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Fighting salt or enemies: shared perception and signaling strategies

Nora Gigli-Bisceglia and Christa Testerink

Abstract

Plants react to a myriad of biotic and abiotic environmental signals through specific cellular mechanisms required for survival under stress. Although pathogen perception has been widely studied and characterized, salt stress perception and signaling remain largely elusive. Recent observations, obtained in the model plant *Arabidopsis thaliana*, show that perception of specific features of pathogens also allows plants to mount salt stress resilience pathways, highlighting the possibility that salt sensing and pathogen perception mechanisms partially overlap. We discuss these overlapping strategies and examine the emerging role of *A. thaliana* cell wall and plasma membrane components in activating both salt- and pathogen-induced responses, as part of exquisite mechanisms underlying perception of damage and danger. This knowledge helps understanding the complexity of plant responses to pathogens and salinity, leading to new hypotheses that could explain why plants evolved similar strategies to respond to these, at first sight, very different types of stimuli.

Addresses

Laboratory of Plant Physiology, Wageningen University and Research, Wageningen, 6708 PB, the Netherlands

Corresponding author: Testerink, Christa (christa.testerink@wur.nl)
Email address: nora.giglibisceglia@wur.nl (N. Gigli-Bisceglia)

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Introduction

Plants are incredibly effective in resisting environmental threats. One of the main characteristics of plant cells is their cell wall (CW), a fine network of polysaccharides and proteins surrounding the plasma membrane (PM) [1]. It protects plants from dehydration, mediates cell adhesion, and maintains cell shape and integrity. When under attack, plants release danger signals named damage-associated molecular patterns (DAMPs) upon sensing conserved molecules of pathogens named pathogen-associated molecular patterns (PAMPs) [2] but also after abiotic stresses. DAMP and PAMP recognition in plants are often mediated by plant-specific families of pattern-recognition receptors (PRRs) [3]. Amongst them, both receptor-like proteins (RLPs) and receptor-like kinases (RLKs) have been reported to play a role during both biotic and abiotic stress responses.

Salinity is one of the most studied abiotic stresses, although the exact perception mechanism required for salt sensing remains elusive [4]. In recent years, the discovery that CW and PM modifications play a crucial role in the induction of intracellular responses activated in response to salinity has led to novel hypotheses where not only osmotic balance but also salt-induced CW distortions and PM composition changes are relevant for mounting a proper response to salinity [5–7]. Previously, *Arabidopsis thaliana* (hereafter Arabidopsis) mutants impaired in CW metabolism and/or composition have been described to show altered responses to both salinity and pathogens. To date, research has been carried out to address the role of the main load-bearing CW component, cellulose, in controlling response to both pathogen and salinity. Interestingly, both primary and secondary cellulose synthases (CESAs) [8,9] as well as proteins involved in their correct localization [such as cellulose synthase interactive 1 (CSI1) and companion of cellulose synthases 1 and 2 (CC1/2)] [10–12] have been reported to be required for a wild-type response to both salt and pathogens, further reinforcing the hypothesis that CW composition plays a role in both types of stress responses [13–15]. Intriguingly, also several intracellular signaling responses, including the function of specific PM receptors, lipid signaling, and the activation of downstream responses, such as mitogen-activated protein kinase (MAPK) activation, cytosolic Ca^{2+} increase, and reactive oxygen species (ROS) production, occur in response to both pathogen recognition and salinity [3,4]. Responses to pathogens and salt might share overlap in perception complexes to signal intracellularly the presence of damage, which is highlighted

by the fact that PAMP-derived elicitors can trigger salinity resistance [16,17].

In this review, we compare known pathogen-triggered immune responses to salt stress-induced mechanisms obtained in our model system Arabidopsis (summarized in Table 1). These include the production of plant-derived danger molecules, which interfere with salt stress responses in either an opposite (i.e. plant elicitor peptides [PEPs]) or in a similar fashion (i.e. rapid alkalinization factor peptides [RALFs]) when compared with pathogen responses. RALF receptors, belonging to the Arabidopsis *Catharanthus roseus*-RLK (CrRLK1L) family [18–21], essential to monitor CW integrity, appear to be crucial links between pathogen and salt stress responses, as they not only mediate CW-dependent sensing but also receptor complex formation. In addition, we discuss how also PM lipid composition and integrity recognition play a role in salt and pathogen responses.

Pathogen-derived elicitor-induced responses and their overlapping role in the regulation of both immune- and salt stress-induced responses

Elicitors are structurally and chemically diverse molecules that share the ability to trigger hypersensitive responses in plants. They can be endogenously released by the plants because of an exogenous stimulus, or they can be characteristic features of pathogens (PAMPs) often recognized at the PM through PRRs [22]. Their perception is vital to activate pathogen sensing and signaling responses essential to resist the attack. For several types of pathogen-derived elicitors (from fungi, bacteria, or insects), the recognition/signaling mechanism of plants is known [3]. Interestingly, application of several different elicitors also triggers enhanced salt tolerance in plants [16,17]. In the following section, we report the current knowledge on pathogen-derived elicitor-induced responses and their recently identified functions in regulating salt stress.

Chitin and chitosan-dependent sensing mechanisms and their role in immune signaling and salt stress responses

Chitin and chitosan (derived from partly deacetylated chitin) both present in the fungal CWs and/or insect exoskeletons are known to improve salt tolerance in several plant species [17], suggesting the presence of a common perception-response mechanism in all land plants. Chitin perception in Arabidopsis requires the formation of a heterotrimeric complex composed of 3 lysin motif (LysM)-containing receptor-like kinases (LYKs): the chitin elicitor receptor kinase 1 CERK1 (also known as LYK1) and LYK5/LYK4 [23]. In wild-type seedlings, chitin or salt application induces a quick $[Ca^{2+}]_{cyt}$ accumulation [5,24]. However, although *cerk1* mutants are not able to accumulate calcium after chitin application, in response to salt, *cerk1* displays a strong calcium burst when compared with the control seedlings [24] likely suggesting a negative role for CERK1 in controlling calcium waves after salinity stress. Whether the enhanced *cerk1*-dependent salt-induced $[Ca^{2+}]_{cyt}$ accumulation would affect salt tolerance is yet unclear, but salt-treated *cerk1* seedling cotyledons do show increased bleaching [24], which is often correlated with increased salt susceptibility [5,25]. Surprisingly, although LYK5 and LYK4 are indispensable for chitin-CERK1 complex formation and response to chitin [23,26,27], the *lyk4lyk5* double mutant displays a wild-type-like response to salt [24], suggesting that even though CERK1 likely regulates salt susceptibility, it is unlikely that this mechanism requires LYK5/4/CERK1 complex formation. We could hypothesize that CERK1 mediates certain salt-induced responses, such as $[Ca^{2+}]_{cyt}$ and that chitin/chitosan application modulates the same downstream responses prompting plants to become more salt resilient.

Interestingly, another LYK family member (LYK3) has also been described to function both in pathogen perception and salinity response regulation [28]. *lyk3* loss-of-function seedlings show reduced responses to the plant hormone abscisic acid (ABA), higher sensitivity to salt and enhanced resistance to pathogens [28]. The latter correlates with the LYK3-dependent enhanced *phytoalexin-deficient 3* (*PAD3*) expression, an enzyme previously reported to control camalexin production and protection against fungal pathogens [28,29]. Unfortunately, salt stress phenotypes of the single *pad3* and the double *lyk3pad3* were not reported. The LYK3-dependent salt tolerance phenotypes likely result from *lyk3* mutant's inability to respond to ABA, consistent with the positive role that ABA plays in controlling salt tolerance [30]. Because no differences in ABA responses have been detected in *cerk1* mutants when compared to wild-type seedlings [24], it could be hypothesized that part of the salt stress responses might be regulated by other LYKs in concert with CERK1.

The complex that CERK1 forms in response to salt application might be functionally different from that induced in response to chitin or chitosan. For example, CERK1 interacts with annexin 1 (ANN1), a NaCl-induced calcium-permeable channel [24,31]. Plants lacking ANN1 and/or annexin 4 (ANN4) show salt stress-resilient phenotypes [32]. ANN1 not only seems responsible for the altered intracellular salt-/chitin-induced $[Ca^{2+}]_{cyt}$ detected in *cerk1*, but also for negatively controlling chitin-induced ROS burst and MPK signaling [24]. Investigation of salt-induced ROS accumulation and MPK phosphorylation in *ann1* or *cerk1* mutants could reveal whether this role would extend to NaCl-triggered responses. Considering the available information (summarized in Figure 1A), we could hypothesize that downstream responses activated after

Table 1

Gene identifier, molecular function, biotic and abiotic stress-triggered phenotypes of mutants, ligands, and interactors of the proteins described in this review.

Name (Gene ID)	Main function	Biotic stress phenotypes	Salt stress phenotypes	Ligand	Interactor
Chitin elicitor receptor kinase 1 (CERK1)/ LYK1 (AT3G21630)	Chitin receptor [73]	*cerk1* adult plants are more susceptible to *Alternaria brassicicola, Erysiphe cichoracearum,* and *Blumeria graminis f.sp hordei* [73–75]	Seedlings and adult *cerk1* plants display salt hypersensitivity: reduced survival associated with enhanced Ca^{2+} burst [24]	Chitin oligosaccharides, peptidoglycan [26,73,76]	BAK1 (suggested), LYK5 [23,37]
LYK4 (AT2G23770)	Required for chitin recognition [23]	*lyk4* mutants display *enhanced susceptibility to Alternaria brassicicola, Fusarium oxysporum,* and *Pseudomonas syringae* pv tomato *DC3000* [23,27]	*LYK4* expression is induced on salt application, *lyk4* displays a wild-type-like Ca^{2+} burst after salt [24]	Unknown	LYK5 [23]
LYK5 (AT2G33580)	Required for chitin recognition [23]	*lyk5* displays enhanced susceptibility to *Alternaria brassicicola. lyk5* displays a wild type-like Ca^{2+} burst after flg22. LYK5 is internalized in response to chitin but not in response to flg22 [26,77]	*LYK5* expression is induced on salt application, *lyk5* displays a wild-type-like Ca^{2+} burst after salt [24]	Chitin oligosaccharides [26]	LYK4, CERK1 [23]
LYK3 (AT1G51940)	Suggested to recognize short chain of lipochitooligosaccarides and chitooligosaccarides [26]	*lyk3* mutant seedlings display enhanced resistance to *Botrytis cinerea* and *Pectobacterium carotovorum* [28]	*lyk3* mutant seedlings display higher sensitivity to salt and reduced primary root elongation on salt [28]	Unknown	Unknown
Annexin 1/AnnAt 1/ ANN1 (AT1G35720)	Ca^{2+}-dependent membrane-binding protein [31]	Annexin 1 is required for both local and systemic defense responses against the leafworm *Spodoptera littoralis.* Plants overexpressing ANN1 show decreased susceptibility to the nematode *Meloidogyne incognita* infection, whereas *ann1* is more susceptible. *ann1* mutants show enhanced chitin-induced ROS, MPK6 but reduced calcium accumulation [24,31,78]	*ANN1* is upregulated in leaves on NaCl, H_2O_2, drought, abscisic acid, salicylic acid. *annexin1* mutant adult plants, show increased salt tolerance, enhanced in the double *annexin1/annexin4. annexin1* mutant seedlings show enhanced salt susceptibility and a reduced survival rate [32,79,80]	/	Annexin 4, CERK1 [24,32]
Annexin 4/AnnAt4/ ANN4 (AT2G38750)	Ca^{2+}-dependent membrane-binding protein [31]	Plants overexpressing ANN4 show decreased susceptibility to the nematode *Meloidogyne incognita* infection, whereas *ann4* is more susceptible [78]	*ANN4* levels are induced in response to NaCl. *annexin4* mutant adult plants, show increased salt tolerance, whereas *annexin4* mutant seedlings show enhanced salt susceptibility and a reduced survival rate [32,80]	/	Annexin1, AtSYP121, AtSYP122, AtSYP123, AtSYP21, AtSYP22 [32,81]

(*continued on next page*)

Table 1. (*continued*)

Name (Gene ID)	Main function	Biotic stress phenotypes	Salt stress phenotypes	Ligand	Interactor
Brassinosteroid-insensitive 1-associated receptor kinase 1 (BAK1)/ Somatic embryogenesis receptor kinase 3 (SERK3) (AT4G33430)	Partner of Several LRR-RLKs [82,83]	*bak1* loss-of-function mutants show enhanced susceptibility to infection with *Botrytis cinerea*, *Alternaria brassicicola*. *bak1* displays reduced responses to flg22, elf18, PEP1, and RALF1. BAK1 is essential for PEP1-triggered response activation [41,83–85]	*bak1-5* seedlings display a reduced survival rate in response to salt. The phenotype is enhanced in the *bak1-5bkk1* double mutant lines. BAK1 is required for PEP1-induced salt tolerance [16]	/	FLS2, CERK1 (suggested), EFR, CNGC20, PEPR1/2, FER [37,38,50,83,84,86,87]
CNGC20 (AT3G17700)	Cyclic nucleotide-gated channel	Gain of function CNGC20 allele (*cngc20-4*) displays enhances PAMP-induced growth inhibition and ROS burst. *cngc20-4* mutant shows enhanced flg22- and PEP1-triggered root inhibition. *cngc20-4* mutant has enhanced *Pseudomonas syringe* pv *tomato* DC3000 susceptibility. Loss-of-function *cngc20* mutants exhibit wild-type-like flg22-induced ROS production and PEP-induced MAPK activation. *cngc20* mutants do not show different responses to *Pseudomonas syringe* pv. *maculicola* when compared with the wild type. CNGC20 regulates cell death phenotypes of the *bak1/ serk4* double mutants [38,86]	*CNGC20* is expressed in the epidermis and in the mesophyll mainly of petioles. After salt treatment, *CNGC20* is strongly upregulated in shoots. T-DNA insertion lines show no visible phenotypes in response to salt stress in both roots and shoots [39]	/	CNGC19, BAK1 [38,86]
CNGC19 (AT3G17690)	Cyclic nucleotide-gated channel	Loss-of-function *cngc19* mutants exhibit wild type-like flg22-induced ROS production. CNGC19 promotes defense against the leafworm *Spodoptera litura*. The *cngc19-1* loss-of-function mutant displays wild-type resistance to *Pst* DC3000. Loss-of-function mutant shows wild-type-like response to PEP1 [38,86,88]	CNGC19 is expressed in the phloem. After salt treatment, *CNGC19* is strongly upregulated in shoots. T-DNA insertion lines show no visible phenotypes in response to salt stress in both roots and shoots [39]	/	CNGC20, BAK1 [38,86]

PEPR1/2 (AT1G73080, AT1G17750)	PEP receptors [89]	PEPR1/2 are essential to respond to PEP treatments. *pepr1/2* mutants show impaired responses to oligogalacturonide (OG)- and flg22 as well as altered oligogalacturonide (OG)- and flg22-induced protection against *Botrytis cinerea*. *PEPR1* and *PEPR2* are induced by wounding, MeJA, flg22 and elf18. *pepr1/2* mutants show wild-type-like basal response to *Pst* DC3000 [90,91]	Doble *pepr1/2* mutants show enhanced salt susceptibility at seedlings levels. Pep1/2/3/4 pretreatments significantly increased salt tolerance. Pep3/4 confers salt resistance without inhibiting root elongation [16,49]	PEPR1: PEP1-6, PEPR2: PEP1-2 [49,87,90,92]	PEPR1: PEP1-6, PEPR2: PEP1-2, BAK1 [49,87,90,92]
FERONIA/SIRENE (AT3G51550)	Pollen tube growth and fertilization [93]	Loss-of-function *fer* mutants are more resistant to *Fusarium oxysporum*, but more susceptible to *Pseudomonas syringae*. *fer* mutants show impaired chitin, flg22-, and elf18-induced ROS burst. *fer* mutants display reduced responses to Fusarium-derived elicitor pools [50,54,58,94,95]	Mutant seedlings display salt hypersensitivity, impaired growth, cell burst, and reduced calcium spikes upon salt treatments [5]	RALF22, RALF23, RALF33, RALF1, RALF17, *F. oxysporum*- RALF, RALF32 [21,50,94,96,97]	BAK1, FLS2 [50]
MIK2/LRR-KISS (AT4G08850)	SCOOP receptor [59,60]	*mik2* loss-of-function mutants respond normally to chitin. MIK2 plays an essential role in controlling responses triggered by the Fusarium-derived elicitor pools. *mik2* loss-of-function mutants are more susceptible to *Fusarium oxysporum*. *mik2* loss-of-function mutants display reduced responses to flg22 and enhanced PEP1 responses. *mik2* loss-of-function mutants are insensitive to SCOOP12 [57,58,60]	Enhanced *MIK2* expression associates with enhanced salt tolerance and increased rosette size in the presence of salt [35,57]	SCOOPs [59,60]	SCOOP12-BAK1 [59,60]
GINT1 (AT5G0450)	Glycosyltransferase involved In glycosylation Of GIPCs [69]	Unknown	Loss-of-function mutant lines show reduced salt sensitivity and enhanced germination rate [69]	/	Unknown
PGSIP6/IPUT1/ MOCA1 (AT5G18480)	Glucuronosyltransferase involved in the glucuronosylation of the IPCs [100]	*iput1* loss-of-functions are lethal. Using a pollen-specific rescue construct, *iput1* mutants were obtained showing severe dwarfism and constitutive hypersensitive response [101]	*moca1* mutants are hypersensitive to salt: with reduced calcium burst, enhanced bleaching and reduced fresh weight on salt [7]	/	Calcium channels (suggested) [7]

CNGC20, Ca^{2+}-permeable cyclic nucleotide-gated channel 20; EFR, elongation factor thermo unstable receptor; GINT1, glucosamine inositolphosphoryceramide transferase 1; FER, Feronia; FLS2, Flagellin-sensitive 2; GIPCs, Glycosylinositol phosphorylceramides; IPC, Inositol phosphorylceramide; IPUT1, IPC glucuronosyltransferase 1; MOCA1, Monocation-induced $[Ca^{2+}]i$;LRR, Leucine-rich repeat; LYK 4/5, LysM-containing receptor-like kinase 4/5; MIK2, MDIS1-interacting receptor-like kinase 2; PAMP, Pathogen-activated molecular pattern; PEP, Plant elicitor peptide; RALF23, Rapid alkalinization factor peptide 23; RLK, Receptor-like kinase; ROS, Reactive oxygen species; SCOOP, Serine-rich endogenous peptide.

chitin/chitosan application are responsible for salt-resistant phenotypes observed in plants. However, it is also possible that chitin/chitosan-induced perception complex formation itself would drive at least part of the salt-induced phenotypes also in the absence of PAMPs.

BAK1-containing receptor complexes and their pleiotropic functions

Other PAMPs, such as flg*22* (derived from bacterial flagellin) or elf18 (from the bacterial elongation factor thermo unstable), are recognized, respectively, by the leucine-rich repeat-RLK flagellin-sensitive *2* (FLS2) and the elongation factor thermo unstable-receptor (EFR). Both flg*22* and elf18 have recently been shown to confer enhanced salt resistance in Arabidopsis [16,33]. Like salt and chitin, also flg*22* application induces intracellular calcium waves, but the flg*22*-dependent $[Ca^{2+}]_{cyt}$ burst seems to be mediated by a different set of calcium channels compared with that activated in response to salt [34] suggesting the presence of two independent pathways converging in the accumulation of the same signaling molecule. Intriguingly, plants lacking both FLS2 and EFR exhibit higher salt susceptibility in the absence of flg*22*/elf18 and reduced PAMP-induced salt survival rate [16] (Figure 1B). Interestingly, the flg*22*-insensitive Ws-0 ecotype shows a Columbia-0-like rosette phenotype in response to salt [35] suggesting that loss of FLS2 alone is not sufficient to impair salt tolerance. Known FLS2 and EFR coreceptors such as brassinosteroid insensitive 1- associated receptor kinase 1 (BAK1) have been recently reported to contribute to salt tolerance, as *bak1-5* (a dominant-negative mutant allele with no alteration in brassinosteroid signaling) is more susceptible to salt application [16,36]. Recently, crosstalk between PM-localized PRRs during immune responses has been observed. For instance, flg*22* triggers CERK1 activation via the FLS2-BAK1 complex, where BAK1 phosphorylates CERK1 activating the CERK1-LYK5-complex formation allowing chitin perception [37].

We could speculate that BAK1 is essential to activate and modulate the establishment of several other salt-induced PM complexes. BAK1 can directly bind and activate the Ca^{2+}-permeable cyclic nucleotide-gated channels (CNGCs) CNGC20 and CNGC19, previously described to be transcriptionally upregulated in response to salt ([38,39], Table 1). Members of this family are nonselective (Na^+, K^+, and Ca^{2+}) channels involved in the uptake of cations [40]. Despite their strong induction in response to salt, the role of CNGC20/19 is yet unclear, because knock-out (KO) mutants do not show any salt-related growth phenotypes [39]. *CNGC19* is induced in response to PAMP treatments, and as for *bak1*, *cngc19* mutants display enhanced *Botrytis cinerea* susceptibility [41,42], likely suggesting that BAK1-dependent CNGC19 regulation is required at least for the protection against fungal pathogens. The pleiotropic roles of BAK1 in regulating the functionality of many receptors complicate the comprehension of its specific functions. Although clearly there is a strong overlap between salt and immune stress responses in plants (Figure 1B), the mechanism through which the application of flg*22*/elf18 can induce salt tolerance remains to be elucidated. The susceptibility-related phenotypes observed in plants lacking both FLS2/EFR, BAK1 or CERK1 cannot be explained only by the possibility that salt induces common downstream responses. It is instead likely that salt perception partly depends on the presence of well-known immune regulators which might take part in the formation of yet unidentified complexes.

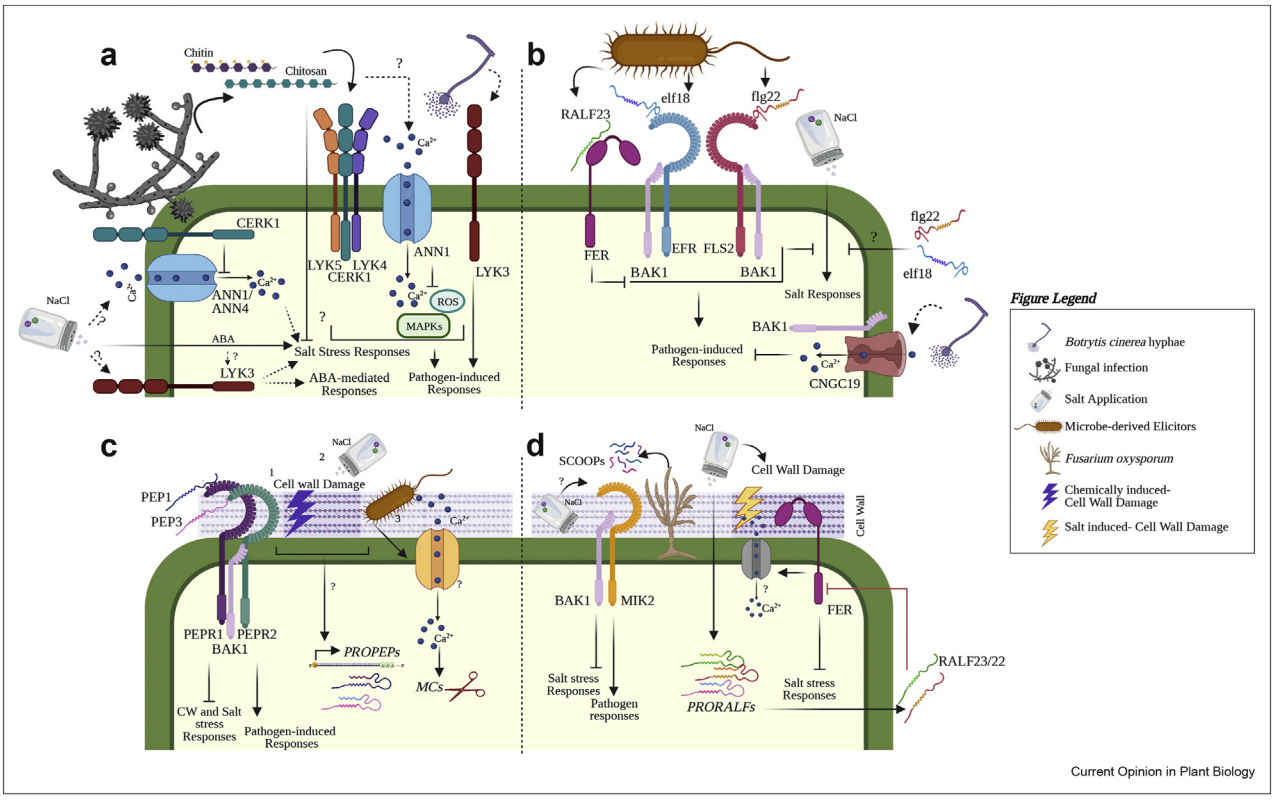
Inducible damage-associated molecular patterns; unraveling their contrasting and synergistic functions in biotic and abiotic stress responses

Danger signals in plants are often released as a direct effect of the cell damage. Known as DAMPs, these endogenous non-PAMP elicitors can be released in response to a plethora of stimuli. They include CW fragments, released after CW degradation and small plant peptides, produced through cleavage of larger propeptides. The consequent sensing of these DAMPs by neighboring cells allows them to activate responses before the danger arrives [2,43]. Here, we describe the current understanding of DAMP peptide function and their dual role in regulating immunity and salinity stress signaling in plants.

Plant elicitor Peptides and their positive and negative role in, respectively, controlling PAMP and Cell Wall Damage-related signaling responses

Plant elicitor peptides (PEPs) are considered DAMPs and are perceived by the leucine-rich repeat (LRR)-RLKs PEP receptor1/2 (PEPR1/2) after their precursors (PROPEPs) are processed in PEPs by Ca^{2+}-activated metacaspases (MCs) [44,45]. During PAMP-triggered immune responses, PEPs amplify the signal and boost immune responses [3]. Recently, it has been shown that in response to flg*22*, an increase in intracellular calcium activates MCs allowing PROPEP cleavage and PEP release ([44], Figure 1C). PEP perception and PROPEP cleavage are essential to preserve the PAMP-induced resistance against necrotrophic fungi, because *pepr1/2* mutants or plants lacking the functionality of 4 MCs (*mc4/5/6/7*) show altered Botrytis susceptibility upon PAMP pretreatment [44,46]. On the other hand, PEP3 accumulates after chemically induced cellulose inhibition [inducing general CW damage (CWD)] and functions to attenuate certain CWD-triggered responses [47]. Plants have evolved a mechanism named CW

Figure 1



Overview of the overlapping signaling pathways involved in regulating pathogen and/or salt stress-induced responses in Arabidopsis. (**a**). Chitin/chitosan-induced perception activates intracellular calcium burst and ROS/MAPK signaling through LYK4/5/CERK1 complex formation as well as ANN1 function. Chitin/chitosan application inhibits salt stress responses in an LYK4/5 independent manner, whereas regulation of salt tolerance requires at least in part CERK1 and LYK3 function. (**b**). PAMP-derived elicitors (flg22/elf18) activate immune responses in a FLS2-BAK1/EFR-BAK1-dependent fashion. PAMP-induced RALF23 maturation and FERONIA-dependent perception regulate FLS2-BAK1 complex stability, consequently controlling pathogen-induced responses. BAK1 also regulates the functionality of CNGC19, negatively regulating *Botrytis cinerea* responses. PAMP-induced salt tolerance likely requiring the function of both FLS2/EFR1 function inhibits salt susceptibility. (**c**). Chemically-induced cellulose impairment (1) or salt application (2) activates cell wall damage responses inducing *PROPEP* expression and consequent perception of the active PEPs through the PEPR1/2. PAMP-derived elicitors (3) trigger intracellular calcium burst, activating metacaspases (MCs) activation and PROPEP processing. During pathogenesis, PEP recognition boosts pathogen-triggered immune responses, whereas CWD-triggered PEP accumulation inhibits both CW and salt stress responses. (**d**). MIK2 is required for the SCOOP-dependent Fusarium-triggered immune responses and for regulating salt stress responses possibly in a BAK1-dependent manner. On the other hand, salt application triggers cell wall damage, RALF processing and release. FERONIA is required for salt-induced cell wall damage sensing, for activating intracellular calcium burst and for RALF binding being RALF22 able to inhibit FERONIA function. EFR, Elongation factor thermo unstable receptor; LYK 4/5, LysM-containing receptor-like kinase 4/5; MIK2, MDIS1-interacting receptor-like kinase 2; PAMP, Pathogen-activated molecular pattern; PEP, Plant elicitor peptide; RALF23, Rapid alkalinization factor peptide 23; ROS, Reactive oxygen species; SCOOP, Serine-rich endogenous peptide; MAPK, mitogen activated protein kinase; CERK1, chitin elicitor receptor kinase 1; CNGC19, cyclic nucleotide-gated channel 19; ANN1, annexin 1; BAK1, Brassinosteroid insensitive 1-associated receptor kinase 1.

integrity (CWI) maintenance comprising sensors that activate responses upon CWD perception [48]. PEP3 also accumulates in response to salt, where it acts as a negative regulator of salt-induced phenotypes [49]. The molecular mechanism regulating CW-related/salt-dependent PEP activation is unknown, but it is likely that the CW modifications observed in response to salt treatments can trigger the accumulation of PEP3 [6]. It is interesting that although PEPs seem to function as positive regulators of the immune responses, amplifying the signals, and spreading them to neighboring cells, certain CWD responses are inhibited by PEP application (Figure 1C). Yet, how PEPs can have these diverse functions and what their relevance is in attenuating salt responses remain to be established.

Rapid alkalinization factor and their *Catharanthus roseus* receptor-like kinase (CrRLK1L) family : active cell wall sensors or anchoring proteins to stabilize complexes required for both biotic and abiotic stresses

Rapid alkalinization factor (RALFs) are also considered to function as DAMPs [3]. Although they have been described as essential in many developmental processes,

RALFs, like the PEPs, are induced in response to several stresses and regulate biotic and abiotic responses [25,50,51]. Members of the Arabidopsis CrRLK1L proteins function as RALFs receptors [19]. Because CrRLK1Ls can also recognize CW pectin *in vitro* [52] and due to the essential role of the CrRLK1L THESEUS1 (THE1) in regulating CWD responses [47], CrRLK1Ls have been suggested to work as CW sensors in the CWI maintenance mechanism. Both RALFs and CrRLK1Ls link abiotic and biotic stress responses [25,50,53,54]. In fact, PAMP-induced RALF23 maturation destabilizes FLS2/BAK1 complex formation (Figure 1B) and the consequent suppression of immune responses in a FERONIA (FER) — (CrRLK1L) and LORELEI-like glycosylphosphatidylinositol (GPI)-anchored protein 1 dependent manner [50,53].

FER regulates the mobility/organization of receptor complexes at the PM [54] which might explain the fact that *fer* mutants display a wide range of phenotypes under different stimuli (i.e. *fer* mutants display high salt susceptibility) [52]. Upon salinity, plants accumulate RALF22, but this seems detrimental to plants because 1.) plants overexpressing *RALF22* or *RALF23* display a *fer*-like salt susceptibility phenotype and 2.) salt-induced RALF22 accumulation leads to FER internalization [25]. Thus, it has been proposed that salt induces RALF22-dependent FER inhibition (Figure 1D). However, this observation requires more understanding at the molecular level, because the presence of a functional FER is essential to maintain a wild-type-like salt response. Many of the CrRLK1L (such as Buddha's Paper Seal 1/2 and ANXUR1/2) play a fundamental role in fertility [55], and interestingly, molecular events associated with salt signaling overlap with the function of well-known fertility regulators. PM-localized receptor kinases male discoverer 1 (MDIS1)-interacting receptor-like kinase 2 (MIK2), first discovered as part of a receptor complex for the female attractant peptides (LUREs/LURE1), was later found to contribute to salt stress responses and tolerance [56,57]. A genome-wide association study (GWAS), performed to identify salt stress resilience regulators, associated higher *MIK2* expression with bigger rosette size under salt [35]. *mik2* KO plants are more sensitive to salt and to the fungal pathogen *Fusarium oxysporum*, likely associating MIK2 also to pathogen responses (Figure 1D) [57,58]. It has been suggested that the plant's CWI surveillance has evolved to monitor rapid cell expansion and CWD, events happening during developmental (i.e. pollen tube growth) and stress-related responses. Interestingly, although THE1 seems to function upstream of MIK2 in regulating CWD responses after cellulose inhibition, it also shows enhanced susceptibility to Fusarium [57], suggesting that CW sensors of the CWI maintenance mechanisms also play a role in response to pathogens.

It can be hypothesized that while salt-induced CW modifications might require the function of CrRLK1Ls together with other LRR-RLKs including MIK2 to inhibit salt stress responses during pathogenesis different receptor complexes might form, suggesting the possibility that distinctive classes of ligands are released and perceived. Even if salt-/pathogen-triggered responses seem to partially overlap at the molecular level, it is possible that fungi-induced CW modifications are structurally different from those induced by salt. Recently, MIK2 was shown to be essential for the recognition of serine-rich endogenous peptides (or SCOOPs), being implicated in activating Fusarium-triggered SCOOP-dependent immune responses [59,60]. However, whether SCOOPs are also required to trigger MIK2-dependent salt responses remains to be established. To date, the genesis, accumulation, and the role of many DAMP peptides in regulating salinity remain elusive. Whether their maturation is induced by salt-dependent signals after alterations of the structural integrity and architecture of the CW needs further investigation.

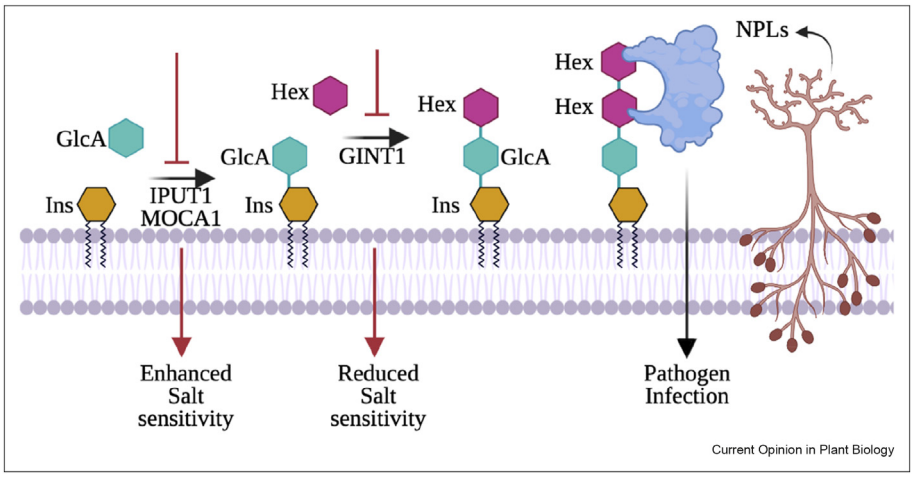
Signals from the plasma membrane: the dual role of lipids in perceiving salinity and pathogen attack

The PM plays a fundamental role in protection and regulation of transport of nutrients and other molecules, as well as in controlling intracellular signaling responses. In plants, the PM lipid bilayer is primarily composed of glycerophospholipids, sphingolipids, and sterols [61], some of which influence cellular signaling. A significant overlap exists in the accumulation of specific signaling phospholipids, such as phosphatidic acid and polyphosphoinositides, in response to biotic and abiotic stresses [62,63]. SCOOP12 application, similar to PAMP elicitors and salinity stress, induces phosphatidic acid accumulation [64]. Recent research now suggests that specific sphingolipids could function as direct sensors, being recognized by PAMPs or directly binding sodium ions, causing the activation of cellular signaling pathways [7,65].

Glycosylinositol phosphorylceramides: membrane lipid modifications and their emerging roles in regulating salinity stress

Glycosylinositol phosphorylceramides (GIPCs) are sphingolipids present in the PM, and recent publications have shown their key signaling roles during stress responses [7,65,66]. GIPCs consist of an inositol phosphorylceramide (IPC) backbone linked to glucuronic acid (GlcA; therefore named GIPC) linked to plant- and tissue-specific hexose residues (Figure 2) [65]. In plants, the pathogen-released ethylene-inducing peptide 1 (Nep1)-like proteins, NLPs act as PAMPs activating immune-related responses. Their cytotoxic effect and their suggested function as actinoporins lead to the discovery that NLPs bind the GIPC's sugar head

Figure 2



Biosynthesis and role of GIPCs in salinity stress and fungal infections. Glycosylinositol phosphorylceramides (GIPCs) sphingolipid biosynthesis from inositol (Ins) and phosphoryl-ceramide (IPC) backbone is mediated by the glucoronosyl-transferase IPUT1/MOCA1, linking glucuronic acid (GlcA) to the IPCs to form GIPCs. Inhibition of IPUT1/MOCA1 enhances salt stress responses resulting in mutant plants being more susceptible to salt application. GIPC glycosylation is partly dependent on the function of the glucosamine inositolphosphoryl-ceramide transferase (GINT1) responsible for the addition of N-acetylglucosamine (here represented as hexose [Hex]) to the GIPCs. Inhibition of GINT1 reduces salt sensitivity as mutant plants exhibit an enhanced germination rate in the presence of salt. Upon fungal infection, the ethylene-inducing peptide 1 (Nep1)-like proteins, NLPs can recognize in dicots the GIPC sugar head made of two hexoses activating membrane disruption and pathogenesis. IPUT1, IPC glucuronosyltransferase 1; MOCA1, Monocation-induced $[Ca^{2+}]_i$.

allowing the creation of pores that trigger cell damage, leakage, and consequently pathogenesis (Figure 2) [67,68].

Modification of GIPC glycosylation and biosynthesis alters plants' ability to response to salt stress. For example, plants lacking the glucosamine inositolphosphoryceramide transferase 1 display significantly enhanced germination rates in the presence of high salt (Figure 2) [69]. In addition, genetic alteration of the head sugar domain causes constitutive defense responses and changes in CW composition, likely suggesting a link between the PM and CW [66]. A recessive mutation localized in one of the transmembrane domains of the IPC glucuronosyltransferase 1 [IPUT1 or glycogenin-like starch initiation protein 6 (PSGSIP6)] involved in transferring the GlcA, to the IPC core, is sufficient to abolish several responses to salt (Figure 2). This mutant called monocation-induced $[Ca^{2+}]_i$ increases 1 (*moca1*) displays reduced salt-induced Ca^{2+} spikes [7]. The mutation in MOCA1 unbalances the relative amount of the GIPC content versus IPC (non-GlcA substituted), leading to reduced GIPC levels [7]. Given the fact that the head sugar domain of the GIPCs is negatively charged, GlcA residues might bind directly sodium ions (and other cations [K^+, Li^+], likely directing the opening of unidentified calcium channels [7]. Interestingly, Voxeur and Fry [70] have suggested that boron, an essential element that contributes to CW assembly, might mediate the interaction between GIPCs and pectins. Thus, the observation that FER-dependent salt susceptibility was mitigated by exogenous boron application [5] suggested to be the result of its ability to crosslink pectin might also involve GIPC-pectin interactions, highlighting a potential link between PM composition and CWI sensing. Collectively, selective modifications of lipid and/or the recognition of specific lipid features during pathogenesis or by cation binding seems to be crucial for controlling both biotic and abiotic stress signaling, suggesting that not only CW but also PM integrity surveillance might be essential for plant stress responses.

Conclusions and outlook

Sensing mechanisms at the PM and CW control plant responses to both biotic and abiotic stress. Interestingly, many of the Arabidopsis receptors mentioned in this review are likely to possess more functions than the ones originally assigned after their first discovery. Similarly, the emerging role of several Arabidopsis-induced danger molecules (i.e. DAMP peptides) in regulating salt-induced responses previously described to play roles in both pathogenesis and developmental regulation [3] reveals a complex interplay of receptor-mediated perception and activation of downstream responses in response to both pathogen and salinity (Table 1). Even though the mechanism that triggers DAMP accumulation in response to salt or pathogens is still unknown, accurate analysis of peptide modification and their mechanism of action will be essential to unravel their function in the regulation of both biotic and abiotic stress responses. Plant CWs and also PM integrity seem to play a crucial role in the induction of both

stresses pointing to the possibility that structural modifications also play an active role in the self-integrity-perception mechanisms required for balancing growth with defense to biotic and abiotic threats. The role of the PM seems crucial in regulating the formation of so-called nanodomains likely influencing the localization of specific receptor complex formation [71]. It is possible that plants, like mammals, have developed mechanisms required to monitor their PM structural integrity [72], and in-depth analyses of the PM structure and complex receptor formation will be essential to unravel the sophisticated role of both PM and the possible crosstalk of PM and CW changes during pathogenesis and salinity.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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