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DARWIN REVIEW

Life and death under salt stress: same players, different timing?

Ahmed Ismail[1,*], Shin Takeda[2] and Peter Nick[3]

[1] Department of Horticulture, Faculty of Agriculture, Damanhour University, Damanhour, Egypt
[2] Bioscience and Biotechnology Center, Nagoya University, Chikusa, Nagoya 464–8601, Japan
[3] Molecular Cell Biology, Botanical Institute, Karlsruhe Institute of Technology (KIT), Germany

* To whom correspondence should be addressed. E-mail: ahmed.ismail@damanhour.edu.eg

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Abstract

Salinity does not only stress plants but also challenges human life and the economy by posing severe constraints upon agriculture. To understand salt adaptation strategies of plants, it is central to extend agricultural production to salt-affected soils. Despite high impact and intensive research, it has been difficult to dissect the plant responses to salt stress and to define the decisive key factors for the outcome of salinity signalling. To connect the rapidly accumulating data from different systems, treatments, and organization levels (whole-plant, cellular, and molecular), and to identify the appropriate correlations among them, a clear conceptual framework is required. Similar to other stress responses, the molecular nature of the signals evoked after the onset of salt stress seems to be general, as with that observed in response to many other stimuli, and should not be considered to confer specificity *per se*. The focus of the current review is therefore on the temporal patterns of signals conveyed by molecules such as Ca^{2+}, H^+, reactive oxygen species, abscisic acid, and jasmonate. We propose that the outcome of the salinity response (adaptation versus cell death) depends on the timing with which these signals appear and disappear. In this context, the often-neglected non-selective cation channels are relevant. We also propose that constraining a given signal is as important as its induction, as it is the temporal competence of signalling (signal on demand) that confers specificity.

Key words: ABA, adaptaion, calcium, cell death, cross-talk, jasmonate, salinity, signal on demand, proton influx, ROS.

Salinity stress: conceptual and economic challenge

Because of their sessile nature, plants have to adapt in order to survive. This implies the ability to cope with numerous and different types of stress factors. Stress, as a concept, has been derived originally from physics, where it is defined as a relationship between inputs and outputs of a system (for instance, in the case of mechanical stress and strain). In biology, however, there seems to be a conceptual problem in defining 'stress' precisely; the term 'stress' has different meanings depending on the respective field of biology. Regardless of its definition, 'stress' represents a central issue in agriculture, and stress-dependent losses of crop yield are estimated to range between 65 and 87% (Buchanan *et al.*, 2002). Hunger and malnutrition still represent the primary health risk, exceeding the impact of AIDS, malaria, and tuberculosis, and leaving 1 billion people in the world without enough food to be healthy (FAO, 2011). This underlines the importance of plant stress for society. Salinity, in particular, has been a threat to agriculture in some areas in the world for more than 3000 years (Flowers, 2006); it affects more than 80 million ha of arable land worldwide (reviewed by Munns and Tester, 2008), with

Abbreviations: ABA, abscisic acid; bHLH, basic helix–loop–helix; CaM, calmodulin; CBL, calcineurin B-like; DA, depolarization-activated; HA, hyperpolarization-activated; JA, jasmonate; MAPK, mitogen-activated protein kinase; MeJA, methyl jasmonate; NSCC, non-selective cation channels; ROS, reactive oxygen species; SOS, salt overly sensitive; UPS, ubiquitin–26S proteasome system; VI, voltage-insensitive.

estimated annual global costs equivalent to US$11 000 million in 2011 (FAO, 2011). High salinity is commonly caused by high concentrations of sodium (Na^+) and chloride (Cl^-) ions in the soluble fraction of the soil resulting in both hyperionic and hyperosmotic conditions, which in turn impair the ability of plants to take up water and micronutrients. This not only leads to increased concentration of ions to levels that are toxic to plants but also causes degraded soil structure. Plants have acquired different adaptive mechanisms to control the negative impacts of salinity and are classified into two groups with respect to their adaptability to salinity: halophytes are efficient in adaptation and therefore are able to inhabit saline environments, whereas glycophytes cannot cope with saline soils and therefore are excluded from saline habitats (reviewed by Flowers *et al.*, 1977; Hasegawa *et al.*, 2000). In this review, we present and discuss recent advances in our understanding of the mechanisms by which plants respond and adapt to salt stress. In particular, we focus on the temporal pattern of signals that are crucial for adaptation and the role of these temporal patterns for the orchestration of cross-talks between signalling pathways. We propose that the correct timing of these cross-talks decides which salinity-triggered signalling will culminate in successful adaptation.

Salinity can trigger two qualitatively different modes of cellular response

Salinity can challenge plants to a degree that may even lead to cell death. Salt stress causes membrane disorganization, metabolic toxicity, formation of reactive oxygen species (ROS), inhibition of photosynthesis, and reduced nutrient acquisition (reviewed by Hasegawa *et al.*, 2000; Tuteja, 2007). When stress intensity reaches non-permissive levels, these processes can culminate in cell death. Growth responses to salinity are comprised of two phases (Munns, 1993). Rapid and often transient changes in growth occur within minutes and are attributed to the osmotic effects of salt ions in the rhizosphere. Hormonal signals originating from the roots are assumed to regulate the growth reduction during this phase. The second phase of growth reduction is the result of a salt-specific effect and needs some time (days, weeks, or months) to develop. This second phase is not a mere consequence of water stress alone (Munns, 2002). Cellular damage in this second phase is due to salt accumulation in transpiring leaves, leading to levels that exceed the ability of the cells to sequester salts into the vacuole (Munns, 2002; reviewed by Läuchli and Grattan, 2007; Munns, 1993, 2005). It should be kept in mind that the resulting cell death may be deleterious for the individual cell but adaptive for the plant as a whole, as plants can dump ions to toxic levels in their older leaves and then remove the salt by simple abscission (Munns and Tester, 2008). Although the ionic effects of salinity stress occur later than the osmotic effects, influx of Na^+ has been observed from very early time points after the onset of salt stress. For maize—an extreme glycophyte—Na^+ ions accumulate in chloroplasts within 4 h, even preceding any changes of water potential in the challenged leaves (De Costa *et al.*, 2007; Zörb *et al.*, 2009). As we will discuss in this review, this early influx of Na^+ might act as a signal to trigger salinity adaptation and thus would not be a mere manifestation of cellular toxicity leading to cell death. Na^+ might play a dual role: as an early signal triggering 'salinity signalling' (which can result in successful adaptation), and as a late noxious factor that, upon accumulation, will lead to cell death. It is thus possible to order the complex salinity-triggered events in terms of a two-mode model for the cellular response. As we will elaborate in the following section, the relationship between (adaptive) salt signalling and (destructive) salt accumulation depends on the timing of the events triggered by salinity stress.

Salinity signals: same inputs, different outputs

Conceptual framework: temporal signatures define response quality

Plants respond to salinity challenges at the level of both cells and the whole organism. It is important to identify factors responsible for the adaptability to stress and to understand the underlying mechanisms connecting these factors to cellular signalling pathways in order to improve plant growth and productivity under stressful conditions. However, to dissect the biological function of the individual stress signals is difficult; the events involved in stress adaptation overlap, at least partially, with those accompanying stress-dependent cellular damage. In addition, in the case of salinity stress, plants experience two stress qualities at a similar time: osmotic and ionic stresses. What determines the fate of a cell under salinity stress? How can virtually the same signalling molecules cause adaptation in one plant but trigger cell death in another? Below, we propose and elaborate a model where not the molecular nature of signals but also their temporal signatures define the cellular response to salinity. The level of explanation will be explicitly cellular; for the sake of scientific reduction we do not consider the systemic level, although it is evident that the cellular events described below are integrated into interactions of different tissues and organs (readers are referred to the comprehensive review by Munns and Tester, 2008).

The central idea of this model is that the two response modes (adaptation versus cell death) depend on the relative timing of two signal chains: one triggered by calcium and the other triggered by oxidative burst in the apoplast (Fig. 1). A delay in generation and dissipation of a salinity-triggered calcium-dependent signal relative to a signal conveyed by ROS will lead in the unconstrained activation of jasmonate (JA) signalling culminating in cell death. In contrast, the same molecular signal carrier (calcium) can, if properly timed, initiate adaptive processes such as sequestration and extrusion of sodium, and induce efficient constraint of JA signalling through the activation of abscisic acid (ABA) signalling.

In the following sections, we will consider, step by step, the details of the individual signalling events (Fig. 1). For each step, we will try to define: (i) by which events the signal is

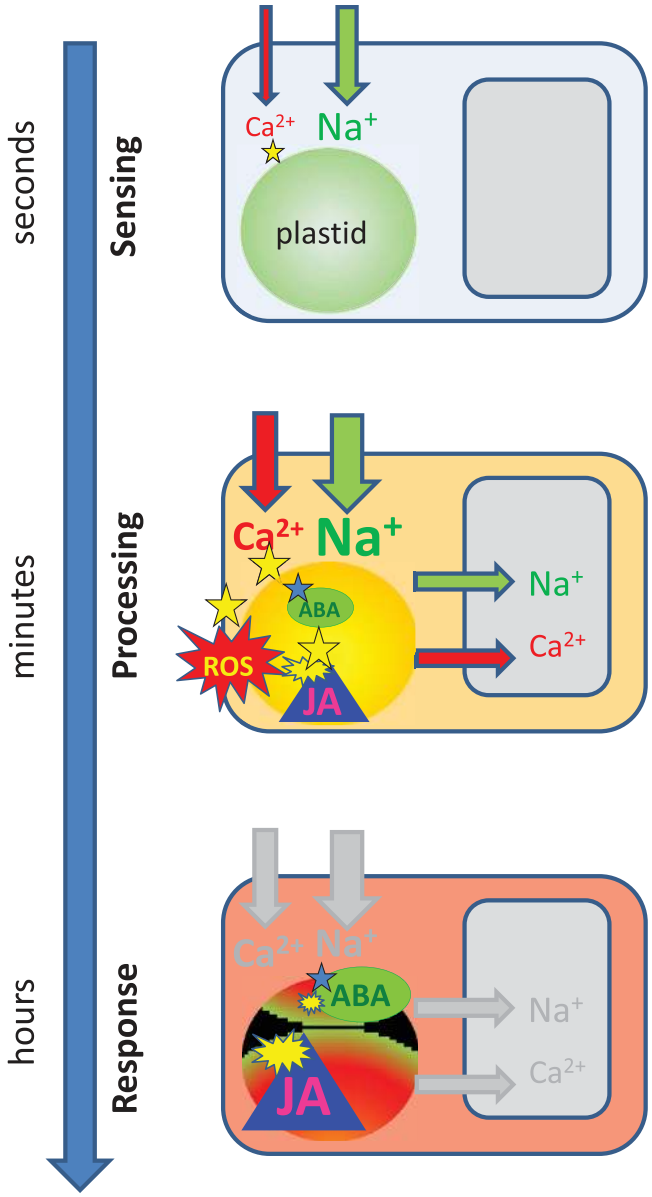

Fig. 1. Simplified model explaining how temporal shifts of stress signals can produce qualitatively different cellular responses to salinity stress. As input, influx of sodium (1), calcium (2), and reactive oxygen species (3) are visualized. The stars represent the signal generated by salinity-triggered calcium influx, while the explosion symbol is the signal generated by salinity-triggered oxidative burst. Note: these signals do not necessarily represent an individual type of molecule, but rather the *information* conveyed by the underlying molecular or cellular processes (the details of these processes are given in the text but not represented graphically). The different cellular outputs (adaptation versus cell death) are executed by relative differences in the status of jasmonate (JA) versus abscisic acid (ABA) signalling. This status depends on both differences in synthesis and the cellular responsiveness for the respective hormone. *Adaptation:* rapid influx of sodium and calcium will efficiently trigger extrusion (SOS1) and vacuolar sequestration (NHX1, CAX) of both ions. The rapid dissipation of the Ca^{2+} signal allows the ROS-triggered activation of the ABA status to escape Ca^{2+}-dependent inhibition by calcineurin B-like proteins and subsequently to constrain ROS-triggered activation of the JA status. *Necrosis:* slower influx of sodium and calcium results in sluggish activation of extrusion and sequestration, such that the Ca^{2+}-dependent signal will be recruited for calcineurin B-dependent inhibition of the ABA status, such that ROS-triggered activation of the JA status will overshoot, culminating in cell death. The central point of the model is that a delay in the timing of inputs 1 (sodium) and 2 (calcium) versus input 3 (ROS) will partition calcium-dependent signalling from processes leading to ion sequestration/extrusion towards processes constraining the ABA status, such that the parallel activation of the JA status will be released from ABA-dependent control. (This figure is available in colour at *JXB* online.)

generated (referred to as the 'on' state), (ii) by which events the signal is dissipated (referred to as the 'off' state), (iii) what is the appropriate target of the signal, and (iv) what is the inappropriate target of this signal in case of a delayed time signature.

Non-selective cation channels (NSCCs): the earliest players but often overlooked

Ions are selectively conducted through channels in the plasma-membrane channels depending on electrochemical potential. In plants, these ion fluxes are tightly controlled by the gating of these channels (reviewed by Yeo, 1998). However, in saline conditions, a rapid influx of Na^+ from the soluble phase of the soil into the cortical cytoplasm of plant roots occurs through NSCCs, and, later, through the high-affinity K^+ transporter (HKT1) (Essah *et al.*, 2003; reviewed by Tester and Davenport, 2003).

NSCCs have been classified according to their voltage dependence or to their responsiveness to certain ligands and physical stimuli, and their physiological roles under salinity have been described previously (reviewed by Demidchik and Maathuis, 2007; Kronzucker and Britto, 2011). Hyperpolarization-activated (HA)-NSCCs, which are activated later and weakly selective for monovalent cations (Davenport and Tester 2000; reviewed by Demidchik *et al.*, 2002), might be the predominant type of channel in plasma membranes of sensitive species. In contrast, more efficient NSCCs [depolarization-activated (DA)-NSCCs and voltage-insensitive (VI)-NSCCs] might take the lead in tolerant species. This idea was tested for cells of grapevine, where otherwise very similar pairs of species can be compared, such as the salt-tolerant *Vitis rupestris* and the salt-sensitive *Vitis riparia* (Ismail *et al.*, 2012). *Vitis rupestris* inhabits rocky, sunny slopes, and therefore has evolved a considerable osmotic tolerance. In contrast, *V. riparia* occurs in alluvial woods and performs poorly under osmotic stress. In the drought-sensitive *V. riparia*, sodium influx was observed to be slow, consistent with the hypothesis that HA-NSCCs might be the predominant type of channel (Ismail *et al.*, 2014). In contrast, the vigorous and rapid influx observed in *V. rupestris* indicates that the more efficient DA-NSCCs and/or VI-NSCCs are the major types of channel. Interestingly, the role of NSCCs and their kinetic activities not only determine the pattern of Na^+ influx but also modulate the cytoplasmic signatures of two crucial signalling elements, Ca^{2+} and H^+. In the sensitive *V. riparia*, gradual and low kinetics of Na^+ influx were observed, while in the tolerant *V. rupestris*, NSCCs catalysed a fast and strong Na^+ influx reaching its maximal amplitude after only 2 min (the first time point measured). This initial and rapid Na^+ uptake could serve as an

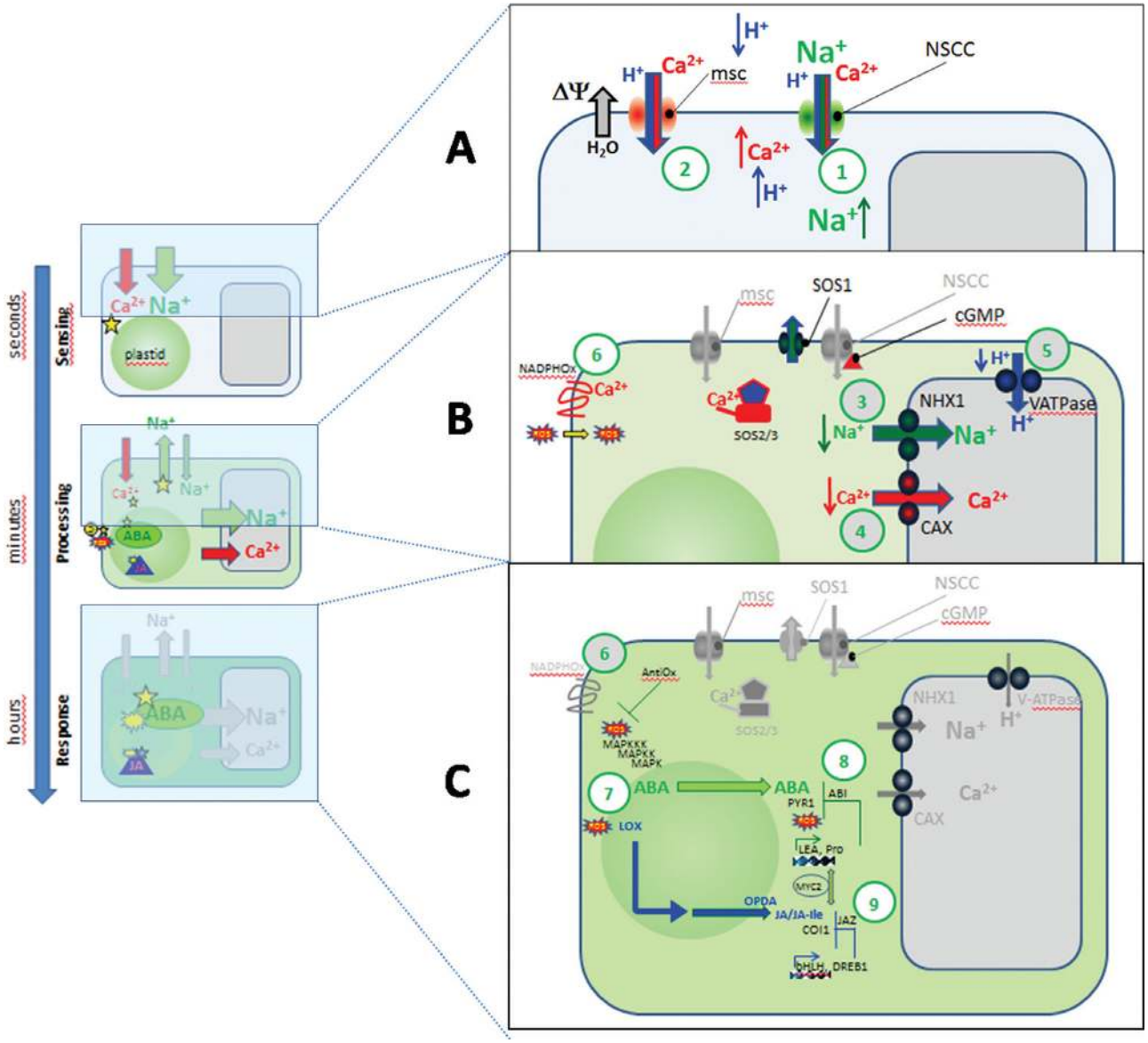

Fig. 2. Molecular working model for the cellular salinity response in case of adaptation. The numbers refer to explanations given in the section on 'Salinity signals'. (A) Sensing of the ionic component of salinity stress occurs through influx of sodium and calcium ions as well as protons through NCCSs (①), sensing of the osmotic component of salinity stress ($\Delta\Psi$ water potential difference) through influx of calcium ions and protons through mechanosensitive calcium channels (msc, ②). (B) Processing involves extrusion of cytoplasmic sodium through the exporter salt overly sensitive 1 (SOS1, ③) and sequestration into the vacuole through NHX1. Further entry of sodium is prevented by deactivation of NCCS through cyclic GMP from a turgor-sensitive cyclase. Calcium is sequestered into the vacuole through the CAX system (④), and protons through the V-ATPase (⑤). The signal carried by calcium is conveyed into activation of the salt overly sensitive 2 and 3 complex (activating SOS1, ③) and the NADPH oxidase (NADPHOx, ⑥) at the plasma membrane, leading to the generation of apoplastic ROS that can enter the cytoplasm through aquaporins. (C) The response involves activation of the MAPK pathway and ABA synthesis (⑦), upon perception of ABA by the receptor pyrabactin resistance 1 (PYR1), and ROS-dependent signalling leads to the activation of osmoprotective genes such as late embryogenesis abundant (LEA) or genes like P5CS1 involved in proline synthesis (PRO). Overshooting of the pathway is prevented by negative feedback through ABI (absicic acid insensitive) signalling factors (⑧). In parallel with ABA signalling, lipoxygenases in the plastid will launch the synthesis of OPDA, which is exported from the plastid and processed into JA and its bioactive isoleucine-conjugate (JA-Ile), leading to activation of the Coronatine-Insensitive 1 (COI1) receptor system culminating in protective gene expression (bHLH, DREB1). Activation of JA signalling remains transient through negative-feedback control through the JAZ/TIFY proteins (⑨). Moreover, the activated ABA pathway recruits MYC2, causing a correlative inhibition of JA signalling. (This figure is available in colour at *JXB* online.)

efficient signal to activate adaptation to the osmotic part of salinity (Fig. 2A, ① ; reviewed by Munns and Tester 2008). Furthermore, the elevated intra- and extracellular Na^+ are partially able to inhibit the K^+ outward rectifiers and thereby prevent the loss of cellular K^+, maintaining cellular K^+/Na^+ homeostasis (Shabala *et al.*, 2006). Thus, in the tolerant line, rapid influx of Na^+ by the more effective NSCCs has advantageous effects, at least during the first phase of the salt stress response. The slower influx in sensitive cells will be less efficient in adjusting the water potential such that cells will lose water (Fig. 3, ①). These differences in sodium content are very short lived and therefore their connection with differential responses at the later stages must be conveyed by signals of adifferent molecular nature.

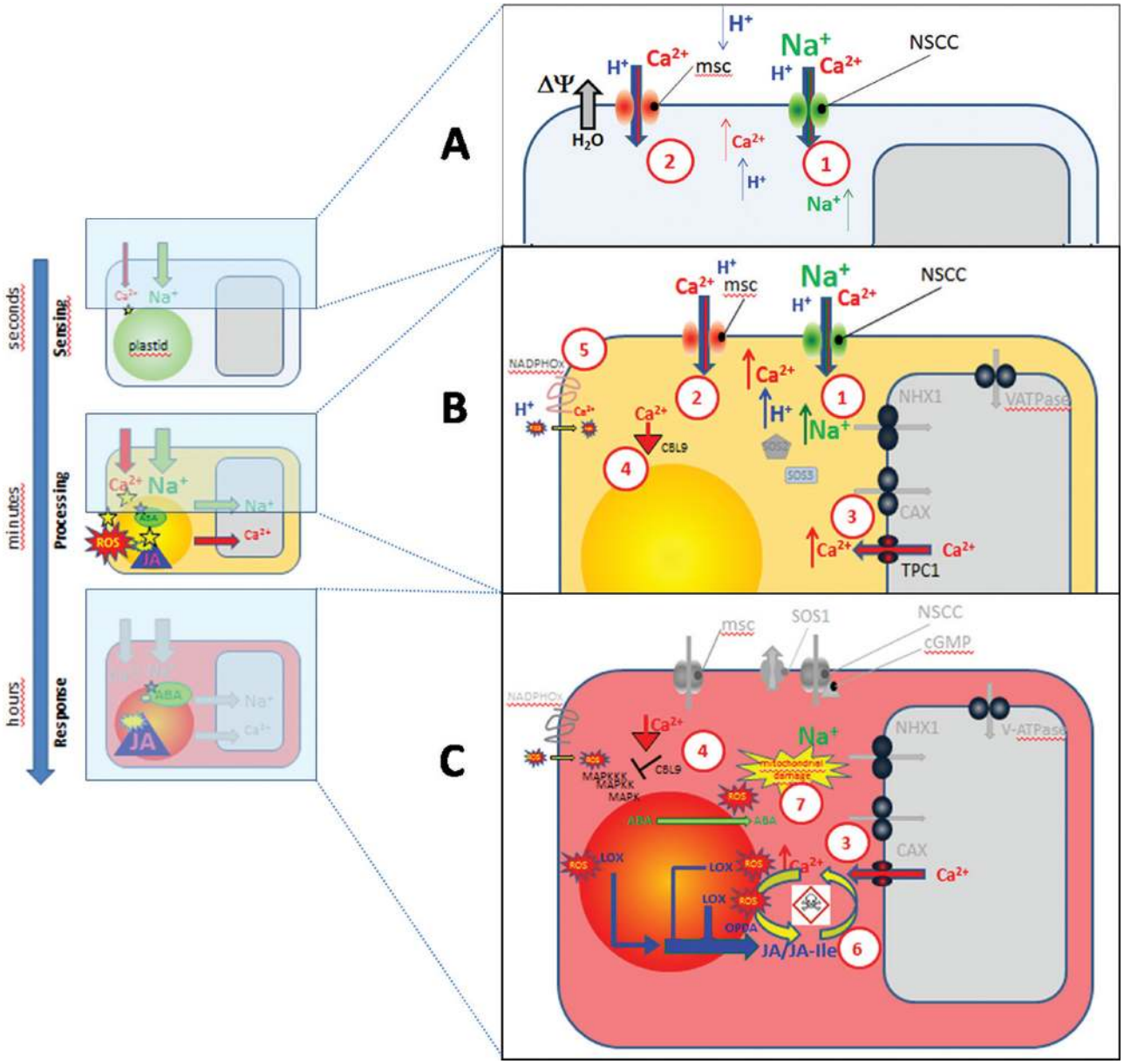

Fig. 3. Molecular working model for the cellular salinity response in case of cell death. The numbers refer to explanations given in the section on 'Salinity signals'. (A) Sensing through NCCS (①) and mechanosensitive calcium channels (msc, ②) is delayed. (B) Due to the sluggish influx of calcium, the SOS2/3 sensor is not activated, such that the CAX and NHX1 sequestration machinery remains silent. The accumulation of calcium in the cytoplasm is further accentuated by activation of the vacuolar TPC1 calcium exporter (③). As the calcium cannot dissipate into activation of the SOS pathway, it is bound by calcineurin B-like proteins (CBL), which will also interfere with the activation of the NADPH oxidase (⑤). Moreover, more apoplastic ROS species are quenched by protons due to the sluggish activation of the NCCS (①) and msc (②). (C) CBL will negatively interfere with the ABA pathway (④), whereas the sustained presence of sodium in the cytoplasm will cause unspecific membrane damage on mitochondria and plastids generating uncontrolled oxidative burst (⑦). This will activate lipoxygenases and generate excessive JA/JA-Ile. Due to the impaired ABA status, the JA pathway will proceed out of control, initiating a deathly cycle of further membrane damage, excessive oxidative burst, and JA synthesis (⑥). (This figure is available in colour at *JXB* online.)

Cells cannot tolerate the harmful effects of Na^+ accumulation in the cytoplasm due to impaired enzyme activities and cytotoxicity (ion-specific effects). To circumvent such toxicity, cells exclude Na^+ from the cytosol and/or sequester sodium inside the vacuole. To block additional influx of sodium, VI-NSCCs are rapidly deactivated by cAMP or cGMP proposed to be generated by turgor-sensitive membrane-located cyclases (Fig. 2B, ③), which results in improved plant salinity tolerance (Maathuis and Sanders, 2001). A second route of entry is the high-affinity K^+ transporter HKT1. However, this sodium entry is later and does not contribute to protective signalling. Conversely, in the *Arabidopsis* mutants *hkt1-1* and *hkt1-2*, Na^+ entry was suppressed to some extent, but these mutants were found to be endowed with enhanced salinity tolerance (Rus *et al.*, 2001; reviewed by Schroeder *et al.*, 2013).

To arrest further influx of sodium is not sufficient, however; ions have to be removed from the cytoplasm. The roles of the salt overly sensitive (SOS) pathway in expelling Na^+ out of the cell or caging it inside the vacuole via an SOS/NHX interaction (Fig. 2B, ③) seems to be the central mechanism

for Na^+ exclusion (reviewed by Ji *et al.*, 2013), although the role of the SOS pathway for plant salt tolerance has been discussed controversially, as reviewed by Kronzucker and Britto (2011). It has been questioned whether extrusion of sodium through the plasma membrane by the SOS1 exporter represents an effective strategy, as Na^+ ions will re-enter the cell though the NSCCs (if these were not deactivated by cAMP/cGMP) and HKT1 channels, respectively, and the accumulation of sodium in the apoplast would generate a more negative water potential such that the cell would lose additional water (reviewed by Shavrukov, 2013). A further caveat was found when the role of SOS1 in stress tolerance was examined at a whole-plant level: In *Arabidopsis thaliana*, SOS1 is expressed preferentially in the rhizodermis near to the root tip, i.e. in cells that are still weakly vacuolated, and in xylem parenchyma cells, from which Na^+ is uploaded to xylem vessels for long-distance transport from the root to the shoot (Shi *et al.*, 2002; reviewed by Munns and Tester, 2008). Mutants impaired in the expression of *sos1* in both *Arabidopsis* (Shi *et al.*, 2002) and tomato (Olías *et al.*, 2009) accumulate more sodium in the shoots under salinity stress. Therefore, Na^+ exclusion by SOS1 seems to be important as a mechanism by which cells get rid of excess Na^+. However, if not accompanied by other adaptive responses, mere enhancement of SOS1 activity (e.g. by overexpression) may not be sufficient to improve salt tolerance (Oh *et al.*, 2010; reviewed by Kronzucker and Britto, 2011;,Ji *et al.*, 2013). As will be given in detail in the section on 'Ca^{2+} ions', SOS1 is activated via a calcium-dependent pathway. Simultaneously, the very long cytoplasmic tail of this transporter has been proposed to sense Na^+ directly (reviewed by Zhu, 2002).

However, the SOS system integrates a second strategy for sodium dissipation: sequestration into the vacuole. As will be outlined in more detail in the following section on calcium, SOS2 and -3 will activate the NHX1 transporter that pumping sodium from the cytoplasm into the vacuole (Fig. 2B, ③). Compared with sodium extrusion, this strategy is efficient in removing noxious sodium from the cytoplasm but at the same time lowers the water potential of the entire protoplast, such that additional water loss to the environment is prevented, and not only the ionic but also the osmotic component of salinity stress is encountered. It should be mentioned that NHX1 is not the only transporter able to sequester sodium into the vacuole. The tonoplast harbours slow-activating and fast-activating channels that can facilitate sodium uptake to the vacuole and improve salinity tolerance in leaves of quinoa (Bonales-Alatorre *et al.*, 2013). In the case of a non-tolerant cell, the SOS system is activated in only a sluggish manner (the reason is linked to the reduced activity of NSCCs, as will be pointed out in the subsequent section) such that sodium will remain in the cytoplasm and accumulate there (Fig. 3B) to toxic levels.

To summarize the main points on sodium as a salinity signal are:

1. The 'on' state is generated by the rapid influx of sodium (along with calcium ions and protons) through DA-NSCCs and/or VI-NSCCs (Fig. 2A, ①). This rapid sodium/calcium peak represents the first signal that allows the discrimination of salinity stress from mere osmotic stress (e.g. as a consequence of drought), i.e. here is the point where the ionic component in salinity signalling bifurcates from osmotic signalling. In parallel, the osmotic challenge will result in activation of mechanosensitive calcium channels yielding additional influx of calcium ions and protons (Fig. 2A, ②).
2. The rapid elevation in the cytoplasmic concentration of sodium/calcium activates a signalling (which is explained in detail in the subsequent sections) that will initiate a rapid dissipation of the sodium signal (Fig. 2B, ③): to achieve the 'off' state, on the one hand, additional influx of sodium ions is prevented by deactivation of the NCCS through cAMP/cGMP-dependent signals (Fig. 2B, ③), as well as deactivation of the slower HKAT channel. On the other hand, sodium ions are removed from the cytoplasm either by extrusion (SOS1), or by sequestration into the vacuole (SOS2/3 and NHX1).
3. The appropriate target for the sodium signal is actually the concomitant influx of calcium (Fig. 2A, ②), which will carry on signalling even after the sodium signal has been dissipated by the mechanisms given in (2).
4. In the case of a delayed sodium/calcium influx through the HA-NCCS (Fig. 3A, ①), activation of the SOS system as well as the block of sustained sodium influx will not be efficient. This not only results in accumulation of cytoplasmic sodium to toxic levels (Fig. 3B), but will also lead to sustained accumulation of calcium that, as pointed out in the subsequent section, will go astray and channel towards overactivation of the JA pathway.

Ca^{2+} ions: promiscuous but choosy

Calcium ions (Ca^{2+}) are considered the most prominent ubiquitous second messenger in cells ranging from bacteria and plants up to specialized neurons (reviewed by Clapham, 1995). The normal cytoplasmic Ca^{2+} (Ca^{2+}_{cyt}) level is ~100–200 nM, while in membrane-enclosed organelles it is ~1–2 mM (reviewed by White, 2000). Ca^{2+}_{cyt} signals are shaped by influx or efflux of ions from the extracellular space (cell wall or apoplast in plants) through a couple of different channels in the plasma membrane, some of which seem to be mechanosensitive, whereas others are voltage gated and might be identical to the NCCS (for a recent review, see Swarbreck *et al.*, 2013). Different channels are localized at the surface of intracellular compartments (such as vacuoles, chloroplasts, or mitochondria). Slow vacuolar channels, such as TPC1, are targets of different signalling molecules including Ca^{2+}, calmodulin (CaM), and nucleotides, and play a crucial role in raising cytosolic Ca^{2+} under a wide range of environmental and developmental cues (Pottosin *et al.*, 2009; reviewed by Hedrich and Martena, 2011; Peiter, 2011). The spatial pattern of Ca^{2+} signals (e.g. cytosol, nucleus, organelles, or other specific regions of the cell), the temporal propagation of Ca^{2+} levels, the amplitude of the signal, and the frequency of Ca^{2+} oscillations are all informative aspects of Ca^{2+} signals, which are perceived by adaptor proteins or Ca^{2+}-modulated

proteins that regulate downstream signalling events (reviewed by Bouché *et al.*, 2005; Kudla *et al.*, 2010). Interestingly, Ca^{2+} signals participate in virtually all developmental, hormonal, and stress cues (reviewed by Reddy *et al.*, 2011). The apparent ambiguity of this signal is even amplified by the fact that nitric oxide (NO), a small, uncharged, short-lived, water- and lipid-soluble, highly diffusible, ubiquitous, volatile, highly reactive free radical, can act as a Ca^{2+}-mobilizing messenger (reviewed by Neill *et al.*, 2003; Besson-Bard *et al.*, 2008; Siddiqui *et al.*, 2011).

Under salinity, the earliest cellular response seems to be a rapid increase in free cytosolic Ca^{2+} within 1–5 s via influx through either NSCCs or a mechanosensitive calcium channel in the plasma membrane, which can be amplified through release from internal stores, especially the vacuole (Knight *et al.*, 1997; Donaldson *et al.*, 2004). NaCl-induced cytosolic Ca^{2+}, in turn, activates the plasma-membrane ATPases mediated by Ca^{2+}/CaM-dependent protein kinases, restoring membrane voltage after Na^+-induced depolarization, maintaining membrane integrity and ionic homeostasis, promoting H^+ influx, and inhibiting both K^+ and H^+ efflux (Klobus and Janicka-Russak, 2004; Shabala *et al.*, 2006; reviewed by Wolf *et al.*, 2012). Moreover, cytosolic Ca^{2+} activates salt overly sensitive 3 (SOS3), a member of the calcineurin B-like (CBL) family known as CBL4, to interact with SOS2 (a CBL-interacting protein kinase, CIPK24). The SOS3/SOS2 complex, in turn, activates SOS1 (a plasma-membrane Na^+/H^+ antiporter) through its phosphorylation (Fig. 2B, ③). The activated SOS1 extrudes Na^+ from the cell, thus reducing its harmful effects on cellular metabolism (reviewed by Zhu, 2002; Harper *et al.*, 2004; Munns and Tester, 2008). SOS1 directly signals to a putative K^+ transporter by-passing SOS2 and SOS3 and therefore was proposed to be necessary for safeguarding the K^+ permeability of the plasma membrane during salinity stress (Qi and Spalding, 2004; Shabala *et al.*, 2005). In addition, the Na^+/H^+ exchanger (NHX) class of transporters (Fig. 2B, ③)—the plant homologue of the yeast Na^+/H^+ exchanger (Apse *et al.*, 1999; Gaxiola *et al.*, 1999) that catalyses the electroneutral exchange of Na^+ or K^+ with H^+, maintaining intracellular pH and Na^+ and K^+ homeostasis in all eukaryotes (reviewed by Martinoia *et al.*, 2012)—is interconnected to Ca^{2+} signals via SOS/NHX interaction (Qiu *et al.*, 2004). To date, six members of the NHX gene family have been identified in *A. thaliana* and classified according to their intracellular localization into vacuolar (NHX1–4) and endosomal (NHX5 and -6) compartments (Bassil *et al.*, 2011). The generation of salt-resistant tomato by overexpression of NHX1 was considered one of the milestones of green genetic engineering (Zhang and Blumwald, 2001). Despite a long history of biotechnological application, the actual reason for salinity tolerance conferred by NHX1 is still under debate. Overexpression of *Arabidopsis* NHX1 or tomato NHX2 in tomato did not yield a consistent elevation of vacuolar Na^+ (Rodriguez-Rosales *et al.*, 2008; Leidi *et al.*, 2010) and the protective effect was attributed to improved potassium partitioning to the vacuole. On the other hand, the *Arabidopsis* double mutant *nhx1 nhx2* showed a similar salinity sensitivity to the wild type but a reduced vacuolar pool of K^+ at simultaneously elevated sequestration of Na^+.

Additionally to steering the SOS pathway, calcium can activate gene expression. For instance, the CaM-binding transcription activators CAMTA1–4, and CAMTA6 are all salt induced (Yang and Poovaiah, 2002). In addition, a specific CaM isoform in soybean (GmCaM4) interacts directly with a MYB2 transcription factor, enhancing the transcription rate of MYB2-dependent genes, such as *P5CS1*, conferring salt adaptation to *Arabidopsis* overexpressing GmCaM4 (Yoo *et al.*, 2005). However, calcium ions can also act directly without the need for a protein adaptor: the *Arabidopsis* salt stress-responsive gene 1 (*AtNIG1*), a basic helix–loop–helix (bHLH)-type transcription factor, is the first known Ca^{2+}-binding transcription factor involved in the plant response to salt stress (Kim and Kim, 2006). Interestingly, Ca^{2+} can also stimulate the NADPH oxidase (Fig. 2B, ⑥), a primary source of stress-related oxidative burst in plants, and thus generates a further important stress signal (Dubiella *et al.*, 2013).

Similar to sodium, the protective function of calcium signalling can turn deleterious when cytosolic calcium levels remain high over a longer period. Under these circumstances, Ca^{2+} can activate degradative processes or cell death by precipitating phosphate (depleting, among others, ATP as 'cellular currency'), cause aggregation of proteins and nucleic acids, and impair the integrity of lipid membranes (reviewed by Clapham, 1995; Case *et al.*, 2007). For example, ROS-activated sustained Ca^{2+} influx (feedback stimulated by threshold levels of H_2O_2) was followed by programmed cell death in soybean (Levine *et al.*, 1996). Therefore, plants have adopted different strategies to restore Ca^{2+}_{cyt} levels after the completion of Ca^{2+} signalling, and the balance between reactions that cause elevated Ca^{2+}_{cyt} ('on' reaction) and reactions through which the Ca^{2+} signal is damped by buffering, pumping, and exchanging machineries ('off' reactions) determines the intracellular Ca^{2+} levels at any time point (reviewed by Berridge *et al.*, 2003; Bouché *et al.*, 2005; Clapham, 2007; Bose *et al.*, 2011). The central plant vacuoles (equivalent to lysosomes of animal cells with regard to their degradation and autophagy functions) represent the major Ca^{2+} store in a mature plant cell. High-capacity vacuolar Ca^{2+} exchangers (CAXs) play crucial roles in ion homeostasis and signal transduction (Hirschi, 2001). In the resting state, these CAX pumps are complemented by auto inhibited Ca^{2+}-ATPase pumps of the P_{IIB}-type. However, upon Ca^{2+}_{cyt} elevation, Ca^{2+}/CaM will bind to the N-terminal autoinhibitory domain, releasing them from autoinhibition and restoring Ca^{2+}_{cyt} by a feedback regulation (Fig. 2B, ④) that is an energy-consumptive process (reviewed by Pittman, 2011). In *A. thaliana*, there are six members of CAX (CAX1–6) that seem to function specifically with regard to different cues. For instance, the *cax1* mutant displayed enhanced freezing tolerance, while *cax3* resulted in higher salinity sensitivity (Catalá *et al.*, 2003; Zhao *et al.*, 2008; reviewed by Bose *et al.*, 2011). Interestingly, CAX1 is also interconnected to the SOS pathway and activated via SOS2, restoring Na^+/Ca^{2+} homeostasis, whereas elevated expression of deregulated CAX1 caused salinity sensitivity (Cheng *et al.*, 2004).

Failure to dissipate a cytosolic calcium signal in a timely fashion will strongly interfere with the signalling status of important stress hormones such as JA and ABA (Fig. 3C). Details on the function of these hormones are given in the sections below—however, here their regulation by calcium is considered. Calcium released from the vacuole through the TPC1 channel can activate JA synthesis (Fig. 3B, ③; Bonaventure *et al.*, 2007), whereas CBL proteins impede both the synthesis and the signal transduction of ABA (Fig. 3C, ④; Pandey *et al.*, 2004).

To summarize the main points on calcium as a salinity signal are:

1. The 'on' state is generated by the rapid influx of calcium through different channels, probably including the NCCS carrying sodium ions (Fig. 2A, ①), and a mechanosensitive calcium channel triggered by membrane load caused by osmotic water loss (Fig. 2A, ②).
2. The 'off' state is restored by rapid dissipation of calcium by either binding to SOS3 (Fig. 2B, ③) or by sequestration by the CAX transporters that are controlled through SOS2, which means that calcium activates its own removal from the cytoplasm (Fig. 2B, ④).
3. The appropriate target for the calcium signal is on the one hand the SOS system driving the elimination of sodium ions from the cytoplasm (Fig. 2B, ③), and the CAX transporters (Fig. 2B, ④) that will contribute to the shut-off of the calcium signal. Calcium-triggered activation of the NADPH oxidase will relay the signal to the next player, apoplastic ROS (Fig. 2B, ⑥).
4. In case of a delayed sodium/calcium influx (Fig. 3A, ①), activation of the SOS system as well as the block of sustained sodium influx will not be efficient. As a result, the sequestration of calcium into the vacuole will be slowed down, and the calcium signal is conveyed to other calcium-adaptor proteins, such as CBL9 (Fig. 3B, ④). This will impede the ABA 'status' as a dynamic product of synthesis and signalling (Fig. 3C, ④).This situation might even become accentuated by sustained calcium released from the vacuole through the slowly activated TPC1 channels (Fig. 3B, ③).

Proton influx: a signal enhancer?

Protons (H^+) play crucial roles for cell signalling either directly or in cross-talk with phytohormones or Ca^{2+} (Gao *et al.*, 2004a). In addition, protons directly regulate enzymatic conformations and thus metabolic activities (Roberts *et al.*, 1980). However, intracellular pH can also act as a second messenger for several signalling pathways. For instance, a cytoplasmic alkalinization is able to convey methyl-JA (MeJA) and ABA signalling during stomatal closure of *A. thaliana* (Suhita *et al.*, 2004), and is also involved in plant responses to salinity and drought stresses, indole-3-acetic acid, and gravity (Gao *et al.*, 2004a; Fasano *et al.*, 2001; reviewed by Kurkdjian and Guern, 1989). Proton influx can occur concomitantly with calcium, and the resulting apoplastic alkalinization has been used extensively as a robust reporter for the rapid activation of calcium influx channels by elicitors (Felix *et al.*, 1993, 1999) or abiotic stresses including salinity stress (Ismail *et al.*, 2012, 2014; Geilfuß and Mühling, 2013). With respect to the downstream signals, it should be noted that pH controls the ratio between the active and the inactive enantiomer of the bioactive JA conjugate JA-Ile (Fonseca *et al.*, 2009).

A comparison of two *Vitis* cell lines differing in salt tolerance (see 'Conceptual framework' section) showed that efficient adaptation in *V. rupestris* correlated with a more rapid and more persistent apoplastic alkalinization compared with the salt-susceptible *V. riparia* (Ismail *et al.*, 2014). Apoplastic alkalinization, in turn, might promote adaptive events such as activation of wall-consolidating enzymes such as pectin methyl esterase, or, on the other hand, inhibition of expansins that render the wall softer (reviewed by Wolf *et al.*, 2012). It should also be considered that depletion of protons in the apoplast will release anionic binding sites to complex sodium ions. In addition, the elevated steady-state level of apoplastic superoxide as a further relevant signal (see following section) will be enhanced if the level of protons is low. Furthermore, stress-induced pH changes in the xylem sap might act as a root signal through ABA anions that redistribute and accumulate due to the low membrane-permeability of the charged anion, promoting stomatal closure (Taiz and Zeiger, 2010).

The impact of proton activity on the enzymes or other proteins in the cytoplasm is very critical, where Ca^{2+}-induced H^+ influx might feedback on Ca^{2+} signalling by affecting Ca^{2+} affinity for CaM (reviewed by Busa and Nuccitelli, 1984). Moreover, the activities of the important transporters NHX1, CAX1, and CAX2 are inhibited by cytosolic protons (Pittman *et al.*, 2005; reviewed by Padan *et al.*, 2001). Thus, the influx of protons would promote the temporary accumulation of the concomitant calcium and sodium signals. However, this fluctuation of cytoplasmic pH will remain transient, because protons are rapidly extruded by powerful proton ATPases at the plasma membrane and especially the V-ATPase at the tonoplast (Fig. 2B, ⑤), and at the same time are complexed by the high buffering capacity of the cytosol (reviewed by Kurkdjian and Guern, 1989).

In summary, although proton influx does not act as an independent signal, it can act as an enhancer of early sodium and calcium signals:

1. The 'on' state is generated by influx together with calcium through the NSCC (Fig. 2A, ①) and the mechanosensitive calcium channels (Fig. 2A, ②).
2. The 'off' state is restored by rapid buffering of protons in the cytosol and active extrusion through the proton ATPases at the plasma membrane, and, most importantly, by vacuolar sequestering by the V-ATPase (Fig. 2B, ⑤).
3. The appropriate target is the inhibition of NHX1 and CAX activities acting as an amplifier of the initial sodium and calcium signal (Fig. 2B, ③, ④). At the same time, the depletion of protons from the apoplast will increase the lifetime of ROS (Fig. 2B, ⑥), and improve the matrix buffering for sodium ions.
4. In the case of a delayed sodium/calcium influx (Fig. 3A, ①), apoplastic protons will be available for quenching

ROS, thus dampening a further important signal (Fig. 3B, ⑤). In the cytosol, the initial sodium/calcium signal would not be enhanced, and later acidification might even interfere negatively with hormonal signalling.

ROS: bifunctional in the response to salinity stress

ROS are continuously produced in plant compartments such as mitochondria, chloroplasts, and peroxisomes as unavoidable by-products of aerobic metabolism such as photosynthesis, photorespiration, and respiration (reviewed by Abogadallah, 2010; Apel and Hirt, 2004). As aerobic metabolism is based on electron flow across membranes, even mild damage of mitochondrial or plastidic membranes will result in uncontrolled intracellular oxidative burst (Fig. 3C, ⑦).The term ROS comprises both free radical ($O_2^{\bullet-}$, superoxide radicals; $OH^{\bullet}$, hydroxyl radical; $HO_2^{\bullet}$, perhydroxy radical; and $RO^{\bullet}$, alkoxy radical), and non-radical (molecular) forms (H_2O_2, hydrogen peroxide; and $^1O_2$, singlet oxygen) (reviewed by Gill and Tuteja, 2010). The different ROS vary not only in their chemical nature but also in their toxicity. The superoxide $O_2^{\bullet-}$ is considered the earliest ROS, while $OH^{\bullet}$ is among the most highly reactive ROS known. The accumulation of ROS causes oxidative damage to DNA, proteins, carbohydrates, and lipids. However, they also could function as signalling molecules regulating responses of development and various aspects of stress. Therefore, they must be closely regulated by orchestrated mechanisms (reviewed by Miller *et al.*, 2010). For different stimuli, the elevated levels of ROS are sensed at the plasma membrane, for instance by two-component signalling systems (membrane-localized histidine kinases) that, in turn, activate the mitogen-activated protein kinase (MAPK) signalling cascades. Under salinity challenge, different MAPK elements are activated such as MAPK4, MAPK6, and MAPKK1 (reviewed by Taj *et al.*, 2010). *Arabidopsis* overexpressors for AtMAPKK2 exhibited constitutive MAPK4 and MAPK6 activity, constitutively unregulated expression of stress-induced marker genes, and increased freezing and salt tolerance. Transcriptomic analysis of this mutant showed altered expression of 152 genes involved in transcriptional regulation [such as *STZ* (slt tolerance zinc finger protein), *WRKY* and *MYB*], signal transduction (such as a MAPKK5-related protein and a putative calmodulin), cellular defence (such as lipoxygenase and the ACC synthase *AtACS-6*), and stress metabolism (including a flavonol synthase and *P5CS*, a gene encoding a key enzyme of proline biosynthesis) (Teige *et al.*, 2004). Although MAPK4 regulates the cross-talk between SA and JA, supporting the JA/ethylene signalling pathway (Brodersen *et al.*, 2006), growth assays and northern blot analysis of transcripts did not detect differences between the *mpk4 Arabidopsis* mutant compared with the wild type under salinity, cold, or heat shock, although differences were noted for pathogen challenge (Petersen *et al.*, 2000), indicating that, in the context of abiotic stress, the alternative MKK2/MAPK6 cascade is relevant. However, MAPK signalling can also act as an antagonist for abiotic stress signalling—for instance, AtMAPK1 negatively regulates a putative Na^+/H^+ antiporter, leading to salinity sensitivity (reviewed by Chinnusamy *et al.*, 2006). In addition to the MAPK pathways, ROS can modulate gene expression by modifying transcription factors (reviewed by Apel and Hirt, 2004). A third mechanism is the reversible oxidation of critical thiols in key signalling enzymes (reviewed by Forman and Torres, 2002).

However, ROS production needs to be tightly controlled to act as a signal, otherwise an excessive oxidative burst would result in cell death. In fact, ROS are a hallmark of plant-specific forms of programmed cell death, so called necroptosis (reviewed by Coll *et al.*, 2011). Interestingly, animals and plants share common apoptosis signal transduction pathways triggered by oxidative stress, where H_2O_2-induced lipoxygenase activities that are able to introduce molecular oxygen into the fatty acid moieties of phospholipids lead to increasing mitochondrial membrane lipid peroxidation and, subsequently, cytochrome *c* release (reviewed by Maccarrone *et al.*, 2001). Singlet oxygen, on the other hand, is used as a substrate of lipoxygenases triggering a metabolic pathway that will generate a further important stress signal, JA (Fig. 3C, ⑥; Farmer and Mueller, 2013). Also, ABA synthesis is activated by ROS (Xiong and Zhu, 2003). Salinity- or drought-stressed plants close their tomata, which in turn limits water loss (favourable effect) and the influx of CO_2 (unfavourable effect) (Hsu and Kao, 2003). Consequently, carbon reduction and photosynthetic NADPH consumption by the Calvin cycle decrease, resulting in electron leakage from photosystem I to O_2 as an alternative electron acceptor, initiating the Mehler reaction (reviewed by Türkan and Demiral, 2009). The resultant $O_2^{\bullet-}$ is considered the earliest ROS that consequently gives rise to other ROS, including the most noxious $OH^{\bullet}$. Additionally, the peroxisomal glycolate oxidase during photorespiration, plasma-membrane located NADPH oxidases, amine oxidases, and cell-wall-bound peroxidases are important sources of ROS that are active to a certain extent even under normal conditions but are activated in response to stress (reviewed by Mittler, 2002). Plants must strictly maintain ROS homeostasis to mitigate the toxicity of ROS. Therefore, plants have employed different scavenging machineries that tightly control ROS levels, both enzymatic and non-enzymatic. Plant enzymatic antioxidant mechanisms include superoxide dismutase (SOD), catalase (CAT), ascorbate peroxidase (APX), glutathione reductase (GR), monodehydroascorbate reductase (MDHAR), dehydroascorbate reductase (DHAR), glutathione peroxidase (GPX), guaicol peroxidase (GOPX), and glutathione *S*-transferase (GST). The metalloenzyme SOD is the most effective intracellular enzymatic antioxidant and acts by dismutating superoxide to H_2O_2, which in turn can be detoxified by APX, GPX, and CAT. The non-enzymatic antioxidants comprise ascorbic acid (ASH), glutathione (GSH), phenolic compounds, alkaloids, non-proteinogenic amino acids, and α-tocopherols (reviewed by Apel and Hirt, 2004; Gill and Tuteja, 2010).

The quelling of ROS accumulation can also be achieved by other signals, such as NO. NO has the ability to neutralize Fenton-type oxidative damage by scavenging superoxide, therefore preventing the formation of oxidants (such as $O_2^{\bullet-}$, H_2O_2, and alkyl peroxides), which makes it easier to recover

a redox homeostasis (Lamattina *et al.*, 2003). For example, pre-treatment with 1 mM sodium nitroprusside, a NO donor, results in enhancement of the antioxidant defence and methylglyoxal detoxification systems in salt-stressed wheat seedlings (Hasanuzzaman *et al.*, 2011). In addition, NO is considered a redox regulator of the NPR1/TGA1 system, a key redox-controlled regulators in plant systemic acquired resistance in plants (Lindermayr *et al.*, 2010). As an additional regulator, hydrogen sulfide (H_2S) has emerged as a signalling molecule in plants that increases GSH levels, alters enzyme activities, and interacts with NO and ROS metabolism (reviewed by Paul and Snyder, 2012; Lisjak *et al.*, 2013). As NO is acting as a secondary messenger of ABA signalling (reviewed by Hancock *et al.*, 2011), this molecule provides cross-talk between oxidative and phytohormonal signalling. This cross-talk is even bilayered, because also ROS deriving from the activity of the NADPH oxidase in the plasma membrane are essential for ABA induced signalling (Kwak *et al.*, 2003).

As with most stress signals, ROS are ambiguous, switching between activation of adaptive events and causing oxidative damage. Again, it depends on timing and regulation as to whether they act as a 'signal on demand' or go wild as cellular terminators:

1. The 'on' state is generated by metabolic disbalance of oxidative processes such as respiration or photosynthesis, but in the context of signalling, calcium-triggered activation of the membrane-bound NADPH oxidase seems to be central(Fig. 2, ⑥). The elevated steady-state level of the resulting apoplastic ROS is increased due to the apoplastic depletion of protons, such that these ROS can enter the cytoplasm, probably through aquaporins.
2. The 'off' state is on the one hand provided by enzymatic and non-enzymatic antioxidants (Fig. 2C, ⑥), and on the other by dissipation into stress signalling (e.g. MAPK cascades) and activation of phytohormone synthesis.
3. The appropriate targets are signal cascades such as the MAPK pathway leading to the activation of adaptive genes but also the activation of JA and ABA synthesis (Fig. 2C, ⑦).
4. In the case where ROS accumulate at later stages (Fig. 3B, ⑤), or are formed as a consequence of mitochondrial damage (Fig. 3C, ⑦) this will result not only in a pertinent hyperactivation of JA synthesis due to excessive lipid peroxidation but also in autocatalytic oxidative burst (Fig. 3C, ⑥), as the membrane damage will impair the functionality of electron transport in both mitochondria and plastids.

ABA: commitment for adaptive responses?

The phytohormone ABA, synthesized via the terpenoid pathway, regulates numerous plant biological processes ranging from development, including the inhibition of growth/germination and bud dormancy, to adaptive stress responses, such as drought, salt, ozone, and pathogen infection, and therefore is seen as a stress-related hormone (reviewed by Xiong and Zhu, 2003). The perception and signalling pathways of ABA have been studied extensively in *A. thaliana* and other species using biochemical and molecular genetic approaches (Ishibashi *et al.*, 2012; reviewed by Cutler *et al.*, 2010; Raghavendra *et al.*, 2010). In 2009, the long search for the ABA receptor succeeded with the identification of pyrabactin resistance 1 (PYR1), a member of the PYR/PYR1-like (PYL)/regulatory component of the ABA receptor (RCAR) group of proteins. This novel ABA-binding protein was demonstrated as a soluble ABA receptor by two independent research groups, considered as a breakthrough for the understanding of ABA signalling (Ma *et al.*, 2009; Park *et al.*, 2009). These receptors, now termed PYR/PYL/RCAR, represent a family of soluble proteins of about 150–200 aa that share a conserved START domain. The ABA-free 'open-lid' conformation of PYR1 is converted to a more compact and symmetric closed-lid dimer upon binding to ABA (Nishimura *et al.*, 2009, 2010). Plants constrain ABA signalling through clade A protein phosphatases 2C (PP2C) [mainly ABI1, ABI2, and HOMOLOGY TO ABI (HAB1 and HAB2), which negatively regulate (dephosphorylate) downstream kinases. However, in response to environmental or developmental signals, ABA is synthesized and bound to PYR1, and this receptor, in turn, binds to PP2Cs inducing a conformational change resulting in its inhibition, and thus terminating the inhibition of the downstream ABA-activated kinases (OST1/SnRK2.6/SRK2E, SnRK2.2, and SnRK2.3). The released SnRK2s are able to phosphorylate downstream factors, such as the majority of osmotic stress-responsive genes harbouring ABA-responsive promoter elements/complexes (ABREs) and bZIP transcription factors (such as ABI5), ion channels (SLAC1, KAT1), and the NADPH oxidase AtrbohF (reviewed by Hubbard *et al.*, 2010; Umezawa *et al.*, 2010; Joshi-Saha *et al.*, 2011). ABA activates genes that encode enzymes for the biosynthesis of compatible osmolytes (as shown for water-stress-induced betaine in pear leaves; Gao *et al.*, 2004b), proline (Strizhov *et al.*, 1997), and cellular chaperones (dehydrins and LEA-like proteins) that protect proteins and membranes under stress (Liu *et al.*, 2013; reviewed by Hasegawa *et al.*, 2000, Shinozaki and Yamaguchi-Shinozaki, 2007). In addition, ABA causes induction of Ca^{2+}_{cyt} via ROS or IP3 recruitment (Murata *et al.*, 2001; Taiz and Zeiger, 2010). Furthermore, ABA and JA play pivotal roles in controlling stomatal closure, which is considered a fast response in stressed plants, although plants cannot keep stomata closed over a long period as they need to fix CO_2 for survive. Interestingly, ABA and JA transduction pathways leading to stomatal closure share overlapping signalling elements. Several ABA mutants with NCED (the key regulatory gene in ABA biosynthesis) overexpression showed better drought adaptation, while ABA-deficient *aba* mutants of *Arabidopsis* perform poorly under drought or salt stress or even die (reviewed by Zhu 2002; Bartels and Sunkar, 2005). Direct comparison of two genetically similar grapevine cell lines differing in their osmotic sensitivity under salt stress revealed that salt susceptibility was accompanied by a delayed accumulation of ABA (Ismail *et al.*, 2014). By keeping in mind that some osmotic stress-responsive genes are ABA independent and are activated via JA signalling including MYC and MYB elements (Ishitani *et al.*, 1997; reviewed

by Bartels and Sunkar, 2005), although both rd22BP1/AtMYC2 and AtMYB2 proteins were firstly identified as ABA-inducible transcriptional activators under drought (Abe *et al.*, 2003), ABA was concluded not to be the only adaptive signal, as will be discussed in the next section.

On the other hand, the ABA transient increase under demanding conditions points to the importance not only of the activation of signalling and biosynthesis but also the suppression strategy. Indeed, ABA enhancement in an *NCED* mutant resulted in accumulation of its catabolite, phaseic acid, via (+)-ABA 8′-hydroxylase activation that catalyses the first step in the oxidative degradation of ABA, in addition to other catabolic pathways (Qin and Zeevaart, 2002; reviewed by Cutler and Krochko, 1999). Oxidative degradation might be complemented by other ABA inactivation strategies, such as ABA conjugation. As the phosphatase activity of ABI1 and ABI2 increases in response to ABA, dephosphorylation of ABA signalling elements will constitute a negative-feedback loop (Merlot *et al.*, 2001). A further (negative) feedback loop is provided by ABA-dependent inhibition of ABI5 degradation and simultaneous ABI-dependent promotion of the RING E3 ABI3-INTERACTING PROTEIN 2 (AIP2) that in turn suppresses ABI3, which interacts with ABI5, enhancing its activity (Vierstra, 2009). Both synthesis (Xiong and Zhu, 2003) and signalling (Kwak *et al.*, 2003) of the ABA pathway are promoted by ROS, whereas calcium, through calcineurin B, constrains both synthesis and signalling of ABA (Pandey *et al.*, 2004).

ABA seems to be the first step that, by its molecular nature, is committed to adaptation, as both calcium and ROS modulate the ABA status (defined as dynamic equilibrium between ABA content and signalling activity, Fig. 2C, ⑦), and this point seems to be important for the decision between adaptation and cell death:

1. The ‘on’ state is activated through both synthesis and activation of signalling by ROS (Fig. 2C, ⑦).
2. The ‘off’ state is achieved by the ABA signalling pathway itself due to the induction of negative regulators (ABI proteins) by ABA (Fig. 2C, ⑧).
3. The appropriate targets are adaptive genes harbouring ABA-inducible adaptive genes that encode osmoprotectans (such as the LEA proteins) but also signalling components that adjust a sustainable ABA status as a balance between constraint (through the ABIs) or promotion (through the NADPH oxidase RboH generating ROS) (Fig. 2C, ⑥, ⑧).
4. In the case of delayed calcium signatures, calcium will, through CBL proteins, impair the ROS-dependent activation of the ABA pathway (Fig. 3C, ④). Due to this delay, the concurrent JA pathway will become dominant, culminating in cell death.

JAs: a dangerous switch

Jasmonic acid and related compounds, collectively named jasmonates (JAs), are ubiquitously occurring lipid-derived compounds, and function as a master switch in plant responses to several abiotic and biotic stresses such as wounding (mechanical stress), drought and salt stress, ozone and pathogen infection, and insect attack (reviewed by Wasternack, 2007; Wasternack and Hause, 2013). Similar to ABA, the synthesis of JA is triggered by ROS, as the first committed step of synthesis, the peroxidation of linoleic acid by lipoxygenases, requires singlet oxygen (Farmer and Mueller, 2013). In contrast to the ABA pathway, which is negatively regulated by CBL proteins, there is evidence that the JA pathway is stimulated (reviewed by Hu *et al.*, 2009). In addition to their role as a general stress signal, JAs regulate many aspects of plant development and growth such as seed germination, fruit ripening, production of viable pollen, root growth, tendril coiling, photomorphogenesis, leaf abscission, and senescence (Creelman and Mullet, 1995, 1997a, *b*; Conconi *et al.*, 1996; Rao *et al.*, 2000; Riemann *et al.*, 2003, 2013; Haga and Iino, 2004; Ma *et al.*, 2006; Robson *et al.*, 2010; reviewed by Wang *et al.*, 2011). Among JA conjugates and derivatives, (+)-7-iso-jasmonoyl-L-isoleucine (JA-Ile) formed by the enzyme JAR1 (Jasmonate-Resistant 1) was found to be an endogenous bioactive form of JA (Fonseca *et al.*, 2009). Under non-stress conditions, JA-Ile is maintained at low levels, and this allows a multimeric protein complex to inactivate JA signalling in plant cells. This machinery is composed of JAZ repressor proteins that bind and repress the transcriptional activator MYC2, via recruiting the Groucho/Tup1-type co-repressor TOPLESS (TPL) and TPL-related proteins (TPRs) through a transcriptional repressor called Novel Interactor of JAZ/TIFY (NINJA) (Chini *et al.*, 2007; Thines *et al.*, 2007; Pauwels *et al.*, 2010; reviewed by Kazan and Manners 2008, 2012, 2013). In response to developmental or environmental cues (including salinity), the levels of JA-Ile are elevated. JA-Ile binds to COI1 and promotes the interaction of JAZ proteins with COI1, leading to SCF^{COI1}-mediated ubiquitination of the JAZ factors, followed by their degradation via the 26S proteasome. This results in the release of MYC-type transcription factors from repression by the JAZ factors and thereby will induce transcription of early JA-responsive genes including the *JAZ* genes themselves. In *Arabidopsis*, derepression of AtMYC2 is induced under dehydration and saline conditions. In addition, *Arabidopsis* plants in which AtMYC2 is overexpressed exhibited less electrolyte leakage under osmotic stress (Abe *et al.*, 2003). When treated with MeJA, protective proteins against oxidative stress (which is a true companion of many abiotic stresses including drought or salt) accumulate in the wild type but at reduced levels in a *myc2* null mutant. These protective proteins include the HSP20-like chaperone protein, the fibrillin precursor protein, a luminal binding protein (BiP2), and GST (Guo *et al.*, 2012). JA-dependent activation of OsbHLH148 upregulates rice OsDREB1A, a functional orthologue of *Arabidopsis* DREB1A (Fig. 2C, ⑨), which plays critical roles in improving drought, salinity, and freezing tolerance but in an ABA-independent manner (Dubouzet *et al.*, 2003; Seo *et al.*, 2011).

These results, at first sight, suggest a role for JA signalling in conferring tolerance to drought and salinity, or oxidative stress. However, a closer look reveals that JA signalling is tightly controlled, as the transcription of *JAZ* genes is induced by JA. The newly synthesized JAZ proteins interact with and restore

the repression of MYC2, which in turn deactivates the JA signal transduction pathway (Chini *et al.*, 2007; Thines *et al.*, 2007; reviewed by Wager and Browse, 2012). This negative-feedback loop and the resulting transient action of JA indicate that unfavourable effects of overshooting JA signalling have to be strictly avoided (Fig. 2C, ⑨). Indeed, MeJA was found to induce cell death in *Arabidopsis* protoplasts (Zhang and Xing, 2008) and *Vitis* cell suspensions (Repka *et al.*, 2004) in a concentration- and time-dependent manner (Zhang and Xing 2008). The MeJA-induced cell death correlates with ROS production, alterations of mitochondrial dynamics, and photosynthetic collapse (Fig. 3C, ⑥). The above-mentioned direct comparison of the two salt-stressed grapevine cell lines showed that the salt-sensitive *V. riparia*, where the accumulation of ABA was delayed, accumulated tenfold higher levels of the bioactive JA-Ile, whereas in the more salt-tolerant *V. rupestris*, ABA accumulated earlier and strongly suppressed formation of the JA-Ile signal (Ismail *et al.*, 2014). This more rapid and more massive induction of JA-Ile was accompanied by a pronounced oxidative burst in *V. riparia* accompanied by synthesis of high amounts of δ-viniferin, a metabolic indicator for ensuing programmed cell death (Chang and Nick, 2012).

The importance of JA tuning is corroborated by analysis of the rice mutant *rice salt sensitive 3* (*rss3*), where root growth is more severely inhibited under salinity compared with the wild type (Toda *et al.*, 2013). This growth phenotype is accompanied by elevated expression of JA-dependent genes. RSS3 binds to JAZ and non-MYC-type bHLH transcription factors, and has been proposed to repress an exaggerated JA response in the root tip (Toda *et al.*, 2013). Collectively, these data suggest that fine-tuning JA signalling is important for the growth and viability of plants under salinity stress. The existence of a multimeric transcriptional co-repression complex machinery to inactivate JA signalling (Chini *et al.*, 2007; Thines *et al.*, 2007; Pauwels *et al.*, 2010), in addition to JA-dependent repression of MYC2 via the MEK2/MAPK6 pathway (Petersen *et al.*, 2000), is evidence that suppression of hazardous side effects of JA signalling is crucial for survival. It should be kept in mind that ABA and JA signalling are antagonistic on several levels—partially by mutual competition for shared signalling factors such as MYC2 (Anderson *et al.*, 2004, Fig. 2C, ⑨).

The ambiguity of the ROS signal seems to be perpetuated at the level of JA—early activation of this pathway seems to be beneficial for salt adaptation, but sustained JA signalling is clearly deleterious and culminates in cell death:

1. The 'on' state is triggered through oxidative cleavage of membrane lipids and is therefore stimulated by ROS (Fig. 2C, ⑦).
2. The 'off' state is achieved by tight negative feedback of the JA signal pathway itself with JAZ/TIFY proteins as central players (Fig. 2C, ⑨).
3. Under adaptive conditions, the JA pathway will initially be under tight constraint, probably triggered by a short transient peak of ROS; some JA will be formed, but signalling will be rapidly shut off, such that concurrent activation of ABA signalling is ahead (Fig. 2A, ⑨).
4. In the case of delayed calcium signatures, impaired ABA signalling (Fig. 3C, ④) in combination with sodium-dependent mitochondrial membrane damage (Fig. 3C, ⑦) will lead to excessive accumulation of JA accompanied by accelerated oxidative burst, membrane damage, and eventually cell death (Fig. 3C, ⑥).

The ubiquitin–26S proteasome system (UPS): executors of cross-talk?

In eukaryotes, such as plants, the UPS constitutes a tightly regulated and highly specific machinery that is devoted to specific proteolysis (reviewed by Sullivan *et al.*, 2003). Plants utilize the UPS to modulate almost all aspects of their biology including growth, development, and stress responses (Santner and Estelle, 2010). The crucial roles of UPS are reflected in the number of genes encoding UPS components. A genomic analysis of *A. thaliana* showed that over 1400 genes (or >5% of the proteome) code for UPS components (Smalle and Vierstra, 2004). Interestingly, several enzymes in the UPS are hormonal receptors. Moreover, the UPS controls the levels of essential downstream signalling proteins in hormonal signal transduction (Santner *et al.*, 2009). Thus, the plant UPS not only removes abnormal proteins that arise due to biosynthetic errors or normal proteins with the wrong configuration (reviewed by Vierstra, 2009), but, in addition to this canonical function, controls signal specificity by removal of specific repressors. Furthermore, the UPS has been reported to be critically involved in plant programmed cell death, as the disruption of proteasome function by gene silencing of the proteasome subunits activates programmed cell death in plant cells (Kim *et al.*, 2003).

As discussed above, salt-stressed plants increase the levels of different hormones such as JA activating specific branches of the UPS. The elevated levels of JA-Ile promote the proteolytic degradation of JAZ proteins via UPS releasing JA transcription factors (reviewed by Wager and Browse, 2012; Fig. 2C, ⑨). Conversely, in ABA signalling, the synthesis of AIP2 is increased, which in turn suppresses the ABA transcriptional regulator ABI3. However, ABA blocks degradation of ABI5 (Fig. 2C, ⑧), a central regulator of ABA signalling during post-germinative growth (Vierstra, 2009).

It is possible to modulate stress tolerance through the UPS. In fact, the functional ubiquitin-specific protease UBP16 was found to increase salt tolerance by stabilization of SERINE HYDROXYMETHYLTRANSFERASE1 (SHM1), which can reduce oxidative burst and therefore repress cell death and at the same time positively regulates plasma-membrane Na^+/H^+ antiporter activity (Zhou *et al.*, 2012). *Arabidopsis thaliana* ABA insensitive RING protein 3 (AtAIRP3/LOG2) is a positive regulator of the ABA-mediated drought and salinity adaptation by targeting RD21 (Responsive to Dehydration 21), which might accelerate cell death progression during senescence and stress conditions (Kim and Kim, 2013). On the other hand, two *A. thaliana* C3HC4 RING domain-containing proteins, named DREB2A-INTERACTING PROTEIN1 (DRIP1) and DRIP2, function as E3 ubiquitin ligases, and negatively

regulate drought-responsive gene expression by mediating DREB2A ubiquitination (Qin *et al.*, 2008).

The convergence of different hormonal pathways on shared elements of the UPS provides a molecular framework that allows the integration of different signals, for instance the relative status of JA versus ABA signalling (Fig. 2C, ⑧,⑨). In other words, it might be this machinery that is dedicated to specific destruction, where plant cells decode the 'meaning' of different concurrent signal pathways.

Concluding remarks

To endow crops with enhanced stress tolerance, it is important to understand the underlying mechanisms. The advances of the last decade have revealed numerous molecular details of salinity-triggered responses and mechanisms of adaptation. In addition, complex and obviously precisely tuned cross-talk between different pathways seems to be relevant. How is the specificity of this cross-talk achieved? Both stress-tolerant and -sensitive plants utilize the same signalling molecules. However, it is important to conceptually discriminate signals from the molecules that convey these signals. The central message transported in this review is that the timing of stress signals is decisive. Stress signals are activated *transiently* and they are subsequently turned off. Whether a plant cell will adapt to salt stress or whether it will yield to cell death appears to be dependent on the correct timing of these transient signalling events. Tolerant plants are tolerant because they can orchestrate cross-talks between different signalling pathways (signal on demand). This is likely to be achieved by controlling the temporal signature and amplitude of the signalling. When this temporal control turns loose, such that a signalling event persists longer or initiates later, this will lead to inappropriate cross-talk with downstream events of other pathways. These downstream events would otherwise not be competent for the respective signal, simply because they proceed at a time point that is later. We have elaborated this heterochronous shift of signalling for the interaction between calcium and JA versus ABA signalling. A delay in the activation and, consequently, also in the deactivation, of the calcium signature will channel ROS-triggered signalling towards the JA pathway, which, in consequence, will run out of control, culminating in cell death. The same molecule (calcium), occurring at the right time, will be recruited for the activation of sodium extrusion and sequestering, such that ROS-triggered signalling will be channelled to (protective) ABA signalling constraining the JA pathway and thus leading to efficient adaptation.

Thus, a deeper understanding of the temporal patterns in signalling will help us to dissect adaptive from damage-related events. But this conclusion also calls for a specific experimental approach to stress physiology: to identify temporal signatures in stress adaptation, we need approaches that are both comparative and integrative—comparative in the sense that systems that are biologically very similar but differ in the outcome of their stress response are investigated side by side under the *same* conditions, and integrative in the sense that the different stages of the stress response are studied in the *same* system in parallel with respect to their time course. Knowledge of the molecular players of stress adaptation is a necessary prerequisite but is t sufficient. We need to consider and investigate molecular activities rather than mere molecules.

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