, L., Yan, L., and Wang, T. (2016). Receptor-like kinase RUPO interacts with potassium transporters to regulate pollen tube growth and integrity in rice. *PLoS Genet.* 12, 1–23. doi: 10.1371/journal.pgen.1006085
- Liu, K. H., Niu, Y., Konishi, M., Wu, Y., Du, H., Sun Chung, H., et al. (2017). Discovery of nitrate-CPK-NLP signalling in central nutrient-growth networks. *Nature* 545, 311–316. doi: 10.1038/nature22077
- Loqué, D., and Von Wirén, N. (2004). Regulatory levels for the transport of ammonium in plant roots. *J. Exp. Bot.* 55, 1293–1305. doi: 10.1093/jxb/erh147
- Mähs, A., Steinhorst, L., Han, J. P., Shen, L. K., Wang, Y., and Kudla, J. (2013). The calcineurin B-like Ca²⁺ sensors CBL1 and CBL9 function in pollen germination and pollen tube growth in *Arabidopsis*. *Mol. Plant* 6, 1149–1162. doi: 10.1093/mp/sst095
- Ma, Q., Tang, R. J., Zheng, X. J., Wang, S. M., and Luan, S. (2015). The calcium sensor CBL7 modulates plant responses to low nitrate in *Arabidopsis*. *Biochem. Biophys. Res. Commun.* 468, 59–65. doi: 10.1016/j.bbrc.2015.10.164
- Maekawa, S., Inada, N., Yasuda, S., Fukao, Y., Fujiwara, M., Sato, T., et al. (2014). The carbon/nitrogen regulator ARABIDOPSIS TOXICOS EN LEVADURA31 controls papilla formation in response to powdery mildew fungi penetration by interacting with SYNTAXIN OF PLANTS121 in *Arabidopsis*. *Plant Physiol.* 164, 879–887. doi: 10.1104/pp.113.230995
- Mahajan, S., Sopory, S. K., and Tuteja, N. (2006). CBL-CIPK paradigm: role in calcium and stress signaling in plants. *Proc. Indian Natl. Sci. Acad.* 78, 63–78. <https://insa.nic.in/Default.aspx>.
- Maierhofer, T., Diekmann, M., Offenborn, J. N., Lind, C., Bauer, H., Hashimoto, K., et al. (2014a). Site- and kinase-specific phosphorylation-mediated activation of SLAC1, a guard cell anion channel stimulated by abscisic acid. *Sci. Signal.* 7, ra86. doi: 10.1126/scisignal.2005703
- Maierhofer, T., Lind, C., Hüttl, S., Scherzner, S., Papenfuß, M., Simon, J., et al. (2014b). A single-pore residue renders the *Arabidopsis* root anion channel SLAH2 highly nitrate selective. *Plant Cell* 3, 1–15. doi: 10.1105/tpc.114.125849
- Manik, S. M. N., Shi, S., Mao, J., Dong, L., Su, Y., Wang, Q., et al. (2015). The calcium sensor CBL-CIPK is involved in plant's response to abiotic stresses. *Int. J. Genomics* 2015, 1–10. doi: 10.1155/2015/493191
- Manishankar, P., Wang, N., Köster, P., Alatar, A. A., and Kudla, J. (2018). Calcium signaling during salt stress and in the regulation of ion homeostasis. *J. Exp. Bot.* 69, 4215–4226. doi: 10.1093/jxb/ery201
- Mao, J., Manik, S. M. N., Shi, S., Chao, J., Jin, Y., Wang, Q., et al. (2016). Mechanisms and physiological roles of the CBL-CIPK networking system in *Arabidopsis thaliana*. *Genes (Basel)* 7, 1–15. doi: 10.3390/genes7090062
- Mendel, R. R. (2013). The molybdenum cofactor. *J. Biol. Chem.* 288, 13165–13172. doi: 10.1074/jbc.R113.455311
- Merchant, S. S. (2010). The elements of plant micronutrients. *Plant Physiol.* 154, 512–515. doi: 10.1104/pp.110.161810
- Meyer, S., Mumm, P., Imes, D., Endler, A., Weder, B., Al-Rasheid, K. A. S., et al. (2010). AtALMT12 represents an R-type anion channel required for stomatal movement in *Arabidopsis* guard cells. *Plant J.* 63, 1054–1062. doi: 10.1111/j.1365-313X.2010.04302.x
- Michard, E., Dreyer, I., Lacombe, B., Sentenac, H., and Thibaud, J. B. (2005a). Inward rectification of the AKT2 channel abolished by voltage-dependent phosphorylation. *Plant J.* 44, 783–797. doi: 10.1111/j.1365-313X.2005.02566.x
- Michard, E., Lacombe, B., Porée, F., Mueller-Roeber, B., Sentenac, H., Thibaud, J.-B., et al. (2005b). A unique voltage sensor sensitizes the potassium channel AKT2 to phosphoregulation. *J. Gen. Physiol.* 126, 605–617. doi: 10.1085/jgp.200509413
- Mogami, J., Fujita, Y., Yoshida, T., Tsukiori, Y., Nakagami, H., Nomura, Y., et al. (2015). Two distinct families of protein kinases are required for plant growth under high external Mg²⁺ concentrations in *Arabidopsis*. *Plant Physiol.* 167, 1039–1057. doi: 10.1104/pp.114.249870
- Mouline, K., Véry, A. A., Gaymard, F., Boucherez, J., Pilot, G., Devic, M., et al. (2002). Pollen tube development and competitive ability are impaired by disruption of a Shaker K⁺ channel in *Arabidopsis*. *Genes Dev.* 16, 339–350. doi: 10.1101/gad.213902
- Munemasa, S., Hauser, F., Park, J., Waadt, R., Brandt, B., and Schroeder, J. I. (2015). Mechanisms of abscisic acid-mediated control of stomatal aperture. *Curr. Opin. Plant Biol.* 28, 154–162. doi: 10.1016/j.pbi.2015.10.010
- Myers, C., Romanowsky, S. M., Barron, Y. D., Garg, S., Azuse, C. L., Curran, A., et al. (2009). Calcium-dependent protein kinases regulate polarized tip growth in pollen tubes. *Plant J.* 59, 528–539. doi: 10.1111/j.1365-313X.2009.03894.x
- Nemoto, K., Takemori, N., Seki, M., Shinozaki, K., and Sawasaki, T. (2015). Members of the plant CRK superfamily are capable of trans- and autophosphorylation of tyrosine residues. *J. Biol. Chem.* 290, 16665–16677. doi: 10.1074/jbc.M114.617274
- Noguero, M., and Lacombe, B. (2016). Transporters involved in root nitrate uptake and sensing by *Arabidopsis*. *Front. Plant Sci.* 7, 1–7. doi: 10.3389/fpls.2016.01391
- Pan, Y., Chai, X., Gao, Q., Zhou, L., Zhang, S., Li, L., et al. (2019). Dynamic interactions of plant CNGC subunits and calmodulins drive oscillatory Ca²⁺ channel activities. *Dev. Cell.* 48, 710–725. doi: 10.1016/j.devcel.2018.12.025
- Pandey, G. K., Cheong, Y. H., Kim, B. G., Grant, J. J., Li, L., and Luan, S. (2007a). CIPK9: a calcium sensor-interacting protein kinase required for low-potassium tolerance in *Arabidopsis*. *Cell Res.* 17, 411–421. doi: 10.1038/cr.2007.39
- Pandey, S., Zhang, W., and Assmann, S. M. (2007b). Roles of ion channels and transporters in guard cell signal transduction. *FEBS Lett.* 581, 2325–2336. doi: 10.1016/j.febslet.2007.04.008
- Parker, J. L., and Newstead, S. (2014). Molecular basis of nitrate uptake by the plant nitrate transporter NRT1.1. *Nature* 507, 68–72. doi: 10.1038/nature13116
- Pyo, Y. J., Gierth, M., Schroeder, J. I., and Cho, M. H. (2010). High-affinity K⁺ transport in *Arabidopsis*: AtHAK5 and AKT1 are vital for seedling establishment and postgermination growth under low-potassium conditions. *Plant Physiol.* 153, 863–875. doi: 10.1104/pp.110.154369
- Qiu, Q.-S., Guo, Y., Dietrich, M. A., Schumaker, K. S., and Zhu, J.-K. (2002). Regulation of SOS1, a plasma membrane Na⁺/H⁺ exchanger in *Arabidopsis thaliana*, by SOS2 and SOS3. *Proc. Natl. Acad. Sci. U. S. A.* 99, 8436–8441. doi: 10.1073/pnas.122246999
- Qiu, J., Henderson, S. W., Tester, M., Roy, S. J., and Gilliam, M. (2016). SLAH1, a homologue of the slow type anion channel SLAC1, modulates shoot Cl⁻ accumulation and salt tolerance in *Arabidopsis thaliana*. *J. Exp. Bot.* 67, 4495–4505. doi: 10.1093/jxb/erw237
- Ragel, P., Ródenas, R., García-Martín, E., Andrés, Z., Villalta, I., Nieves-Cordones, M., et al. (2015). CIPK23 regulates HAK5-mediated high-affinity K⁺ uptake in *Arabidopsis* roots. *Plant Physiol.* 169, 01401.2015. doi: 10.1104/pp.15.01401
- Ragel, P., Raddatz, N., Leidi, E. O., Quintero, F. J., and Pardo, J. M. (2019). Regulation of K⁺ nutrition in plants. *Front. Plant Sci.* 10, 281. doi: 10.3389/fpls.2019.00281
- Rains, W. D., and Floyd, A. R. (1970). Influence of calcium on sodium and potassium absorption by fresh and aged bean stem slices. *Plant Physiol.* 46, 93–98. doi: 10.1104/pp.46.1.93
- Ratajczak, R. (2000). Structure, function and regulation of the plant vacuolar H⁺ translocating ATPase. *Biochim. Biophys. Acta Biomembr.* 1465, 17–36. doi: 10.1016/S0005-2736(00)00129-2
- Ren, X. L., Qi, G. N., Feng, H. Q., Zhao, S., Zhao, S. S., Wang, Y., et al. (2013). Calcineurin B-like protein CBL10 directly interacts with AKT1 and modulates K⁺ homeostasis in *Arabidopsis*. *Plant J.* 74, 258–266. doi: 10.1111/tpj.12123

- Rigó, G., Ayaydin, F., Tietz, O., Zsigmond, L., Kovács, H., Páy, A., et al. (2013). Inactivation of plasma membrane-localized CDPK-RELATED KINASE5 decelerates PIN2 exocytosis and root gravitropic response in *Arabidopsis*. *Plant Cell* 25, 1592–1608. doi: 10.1105/tpc.113.110452
- Riveras, E., Alvarez, J. M., Vidal, E. A., Oses, C., Vega, A., and Gutiérrez, R. A. (2015). The calcium ion is a second messenger in the nitrate signaling pathway of *Arabidopsis*. *Plant Physiol.* 169, 1397–1404. doi: 10.1104/pp.15.00961
- Rolland, F., and Sheen, J. (2005). Sugar sensing and signalling networks in plants. *Biochem. Soc. Trans.* 33, 269–271. doi: 10.1042/BST0330269
- Ronzier, E., Corratgé-Faillie, C., Sanchez, F., Prado, K., Brière, C., Leonhardt, N., et al. (2014). CPK13, a noncanonical Ca²⁺-dependent protein kinase, specifically inhibits KAT2 and KAT1 Shaker K⁺ channels and reduces stomatal opening. *Plant Physiol.* 166, 314–326. doi: 10.1104/pp.114.240226
- Rubio, F., Alemán, F., Nieves-Cordones, M., and Martínez, V. (2010). Studies on *Arabidopsis* athak5, atakt1 double mutants disclose the range of concentrations at which ATHAK5, AtAKT1 and unknown systems mediate K⁺ uptake. *Physiol. Plant.* 139, 220–228. doi: 10.1111/j.1399-3054.2010.01354.x
- Saito, S., and Uozumi, N. (2019). Guard cell membrane anion transport systems and their regulatory components: an elaborate mechanism controlling stress-induced stomatal closure. *Plants* 8, 9. doi: 10.3390/plants8010009
- Saito, S., Hoshi, N., Zulkifli, L., Widyastuti, S., Goshima, S., Dreyer, I., et al. (2017). Identification of regions responsible for the function of the plant K⁺ channels KAT1 and AKT2 in *Saccharomyces cerevisiae* and *Xenopus laevis* oocytes. *Channels* 11, 510–516. doi: 10.1080/19336950.2017.1372066
- Saito, S., Hamamoto, S., Moriya, K., Matsuura, A., Sato, Y., Muto, J., et al. (2018). N-myristoylation and S-acylation are common modifications of Ca²⁺-regulated *Arabidopsis* kinases and are required for activation of the SLAC1 anion channel. *New Phytol.* 218, 1504–1521. doi: 10.1111/nph.15053
- Sanders, D., Brownlee, C., and Harper, J. F. (1999). Communicating with calcium. *Plant Cell* 11, 691–706. doi: 10.1105/tpc.11.4.691
- Sandmann, M., Skłodowski, K., Gajdanowicz, P., Michard, E., Rocha, M., Gomez-Porrás, J. L., et al. (2011). The K⁺ battery-regulating *Arabidopsis* K⁺ channel AKT2 is under the control of multiple post-translational steps. *Plant Signal. Behav.* 6, 558–562. doi: 10.4161/psb.6.4.14908
- Scherzer, S., Maierhofer, T., Al-Rasheid, K. A. S., Geiger, D., and Hedrich, R. (2012). Multiple calcium-dependent kinases modulate ABA-activated guard cell anion channels. *Mol. Plant* 5, 1409–1412. doi: 10.1093/mp/sss084
- Schmidt, S. B., and Husted, S. (2019). The biochemical properties of manganese in plants. *Plants* 8, 381. doi: 10.3390/plants8100381
- Schmidt, S. B., Jensen, P. E., and Husted, S. (2016). Manganese deficiency in plants: the impact on photosystem II. *Trends Plant Sci.* 21, 622–632. doi: 10.1016/j.tplants.2016.03.001
- Schulz, P., Herde, M., and Romeis, T. (2013). Calcium-dependent protein kinases: hubs in plant stress signaling and development. *Plant Physiol.* 163, 523–530. doi: 10.1104/pp.113.222539
- Shabala, S. (2003). Regulation of potassium transport in leaves: from molecular to tissue level. *Ann. Bot.* 92, 627–634. doi: 10.1093/aob/mcg191
- Shi, H., Quintero, F. J., Pardo, J. M., and Zhu, J. K. (2002). The putative plasma membrane Na⁺/H⁺ antiporter SOS1 controls long-distance Na⁺ transport in plants. *Plant Cell* 14, 465–477. doi: 10.1105/tpc.010371
- Shi, S., Li, S., Asim, M., Mao, J., Xu, D., Ullah, Z., et al. (2018). The *Arabidopsis* calcium-dependent protein kinases (CDPKs) and their roles in plant growth regulation and abiotic stress responses. *Int. J. Mol. Sci.* 19, e1900. doi: 10.3390/ijms19071900
- Singh, M., Gupta, A., and Laxmi, A. (2014). Glucose control of root growth direction in *Arabidopsis thaliana*. *J. Exp. Bot.* 65, 2981–2993. doi: 10.1093/jxb/eru146
- Singh, A., Yadav, A. K., Kaur, K., Sanyal, S. K., Jha, S. K., Fernandes, J. L., et al. (2018). A protein phosphatase 2C, AP2C1, interacts with and negatively regulates the function of CIPK9 under potassium-deficient conditions in *Arabidopsis*. *J. Exp. Bot.* 69, 4003–4015. doi: 10.1093/jxb/ery182
- Song, S.-J., Feng, Q.-N., Li, C., Li, E., Liu, Q., Kang, H., et al. (2018). A tonoplast-associated calcium-signaling module dampens ABA signaling during stomatal movement. *Plant Physiol.* 177, 00377.2018. doi: 10.1104/pp.18.00377
- Steinhorst, L., and Kudla, J. (2013a). Calcium—a central regulator of pollen germination and tube growth. *Biochim. Biophys. Acta Mol. Cell Res.* 1833, 1573–1581. doi: 10.1016/j.bbamcr.2012.10.009
- Steinhorst, L., and Kudla, J. (2013b). Calcium and reactive oxygen species rule the waves of signaling. *Plant Physiol.* 163, 471–485. doi: 10.1104/pp.113.222950
- Steinhorst, L., Mähns, A., Ischebeck, T., Zhang, C., Zhang, X., Arendt, S., et al. (2015). Vacuolar CBL-CIPK12 Ca²⁺-sensor-kinase complexes are required for polarized pollen tube growth. *Curr. Biol.* 25, 1475–1482. doi: 10.1016/j.cub.2015.03.053
- Straub, T., Ludewig, U., and Neuhaeuser, B. (2017). The kinase CIPK23 inhibits ammonium transport in *Arabidopsis thaliana*. *Plant Cell*, 29, 409–422. doi: 10.1105/tpc.16.00806
- Sun, J., Bankston, J. R., Payandeh, J., Hinds, T. R., Zagotta, W. N., and Zheng, N. (2014). Crystal structure of the plant dual-affinity nitrate transporter NRT1.1. *Nature* 507, 73–77. doi: 10.1038/nature13074
- Szyroki, A., Ivashikina, N., Dietrich, P., Roelfsema, M. R. G., Ache, P., Reintanz, B., et al. (2001). KAT1 is not essential for stomatal opening. *Proc. Natl. Acad. Sci.* 98, 2917–2921. doi: 10.1073/pnas.051616698
- Tang, R.-J., Liu, H., Yang, Y., Yang, L., Gao, X.-S., Garcia, V. J., et al. (2012). Tonoplast calcium sensors CBL2 and CBL3 control plant growth and ion homeostasis through regulating V-ATPase activity in *Arabidopsis*. *Cell Res.* 22, 1650–1665. doi: 10.1038/cr.2012.161
- Tang, R.-J., Zhao, F.-G., Garcia, V. J., Kleist, T. J., Yang, L., Zhang, H.-X., et al. (2015). Tonoplast CBL-CIPK calcium signaling network regulates magnesium homeostasis in *Arabidopsis*. *Proc. Natl. Acad. Sci.* 112 (10), 3134–3139. doi: 10.1073/pnas.1420944112
- Taochy, C., Gaillard, I., Ipotesi, E., Oomen, R., Leonhardt, N., Zimmermann, S., et al. (2015). The *Arabidopsis* root stele transporter NPF2.3 contributes to nitrate translocation to shoots under salt stress. *Plant J.* 83, 466–479. doi: 10.1111/tbj.12901
- Tester, M., and Davenport, R. (2003). Na⁺ tolerance and Na⁺ transport in higher plants. *Ann. Bot.* 91, 503–527. doi: 10.1093/aob/mcg058
- Tian, Q., Zhang, X., Yang, A., Wang, T., and Zhang, W. H. (2016). CIPK23 is involved in iron acquisition of *Arabidopsis* by affecting ferric chelate reductase activity. *Plant Sci.* 246, 70–79. doi: 10.1016/j.plantsci.2016.01.010
- Toyota, M., Spencer, D., Sawai-toyota, S., Jiaqi, W., Zhang, T., Abraham, K. J., et al. (2018). Glutamate triggers long-distance, calcium-based plant defense signaling. *Science* (80-), 1112–1115. doi: 10.1126/science.aat7744
- Undurraga, S. F., Ibarra-Henríquez, C., Fredes, I., Álvarez, J. M., and Gutiérrez, R. A. (2017). Nitrate signaling and early responses in *Arabidopsis* roots. *J. Exp. Bot.* 68, 2541–2551. doi: 10.1093/jxb/erx041
- Vahisalu, T., Kollist, H., Wang, Y.-F., Nishimura, N., Chan, W.-Y., Valerio, G., et al. (2008). SLAC1 is required for plant guard cell S-type anion channel function in stomatal signalling. *Nature* 452, 487–491. doi: 10.1038/nature06608
- van Kleeff, P. J. M., Gao, J., Mol, S., Zwart, N., Zhang, H., Li, K. W., et al. (2018). The *Arabidopsis* GORK K⁺-channel is phosphorylated by calcium-dependent protein kinase 21 (CPK21), which in turn is activated by 14-3-3 proteins. *Plant Physiol. Biochem.* 125, 219–231. doi: 10.1016/j.plaphy.2018.02.013
- Walker, D. J., Leigh, R. A., and Miller, A. J. (1996). Potassium homeostasis in vacuolate plant cells. *Proc. Natl. Acad. Sci. U. S. A.* 93, 10510–10514. doi: 10.1073/pnas.93.19.10510
- Welch, R. M. (1995). Micronutrient nutrition of plants. *CRC Crit. Rev. Plant Sci.* 14, 49–82. doi: 10.1080/07352689509701922
- Williams, S. P., Rangarajan, P., Donahue, J. L., Hess, J. E., and Gillaspay, G. E. (2014). Regulation of sucrose non-fermenting related kinase 1 genes in *Arabidopsis thaliana*. *Front. Plant Sci.* 5, 1–13. doi: 10.3389/fpls.2014.00324
- Wu, J. Y., Jin, C., and Zhang, S. L. (2011). Potassium flux in the pollen tubes was essential in plant sexual reproduction. *Plant Signal. Behav.* 6, 898–900. doi: 10.4161/psb.6.6.15322
- Xu, J., Li, H. D., Chen, L. Q., Wang, Y., Liu, L. L., He, L., et al. (2006). A protein kinase, interacting with two calcineurin B-like proteins, regulates K⁺ transporter AKT1 in *Arabidopsis*. *Cell* 125, 1347–1360. doi: 10.1016/j.cell.2006.06.011
- Xuan, W., Beeckman, T., and Xu, G. (2017). Plant nitrogen nutrition: sensing and signaling. *Curr. Opin. Plant Biol.* 39, 57–65. doi: 10.1016/j.pbi.2017.05.010
- Yamada, K., Kanai, M., Osakabe, Y., Ohiraki, H., Shinozaki, K., and Yamaguchi-Shinozaki, K. (2011). Monosaccharide absorption activity of *Arabidopsis* roots depends on expression profiles of transporter genes under high salinity conditions. *J. Biol. Chem.* 286, 43577–43586. doi: 10.1074/jbc.M111.269712
- Yan, J., Niu, F., Liu, W. Z., Zhang, H., Wang, B., Yang, B., et al. (2014). *Arabidopsis* CIPK14 positively regulates glucose response. *Biochem. Biophys. Res. Commun.* 450, 1679–1683. doi: 10.1016/j.bbrc.2014.07.064

- Yang, Y., Qin, Y., Xie, C., Zhao, F., Zhao, J., Liu, D., et al. (2010). The *Arabidopsis* chaperone J3 regulates the plasma membrane H⁺-ATPase through interaction with the PKS5 kinase. *Plant Cell* 22, 1313–1332. doi: 10.1105/tpc.109.069609
- Yao, F. Y., Qi, G. N., and Hussain, J. (2017). Investigation of the regulation mechanism of *Arabidopsis thaliana* anion channel SLAH2. *Turk. J. Bot.* 41, 543–551. doi: 10.3906/bot-1702-23
- Yasuda, S., Sato, T., Maekawa, S., Aoyama, S., Fukao, Y., and Yamaguchi, J. (2014). Phosphorylation of *Arabidopsis* ubiquitin ligase ATL31 is critical for plant carbon/nitrogen nutrient balance response and controls the stability of 14-3-3 proteins. *J. Biol. Chem.* 289, 15179–15193. doi: 10.1074/jbc.M113.533133
- Yasuda, S., Aoyama, S., Hasegawa, Y., Sato, T., and Yamaguchi, J. (2017). *Arabidopsis* CBL-interacting protein kinases regulate carbon/nitrogen-nutrient response by phosphorylating ubiquitin ligase ATL31. *Mol. Plant* 10, 605–618. doi: 10.1016/j.molp.2017.01.005
- Yuan, T.-T., Xu, H.-H., Zhang, K.-X., Guo, T.-T., and Lu, Y.-T. (2014). Glucose inhibits root meristem growth via ABA INSENSITIVE 5, which represses PIN1 accumulation and auxin activity in *Arabidopsis*. *Plant Cell Environ.* 37, 1338–1350. doi: 10.1111/pce.12233
- Zhang, G. B., Meng, S., and Gong, J. M. (2018). The expected and unexpected roles of nitrate transporters in plant abiotic stress resistance and their regulation. *Int. J. Mol. Sci.* 19, 1–15. doi: 10.3390/ijms19113535
- Zhao, J., Cheng, N. H., Motes, C. M., Blancaflor, E. B., Moore, M., Gonzales, N., et al. (2008). AtCHX13 is a plasma membrane K⁺ transporter. *Plant Physiol.* 148, 796–807. doi: 10.1104/pp.108.124248
- Zhao, L.-N., Shen, L.-K., Zhang, W.-Z., Zhang, W., Wang, Y., and Wu, W.-H. (2013). Ca²⁺-dependent protein kinase11 and 24 modulate the activity of the inward rectifying K⁺ channels in *Arabidopsis* pollen tubes. *Plant Cell* 25, 649–661. doi: 10.1105/tpc.112.103184
- Zhao, L., Liu, F., Crawford, N. M., and Wang, Y. (2018a). Molecular regulation of nitrate responses in plants. *Int. J. Mol. Sci.* 19, e2039. doi: 10.3390/ijms19072039
- Zhao, L., Zhang, W., Yang, Y., Li, Z., Li, N., Qi, S., et al. (2018b). The *Arabidopsis* NLP7 gene regulates nitrate signaling via NRT1.1-dependent pathway in the presence of ammonium. *Sci. Rep.* 8, 1–13. doi: 10.1038/s41598-018-20038-4
- Zheng, X., He, K., Kleist, T., Chen, F., and Luan, S. (2015). Anion channel SLAH3 functions in nitrate-dependent alleviation of ammonium toxicity in *Arabidopsis*. *Plant Cell Environ.* 38, 474–486. doi: 10.1111/pce.12389
- Zheng, R. H., de Su, S., Xiao, H., and Tian, H. Q. (2019). Calcium: a critical factor in pollen germination and tube elongation. *Int. J. Mol. Sci.* 20, e420. doi: 10.3390/ijms20020420
- Zheng, Z.-L. (2009). Carbon and nitrogen nutrient balance signaling in plants. *Plant Signal. Behav.* 4, 584–591. doi: 10.4161/psb.4.7.8540
- Zhong, M., Li, S., Huang, F., Qiu, J., Zhang, J., Sheng, Z., et al. (2017). The phosphoproteomic response of rice seedlings to cadmium stress. *Int. J. Mol. Sci.* 18, e2055. doi: 10.3390/ijms18102055
- Zhou, L., Lan, W., Chen, B., Fang, W., and Luan, S. (2015). A calcium sensor-regulated protein kinase, CALCINEURIN B-LIKE PROTEIN-INTERACTING PROTEIN KINASE19, is required for pollen tube growth and polarity. *Plant Physiol.* 167, 1351–1360. doi: 10.1104/pp.114.256065
- Zhu, J. K. (2016). Abiotic stress signaling and responses in plants. *Cell* 167, 313–324. doi: 10.1016/j.cell.2016.08.029

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2020 Saito and Uozumi. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.