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REVIEW: PART OF A SPECIAL ISSUE ON PLANT CELL WALLS

An update on receptor-like kinase involvement in the maintenance of plant cell wall integrity

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• **Background** Plant cell walls form the interface between the cells and their environment. They perform different functions, such as protecting cells from biotic and abiotic stress and providing structural support during development. Maintenance of the functional integrity of cell walls during these different processes is a prerequisite that enables the walls to perform their particular functions. The available evidence suggests that an integrity maintenance mechanism exists in plants that is capable of both detecting wall integrity impairment caused by cell wall damage and initiating compensatory responses to maintain functional integrity. The responses involve 1-aminocyclopropane-1-carboxylic acid (ACC), jasmonic acid, reactive oxygen species and calcium-based signal transduction cascades as well as the production of lignin and other cell wall components. Experimental evidence implicates clearly different signalling molecules, but knowledge regarding contributions of receptor-like kinases to this process is less clear. Different receptor-like kinase families have been considered as possible sensors for perception of cell wall damage; however, strong experimental evidence that provides insights into functioning exists for very few kinases.
• **Scope and Conclusions** This review examines the involvement of cell wall integrity maintenance in different biological processes, defines what constitutes plant cell wall damage that impairs functional integrity, clarifies which stimulus perception and signal transduction mechanisms are required for integrity maintenance and assesses the available evidence regarding the functions of receptor-like kinases during cell wall integrity maintenance. The review concludes by discussing how the plant cell wall integrity maintenance mechanism could form an essential component of biotic stress responses and of plant development, functions that have not been fully recognized to date.

Key words: Receptor-like kinase, RLK, plant cell wall integrity maintenance, cell wall signalling.

INTRODUCTION

Two hallmark features differentiating plants from animals are their sessile lifestyle and the walls surrounding all plant cells. The sessile lifestyle implies that the ability to resist both abiotic and biotic stress is significantly more important for plants than for animals. Specialized mechanisms enabling plants to adapt to stresses, such as drought and pathogen infection, influence the survival probability of plants. Importantly, the plant cell wall is intimately involved in all these processes and influences their outcome while in parallel also being a cornerstone of developmental processes. During cell morphogenesis the wall has to be plastic to allow controlled directional expansion, whereas after termination of morphogenesis it has to be sturdy and/or waterproof to provide mechanical support and resistance to pathogen infection and to enable long-distance water transport. The integrity of the wall has to be maintained throughout these different biological processes with sometimes opposite functional requirements.

Although *Saccharomyces cerevisiae* represents a significantly simpler organism compared with a plant, the functional requirements for the yeast cell wall during growth and interaction with the environment, as well as the need to maintain functional integrity, are similar to those of an individual plant cell wall. Previous research has shown that a dedicated cell wall integrity (CWI) maintenance mechanism exists in yeast that monitors the functional integrity of the wall and initiates compensatory responses upon exposure to cell wall damage (Levin, 2011). In yeast, cell wall damage occurs during different processes, such as enzymatic degradation of the wall, cell cycle progression, response to hypo-/hyper-osmotic, heat or cold shock and pheromone-induced cell morphogenesis (Kopecka and Gabriel, 1992; Davenport *et al.*, 1995; Errede *et al.*, 1995; Kamada *et al.*, 1995; Buehrer and Errede, 1997). Compensatory responses to maintain integrity can involve changes in cell wall composition and structure (e.g. increase in chitin), reorganization of the cytoskeleton and cell cycle arrest (Levin, 2011). These observations support the notion that the yeast CWI maintenance mechanism is active during and represents an integral element of a large number of different biological processes.

Research in yeast suggests that the primary physical consequences of cell wall impairment, in conjunction with the high turgor pressure prevalent in the cells, are changes in surface tension of the wall and plasma membrane stretch (Kamada *et al.*, 1995; Beese *et al.*, 2009). In yeast cells, three different sensor mechanisms (mechanoreception, turgor perception and CWI perception) have been implicated in cell wall damage detection and CWI maintenance. The available data show that, in response to cell wall damage, a stretch-activated, plasma membrane-localized channel complex (MID1 CCH1) causes

an increase in intracellular Ca^{2+} levels (Paidhungat and Garrett, 1997). The changes in Ca^{2+} levels lead (via calcineurin) to activation of the transcription factor CRZ1, which regulates expression of downstream response genes such as FKS2 (the yeast β-1,3 glucan synthase) (Zhao *et al.*, 1998). Interestingly, activity of CRZ1 is also regulated by SKN7, a transcriptional regulator exhibiting similarity to the bacterial two-component system (Maeda *et al.*, 1994). SKN7 activity is controlled mainly by turgor pressure (SLN1 SHO1) and CWI (WSC1, 2, 3, MID2 and MTL1) sensors (Maeda *et al.*, 1994; Alberts *et al.*, 1998; Ketela *et al.*, 1999; Williams and Cyert, 2001). Changes in the phosphorylation state of SLN1 enable the yeast cell to detect the occurrence of hyper- and hypo-osmolarity, which is also indicative of CWI impairment. SLN1 regulates the activity of SKN7 through signals relayed by the HOG1 signalling pathway (Levin, 2011). Recent results from the characterization of WSC1, one of the plasma membrane localized sensors of the yeast CWI pathway, using atomic force microscopy, suggest that this plasma membrane-localized protein functions as a linear nanospring (Heinisch *et al.*, 2010). The highly *O*-mannosylated extracellular domain residing within the cell wall functions as a mechanical probe that undergoes a conformational change upon changes in the surface tension of the yeast cell wall, leading to activation of the small G protein RHO1 via ROM2 [a RHO1 guanine nucleotide exchange factor (GEF)]. RHO1 in turn relays the signal to PKC1, which activates a MAP kinase cascade involving MPK1 (associated with the PAF1C complex) and leads to activation of FKS2 (Kim and Levin, 2011). Interestingly, RHO1 also directly interacts with and regulates the activity of the previously mentioned SKN7, supporting the notion that the different signalling cascades are interconnected and not independent of each other (Alberts *et al.*, 1998; Ketela *et al.*, 1999).

While a reasonable amount of knowledge exists regarding the different sensors and their respective signal transduction cascades, information regarding the mechanisms integrating the different signals into coordinated responses is limited. Garcia *et al.* (2009) have shown that the HOG and CWI pathway jointly coordinate the responses to yeast cell wall degrading zymolase treatment. More recently, Baltanás *et al.* (2013) have provided intriguing insights into how inputs from the pheromone response and the CWI maintenance mechanism are integrated and lead to an improved ability to adapt to osmotic change. These observations highlight that, in yeast, a matrix consisting of different signalling cascades jointly regulates the processes responsible for CWI maintenance. To summarize, a sophisticated mechanism exists in yeast that is active during different biological processes, monitors the integrity of the cell wall, detects qualitatively different inputs and integrates the incoming signals to modulate cellular metabolism in an adaptive manner.

Cell wall damage in plants can be caused by changes in turgor pressure levels or physical impairment of one or more cell wall components, with effects ranging from loosening of the cell wall polysaccharide network to the generation of low-molecular weight breakage products (e.g. oligogalacturonides), which results in weakening or breakdown (i.e. integrity impairment) of the cell wall. Examples of compounds having such effects are osmotica, inhibitors of cellulose biosynthesis such as isoxaben, plant pathogen-derived enzymes such as cellulases and pectinases, and commercial enzyme preparations such as driselase

(Zeiger and Hepler, 1976; Dongowski and Sembries, 2001; Scheible *et al.*, 2001). While the use of cell wall degrading enzymes might represent a valuable approach for the characterization of the plant CWI maintenance mechanism, it is important to bear in mind that enzyme preparations from plant pathogens have the intrinsic disadvantage of also containing epitopes activating plant immune responses.

During recent years substantial evidence has accumulated supporting the existence of a CWI maintenance mechanism in plants. Several recently published articles review our current knowledge of the plant CWI maintenance mechanism competently and provide excellent global overviews (Nühse, 2012; Wolf *et al.*, 2012). Therefore, we will focus here on particular aspects that have not been covered in detail before. Knowledge regarding the mode of action of the *yeast* CWI maintenance mechanism is useful when considering possible modes of action of the *plant* CWI maintenance mechanism. This notion is supported by the evidence available regarding the conservation of molecular activities between plants and yeast. Expression of the *Arabidopsis thaliana* proteins MID1 COMPLEMENTING ACTIVITY1 (MCA1) and MCA2 in MID1-deficient yeast strains leads to at least partial rescue (Nakagawa *et al.*, 2007; Yamanaka *et al.*, 2010). In parallel, expression of ARABIDOPSIS HISTIDINE KINASES (AHK) 1, 2, 3 and 4 complements yeast strains deficient in SLN1-dependent osmo-sensing (Urao *et al.*, 1999; Inoue *et al.*, 2001; Tran *et al.*, 2007). The localization of AHK1 to the plasma membrane indicates the closest functional similarity to SLN1, while the endoplasmic reticulum-localized AHK2, 3 and 4 seem to function as organ-specific cytokinin receptors that cannot easily be integrated into a model of osmo-sensitive CWI maintenance (Inoue *et al.*, 2001; Ueguchi *et al.*, 2001; Yamada *et al.*, 2001; Higuchi *et al.*, 2004; Nishimura *et al.*, 2004; Caesar *et al.*, 2011; Wulfetange *et al.*, 2011). AHK1 acts as positive regulator of stress responses, whereas the cytokinin receptor AHKs have been demonstrated to negatively regulate stress responses in a cytokinin-dependent manner, indicating opposing involvement in common pathways (Tran *et al.*, 2007). Recently, Žd'árská *et al.* (2013) have shown that cytokinins regulate the abundance of proteins involved in primary metabolism, such as carbohydrate metabolism, a pathway that is controlled in an osmo-sensitive manner in the context of CWI impairment (Wormit *et al.*, 2012). It will thus be interesting to know if, and to what extent, different AHKs contribute to this osmo-sensitive regulation. Figure 1 provides a global overview of the signalling cascades and of several key components mediating yeast CWI maintenance. It also summarizes candidate genes (and possible plant-specific signalling cascades) from arabidopsis that have been implicated in plant CWI maintenance based on currently available knowledge.

However, there are also limitations of such a comparison due to differences between the model systems that have to be considered. Currently it remains to be determined how/if the single-cell situation of the yeast cell versus the multicellular plant structure affects the design and mode of action of the CWI maintenance mechanism. In parallel, it is reasonable to assume that in plants cell wall damage occurs during wounding and infection by pathogens that break down or modify cell walls, which is not a common problem in yeast. Examples of such pathogens are the necrotrophs *Botrytis cinerea* and *Plectosphaerella cucumerina* and the (hemi-) biotrophs *Erysiphe cichoracearum* and *Pseudomonas syringae*,
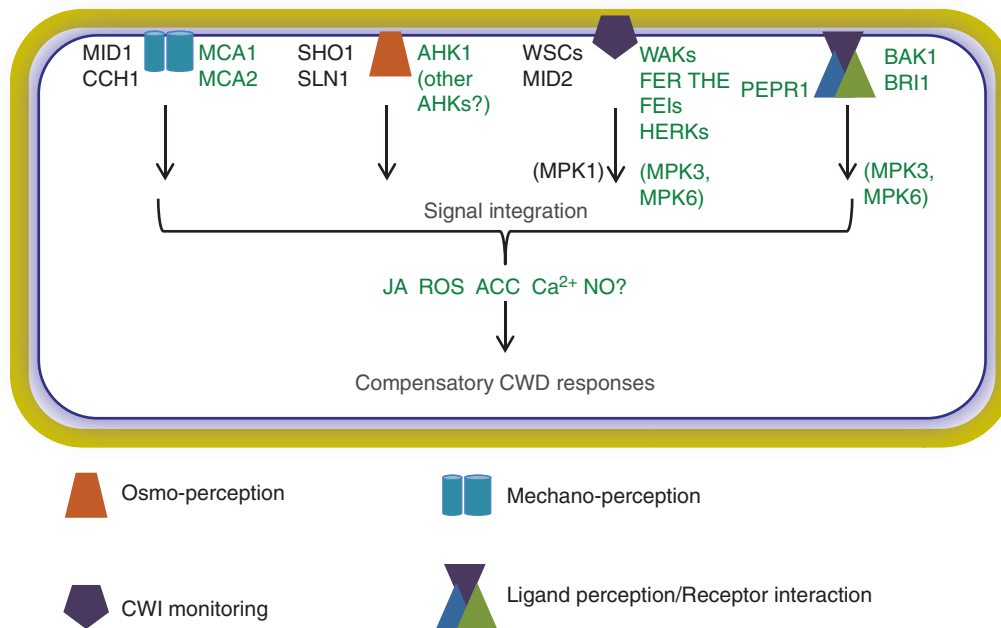
FIG. 1. Comparative overview of CWI signalling cascades in yeast and plant cells. Black font highlights yeast genes, green indicates arabidopsis genes and grey indicates processes common to both plant and yeast cells. The cell wall is coloured yellow, while the dark blue line represents the plasma membrane and the light blue area indicates the apoplast.

which could be of particular interest with respect to plant CWI research, since previous work has shown that mutations affecting plant cell wall metabolism affect their infection success (Hernandez-Blanco *et al.*, 2007; Delgado-Cerezo *et al.*, 2011). In addition, the plant cell wall is significantly more complex than the yeast cell wall with respect to both structure and composition. The large number of different cell wall polysaccharides and proteins could give rise to a large number of ligands for potential CWI sensors. In this context it is sensible to bear in mind that although more than 600 and 1131 receptor-like kinases (RLKs) have been identified in the arabidopsis and rice genomes, respectively, corresponding ligands have been assigned only for a very small number of these RLKs (Shiu *et al.*, 2004). Combining ligands (deriving from specific cell wall components either released or made accessible by cell wall damage) with particular RLKs would allow the generation of a large number of highly specific signals indicating plant cell wall changes.

ELICITORS OF THE SIGNAL: CELL WALL (DAMAGE)-ASSOCIATED RLK LIGANDS

In the recent past, two types of ligand have been shown to bind to cell wall (damage)-associated RLKs. The first ligand type to elicit signals upon structural changes in the cell wall resides in the wall itself and includes specific individual carbohydrate polymers and cell wall proteins that are attached to RLKs under non-stress conditions. While the scaffold structure composed of cellulose microfibrils is not readily modifiable, hemicellulosic and pectic polymers are subject to multiple and often fast modifications and turnover. For example, induction of glycosyl hydrolase expression upon carbohydrate starvation is associated with a reduction in hemicellulosic and pectic, but

not cellulosic, monosaccharide content (Lee *et al.*, 2007). Methylesterification of pectin is important for cell wall extensibility/stiffness as it regulates accessibility of pectin-degrading enzymes and controls Ca^{2+}-dependent binding of pectic polymers (reviewed by Peaucelle *et al.*, 2012). *O*-acetylation is common to pectin and hemicellulose and has been implicated in CWI, enzyme accessibility and the stress response (reviewed by Gille and Pauly, 2012). It seems likely that the availability of epitopes for binding to receptors, which function as potential sensors of CWI, is similarly affected by cell wall modification. Wall-associated kinases (WAKs) are bound to pectin *in planta* and bind to pectic polymers and fragments *in vitro* (Wagner and Kohorn, 2001; Decreux and Messiaen, 2005; Kohorn *et al.*, 2009). *In vitro* binding was shown to depend on Ca^{2+} and de-methylesterified pectin (Decreux and Messiaen, 2005). In addition, the interaction of WAK1 with glycine-rich proteins has been observed in a yeast-two-hybrid assay, whereas an *in vivo* interaction has not been clearly demonstrated so far (Park *et al.*, 2001). Another RLK that has been shown to bind pectin belongs to the proline-rich extensin-like receptor kinase (PERK) family. Bai *et al.* (2009) demonstrated that PERK4 can be released from root tissue by pectolyase digestion in a time-dependent manner.

The second type of ligand emerges upon damage and includes breakdown products originating in both the wall and the lumen of the cell. These molecules are commonly referred to as damage-associated molecular patterns (DAMPs), a term based on the term 'microbe-associated molecular patterns' (MAMPs), highly conserved molecules of microbial origin that elicit defence responses in plants. By now, DAMPs and MAMPs have been described in different species in which they enable the plant to distinguish between self and non-self and generate similar

RLK-dependent signals (reviewed by Monaghan and Zipfel, 2012). Oligogalacturonides are particularly well-characterized DAMPs that can arise from pectic homogalacturonan upon digestion by wound-induced or microbial pectin-degrading enzymes in a process that is controlled by plant polygalacturonase-inhibiting proteins (Cervone *et al.*, 1989; Bergey *et al.*, 1999). It has been demonstrated that WAK1 binds oligogalacturonides, and that oligogalacturonide binding elicits defence responses in a chimaeric RLK consisting of an extracellular WAK1 domain and an intracellular kinase domain of the EF-Tu receptor (Brutus *et al.*, 2010). Oligogalacturonides have been shown to antagonize auxin-dependent developmental processes in different plants and tissues, demonstrating the potential of this molecule to modulate both developmental and defence-dependent signalling (Branca *et al.*, 1988; Bellincampi *et al.*, 1993; Altamura *et al.*, 1998; Savatin *et al.*, 2011). This impact on auxin signalling is especially interesting considering the broad influence of auxin on transcription of cell wall-related genes (Lewis *et al.*, 2013).

Arabidopsis elicitor peptides (*At*Peps) induce defence signalling after release from their wounding-/pathogen-induced PROPEP precursors (Huffaker *et al.*, 2006). PROPEP isoforms show tissue-specific expression patterns and have been implicated in different physiological processes based on transcriptional data (Bartels *et al.*, 2013). However, due to the subcellular localization of PROPEPs in the cytosol or the tonoplast, *At*Peps are unlikely to constitute the initial signal (Huffaker and Ryan, 2007; Bartels *et al.*, 2013). Rather, they seem to be required for amplification/modulation of defence responses after elicitation. Phosphosulphokines (PSKs) might also have a function in the RLK-dependent regulation of DAMP/MAMP signalling. PSK peptides stimulate growth and attenuate defence signalling in arabidopsis after cleavage from secreted precursor proteins and might thus function as apoplastic signals for balancing growth and defence responses (Srivastava *et al.*, 2008; Igarashi *et al.*, 2012).

RECEPTOR-LIKE KINASES IN CELL WALL INTEGRITY MONITORING

To date, several RLKs have been implicated in CWI monitoring, based either on the nature of their ligands or on altered responses in the respective arabidopsis mutants upon cell wall damage (summarized in Table 1). Receptor–ligand interactions are particularly well documented for WAKs (see above). The WAKs comprise a family of five members and 22 *WAK*-like genes that have been identified based on protein sequence homology (Verica and He, 2002). Pectin-induced activation of gene expression has been shown to depend to a great extent on *WAK2* and the associated stress response was mimicked by a dominant active *WAK2* allele (*WAK2cTAP*) (Kohorn *et al.*, 2009, 2012). The growth phenotype of *WAK2cTAP* plants was suppressed by *mpk6*; *WAK2*-dependent gene expression, however, was only partially dependent on *MPK6*, indicating that additional pathways might be involved in signal transduction (Kohorn *et al.*, 2012). WAKs have been shown to be required for both cell elongation and the activation of stress responses (Wagner and Kohorn, 2001; Kohorn *et al.*, 2006, 2012). However, the activation of these different (and most likely opposing) programmes might depend on the nature of the particular ligand bound and require distinct downstream signalling events (for a model see Kohorn and Kohorn, 2012). By contrast, pectin-associated PERK4 is

required for abscisic acid (ABA)-induced Ca^{2+} accumulation and inhibition of root cell elongation (Bai *et al.*, 2009). While it is not known if the association with pectin influences PERK4 kinase function, this observation hints at possible interactions between CWI maintenance and the drought stress response mechanisms.

Leucine-rich repeat (LRR) RLKs form the largest group within the RLK superfamily (Gish and Clark, 2011). Within this family, several receptors have been shown to bind the small signalling peptides *At*Peps and PSK. Recent evidence indicates that PSK receptor 1 (PSKR1) is important for jasmonic acid-dependent signalling and, together with the related RLKs PSKR2 and PSY1R, the regulation of hormone balance upon pathogen infection, suggesting a role in balancing developmental processes versus defence responses (Mosher *et al.*, 2013). *At*Peps receptor 1 (PEPR1) and its at least partially redundant homologue PEPR2 have been shown to influence defence signalling and pathogen susceptibility (Krol *et al.*, 2010; Yamaguchi *et al.*, 2010). Interestingly, PEPR1 interacts with BAK1, a LRR-RLK that also functions as co-receptor of the MAMP receptors FLS2 and EFR to mediate pathogen resistance, to amplify signal intensity upon elicitor binding (Schulze *et al.*, 2010; Roux *et al.*, 2011). Upon *At*Peps or flg22 treatment, BAK1 contributes to a signalling cascade involving Ca^{2+}, nitric oxide and reactive oxygen species (ROS), revealing functional interdependence between PEPR1- and FLS2-induced responses (Ma *et al.*, 2013). Initially, BAK1 was identified as co-receptor of the brassinosteroid receptor BRI1 (Li *et al.*, 2002; Nam and Li, 2002). It has been shown that co-activation of the BRI1 and FLS2/ERF pathways is differentially regulated in a phosphorylation-dependent manner (Schwessinger *et al.*, 2011). BAK1 is thus involved in the regulation of both developmental and stress-dependent processes and might provide an interface for adjustment of different energy-consuming programmes. However, switching between these pathways is not achieved by competition for a limited BAK1 pool, but its regulation seems to be either dependent on differential binding characteristics of BAK1 with RLKs or downstream/independently of RLK interaction (Albrecht *et al.*, 2012).

The homologous LRR-RLKs FEI1 and FEI2 have been identified based on the sucrose-dependent swollen-root phenotype of *fei1 fei2* double mutant seedlings. A similar phenotype has been observed in mutants such as *procuste1* (*prc1*; *CESA6* loss-of-function allele) and isoxaben-treated wild-type seedlings, which are all impaired in the formation of load-bearing cellulose microfibrils (Fagard *et al.*, 2000; Xu *et al.*, 2008; Hamann *et al.*, 2009). Interestingly, cellulose biosynthesis is also reduced in *fei1 fei2* mutants, and ectopic deposition of lignin is detectable in the swollen roots. In both *prc1* and *fei1 fei2* mutants, isoxaben sensitivity is increased compared with wild-type, indicating impaired CWI. The *fei1 fei2* root phenotype was, however, not dependent on a functional kinase domain, suggesting that interaction partners are necessary for signal transduction (Xu *et al.*, 2008). Genetic studies suggested that the extracellular glycosylphosphatidylinositol-anchored protein SALT OVERLY SENSITIVE5 (SOS5), which was previously shown to display a similar conditional phenotype, acts in the same pathway as FEI1/2 (Shi *et al.*, 2003; Xu *et al.*, 2008).

Recently, evidence has been accumulating that members of the *Catharanthus roseus* RLK1-like (*Cr*RLK1L) protein family could function as sensors of CWI during growth. Based on homology to

TABLE 1. *Receptor-like kinase (RLK) families whose members have been implicated in cell wall damage signalling*

RLK family	RLK	Ligands	Downstream signalling elements	References
LRR-RLK	BAK1		Ca^{2+}, ROS, MPK3, MPK4, MPK6	Roux *et al.*, 2011; Fàbregas *et al.*, 2013; Ma *et al.*, 2013
	FEI1/2		ACC	Xu *et al.*, 2008
	PEPR1/2	*At*Peps	MPK3, MPK6, ethylene, Ca^{2+}, NO, ROS	Krol *et al.*, 2010; Yamaguchi *et al.*, 2010; Ma *et al.*, 2012, 2013
	PSKR1/2	PSK	Jasmonic acid	Matsubayashi *et al.*, 2002, 2006; Igarashi *et al.*, 2012; Mosher *et al.*, 2013
	PSY1R	PSY1		Amano *et al.*, 2007; Mosher *et al.*, 2013
*Cr*RLK1L	ANXUR1/2			Boisson-Dernier *et al.*, 2009; Miyazaki *et al.*, 2009
	FERONIA	RALF	RAC/ROP GTPases, ROS, Ca^{2+}	Guo *et al.*, 2009*a*; Deslauriers and Larsen, 2010; Duan *et al.*, 2010; Kessler *et al.*, 2010; Fàbregas *et al.*, 2013; Haruta *et al.*, 2014
	HERKULES 1/2			Guo *et al.*, 2009*a, b*
	THESEUS		ROS	Hématy *et al.*, 2007; Guo *et al.*, 2009*a*; Denness *et al.*, 2011
PERK	PERK4	Pectin	Ca^{2+}	Bai *et al.*, 2009
WAK	WAK1	Pectin, oligogalacturonides		Decreux and Messiaen 2005; Brutus *et al.*, 2010
	WAK2	Pectin	MPK3, MPK6, invertase	Kohorn *et al.*, 2006, 2009, 2012

Known ligands, signalling molecules and pathways shown to be activated downstream of specific RLKs are listed in the table.

the *Xenopus laevis* protein malectin, two extracellular domains of *Cr*RLK1L proteins have been predicted to have a putative carbohydrate-binding function and might thus directly bind cell wall polymers, carbohydrate DAMPs or glycosylated proteins (Schallus *et al.*, 2008; Boisson-Dernier *et al.*, 2011). Cellulose deficiency in *prc1* can be partially uncoupled from growth inhibition and ectopic lignification by a mutation in *THESEUS1* (*THE1*), suggesting that THE1 mediates signals indicative of impaired CWI (Hématy *et al.*, 2007). This notion was further supported by the finding that *THE1* is involved in isoxaben-induced accumulation of ROS and ectopic root lignification (Denness *et al.*, 2011). In addition to this role in CWI monitoring, *THE1* was shown to be involved in brassinosteroid-sensitive vegetative cell elongation jointly with *HERKULES1/2* (*HERK1/2*). Based on the growth phenotypes and results of gene expression analysis in mutant plants, *FERONIA* (*FER*) might affect the same pathway (Guo *et al.*, 2009*a, b*). Deslauriers and Larsen (2010) reported that *FER* is required for full brassinosteroid-dependent hypocotyl elongation in etiolated seedlings, while sensitivity to exogenously applied brassinosteroid is increased in *fer* mutants when grown in the light. These apparently contrasting responses might reflect the absence of efficient CWI monitoring that coordinates cell elongation with cell wall expansion under particular growth conditions and/or developmental programs. Recently it has been shown that FER, BAK1, BR SIGNALING KINASE1 (BSK1) and BSK3 co-immunoprecipitate with a green fluorescent protein-tagged BRI1 homologue, BRI1-like3 (BRL3), indicating that these RLKs might form a receptor complex required for root growth (Fàbregas *et al.*, 2013). FER and its close homologues ANXUR1 (ANX1) and ANX2 are required for functional integrity of polarly growing root hair cells and pollen tubes, respectively (Boisson-Dernier *et al.*, 2009; Miyazaki *et al.*, 2009; Duan *et al.*, 2010). Recently, Haruta and colleagues (2014) demonstrated that the secreted peptide RALF (rapid alkalization factor) is bound by FER and that this interaction leads to both inhibition of H^+-ATPase2 (AHA2) and a reduction in root cell elongation. The requirement of FER for rapid RALF-induced Ca^{2+} accumulation

suggests that downstream signalling depends on Ca^{2+}, a hypothesis that is further supported by transcriptome analysis (Haruta *et al.*, 2014). Regulation of polar growth in root hairs also involves interaction of FER with GEFs of Rho-like RAC/ROP GTPases (ROPGEFs) to control RAC/ROP-dependent and auxin-sensitive accumulation of ROS, while some functional specificity is provided by different ROPGEFs (Duan *et al.*, 2010, 2014; Huang *et al.*, 2013). The same pathway seems to be responsible for suppression of ABA signalling, further supporting the comprehensive impact of FER-mediated signalling on the regulation of cell development and stress responses (Yu *et al.*, 2012). Taking these findings together, it seems likely that FER and ANX1/2 are required for the coordination of cell elongation and cell wall assembly in fast-growing cells to permit tightly controlled cell wall breakdown. Remarkably, FER is also required for successful cell wall penetration by powdery mildew pathogens, a process that requires reorganization of the plasma membrane and the cell wall to form a novel matrix at the interface between fungal and plant cells, which also involves RAC/ROP GTPases (Kessler *et al.*, 2010; Hückelhoven and Panstruga, 2011). Kessler *et al.* (2010) suggest that a similar mechanism is activated both during pollen tube reception and powdery mildew penetration, as both pathways involve FER and MILDEW RESISTANCE LOCUS O (MLO) proteins. Pollen tube recognition and rupture depend on asymmetrical accumulation of FER in synergid cells and might involve competition with ANX1/2 for the same ligand (Escobar-Restrepo *et al.*, 2007; Kanaoka and Torii, 2010). These results suggest that CWI maintenance and pollen tube wall modification during fertilization are both regulated by *Cr*RLK1L proteins in a cooperative manner.

SIGNAL TRANSDUCTION AND DOWNSTREAM RESPONSES

Downstream responses of impaired CWI have mainly been analysed in arabidopsis mutants either genetically or chemically impaired in cellulose biosynthesis. These analyses have shown

that a wide range of signalling pathways are induced upon CWI impairment, overlapping in large part with responses to biotic and abiotic stress. Induced responses included accumulation of ROS and activation of jasmonic acid-, ABA-, salicylic acid- and ethylene-dependent signalling (Ellis *et al.*, 2002; Manfield *et al.*, 2004; Hernandez-Blanco *et al.*, 2007; Hamann *et al.*, 2009; Denness *et al.*, 2011). Ultimately, impaired cellulose biosynthesis leads to compensatory changes in cell wall composition, which include increased uronic acid content, callose deposition and ectopic root lignification (Cano-Delgado *et al.*, 2000, 2003; Manfield *et al.*, 2004; Hématy *et al.*, 2007; Hamann *et al.*, 2009). In the presence of glucose or sucrose, impaired cellulose biosynthesis leads to a swollen root phenotype, suggesting that regulation of cell elongation and monitoring of CWI are severely impaired under favourable growth conditions (Cano-Delgado *et al.*, 2000; Hamann *et al.*, 2009). Ectopic lignification, however, is partially maintained in non-swollen roots in the presence of glucose or sucrose analogues, indicating that responses induced by cellulose biosynthesis inhibition are influenced by non-metabolic monitoring of sugar availability (Hamann *et al.*, 2009).

Up to now, little has been known about the signalling cascade(s) leading to the observed changes in hormone balance and cell wall composition. Ectopic lignification depends on ROS accumulation and is inhibited by jasmonic acid, while both pathways seem to depend on Ca^{2+} signalling (Denness *et al.*, 2011). Isoxaben-induced ROS accumulation depends on the NADPH oxidases RESPIRATORY BURST OXIDASE HOMOLOG D (RBOHD) and RBOHF (Denness *et al.*, 2011), which are regulated by Ca^{2+} signalling and phosphorylation and contribute to both local and systemic signalling in response to a variety of stress triggers. The mutual influence of Ca^{2+} and ROS signalling has been studied in detail and recent reports suggest that both pathways interact directly during both signal elicitation and cell-to-cell propagation (for a recent review see Steinhorst and Kudla, 2013). Currently, however, only results from studies using different signalling inhibitors implicate Ca^{2+} in the response to cellulose biosynthesis inhibition (Denness *et al.*, 2011). Treatment with oligogalacturonide elicitors induces transient Ca^{2+} accumulation and partially Ca^{2+}-dependent transcriptional responses, suggesting a possible role of Ca^{2+} in WAK-dependent signalling (Moscatiello *et al.*, 2006). Remarkably, isoxaben-dependent accumulation of ROS depends on *THE1*, indicating specific activation of this pathway upon inhibition of cellulose biosynthesis (Denness *et al.*, 2011). The Ca^{2+} and ROS pathways have both been demonstrated to interact with nitric oxide signalling; nitric oxide is a signalling molecule that accumulates upon stress and oligogalacturonide-treatment and might contribute up to 50 % of oligogalacturonide-induced deregulation of gene expression according to recent analyses (Rasul *et al.*, 2012; Scheler *et al.*, 2013; Jeandroz *et al.*, 2013). Accumulation of nitric oxide after treatment with flg22 or *At*Peps strongly depended on the RLKs FLS2 and PEPR1, respectively, indicating tight regulation by pattern recognition pathways (Ma *et al.*, 2013).

It is well established that root cell elongation is inhibited by both ethylene and the ethylene precursor 1-aminocyclopropane-1-carboxylic acid (ACC) in an auxin-dependent manner (reviewed by Muday *et al.*, 2012). Tsang *et al.* (2011) have shown that this mechanism is required to mediate root growth inhibition in response to cellulose biosynthesis inhibition. Short-term responses were specifically dependent on ACC but not ethylene, suggesting that ACC represents an important signal in this process. Consistent with this observation, manipulation of ACC but not ethylene signalling resulted in rescue of the cell elongation defect observed in *fei1 fei2* roots. FEI1/2 interacted with ACC synthase in a yeast two-hybrid assay, suggesting that these RLKs are required for ACC synthesis in a pathway that links cell wall biosynthesis and root cell elongation (Xu *et al.*, 2008).

So far, no direct targets for phosphorylation by candidate CWI-monitoring RLKs have been identified. However, MAPK cascades are involved in WAK2-dependent signalling upon perception of pectin and oligogalacturonides (Kohorn *et al.*, 2009, 2012). In the future, it will be pivotal to discover phosphorylation targets of the discussed RLKs and additional players in downstream kinase cascades. Furthermore, it will be interesting to study the interactions of RLK-dependent pathways with signalling cascades involved in turgor pressure and mechano-perception that are activated by cell wall damage.

CONCLUSION

To summarize, recently a significant amount of evidence supporting the existence of a dedicated plant CWI maintenance mechanism has accumulated. The available data suggest some degree of similarity between the plant and yeast mechanisms with respect to the signalling cascades and proteins involved. They also highlight differences. For example, the yeast genome does not encode a large number of RLKs (like plant genomes tend to), hinting at possible fundamental differences between the modes of action of the plant and yeast CWI maintenance mechanisms. In addition, the possible consequences of the multi-cellular organization of plants with respect to the processes maintaining CWI integrity have not been discussed here simply because there is still pretty much a black hole in our knowledge.

Probably the most interesting questions that need to be addressed in the near future regard whether cell wall derived DAMPs may actually represent the signals indicating CWI impairment, and which specific cell wall components are affected by cell wall damage. This type of qualitative information, in conjunction with quantitative information about physical stimuli generated by mechanosensors and turgor sensors (such as MCA1 and 2, as well as AHKs), would provide the plant cell with a detailed overview of events taking place at its interface with the environment and enable it to produce adaptive responses that increase its probability of survival.

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