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Cell Wall Signaling in Plant Development and Defense

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Abstract

Plant architecture fundamentally differs from that of other multicellular organisms in that individual cells serve as osmotic bricks, defined by the equilibrium between the internal turgor pressure and the mechanical resistance of the surrounding cell wall, which constitutes the interface between plant cells and their environment. The state and integrity of the cell wall are constantly monitored by cell wall surveillance pathways, which relay information to the cell interior. A recent surge of discoveries has led to significant advances in both mechanistic and conceptual insights into a multitude of cell wall response pathways that play diverse roles in the development, defense, stress response, and maintenance of structural integrity of the cell. However, these advances have also revealed the complexity of cell wall sensing, and many more questions remain to be answered, for example, regarding the mechanisms of cell wall perception, the molecular players in this process, and how cell wall–related signals are transduced and integrated into cellular behavior. This review provides an overview of the mechanistic and conceptual insights obtained so far and highlights areas for future discoveries in this exciting area of plant biology.

Contents

1. INTRODUCTION

1.1. Plants as Multicellular, Wall-Encased Organisms

Plant life is dictated by the predicament of being a multicellular organism in which virtually all cells are encased by rigid, polysaccharide-rich cell walls. Due to their ability to fix atmospheric carbon in sugar backbones, polysaccharides are building blocks with favorable energetic costs, allowing the massive accumulation of biomass (7). Specific modifications of the cell walls, such as the incorporation of the polyphenol lignin, enabled the innovation of water-conducting cells, which further enlarged the potential of plants to conquer land and grow toward the light (137). However, the presence of cell walls eliminates cell migration as a means to drive morphogenesis. Thus, cellular growth generally occurs within the confinements of the wall, requiring controlled cell wall loosening. The plant cell wall is typically composed of cellulose, hemicelluloses, and pectins, as well as a smaller portion of structural and enzymatically active proteins (37). In the resting state, this rigid cell wall, the physical properties of which depend as much on the multitude of chemical interactions between its components as on the components' intrinsic properties, is in equilibrium with the internal turgor pressure. Cellular growth requires breaking this equilibrium. While an increase in turgor pressure alone could theoretically provide the force for cell elongation, it cannot control the directionality of the growth. Instead, plant morphogenesis is controlled by the extensibility of the cell wall, which is itself controlled by the organization of polymer placement and enzymatic and nonenzymatic modification of cell wall properties (1). Turgor pressure provides the driving force for displacing cell wall components relative to each other until a new equilibrium is reached. Thus, cell wall integrity (CWI) is challenged by growth itself, and tight control must

be exerted on this process to prevent swelling or bursting of cells. To ensure CWI and homeostasis during growth, as well as to enable cell wall fortifications in response to extrinsic challenges, cell wall surveillance pathways perceive changes in the state of cell walls and elicit intracellular responses (**Figure 1*a***).

Cell wall signaling (CWS): any signaling event triggered by cell wall–derived cues

In addition to their role in growth control, cell walls are part of cell type–specific differentiation programs, which is apparent in sections of any plant organ (**Figure 1*b***). These specialized cell wall deployments are controlled by intricate transcriptional networks, which are best understood for their role in the production of secondary cell walls in xylem cells (204, 241). However, recent advances strongly suggest that there is also feedback from the cell wall to growth regulatory and stress response networks (**Figure 1*c***). This review is focused on the evidence for this cell wall feedback pathway in development and under stress conditions and therefore provides only a brief overview of plant cell wall architecture as it pertains to the cell wall signaling (CWS) mechanisms discussed below. However, excellent recent reviews that address the biosynthesis, structure, and function of plant cell walls are available (1, 40, 92, 106).

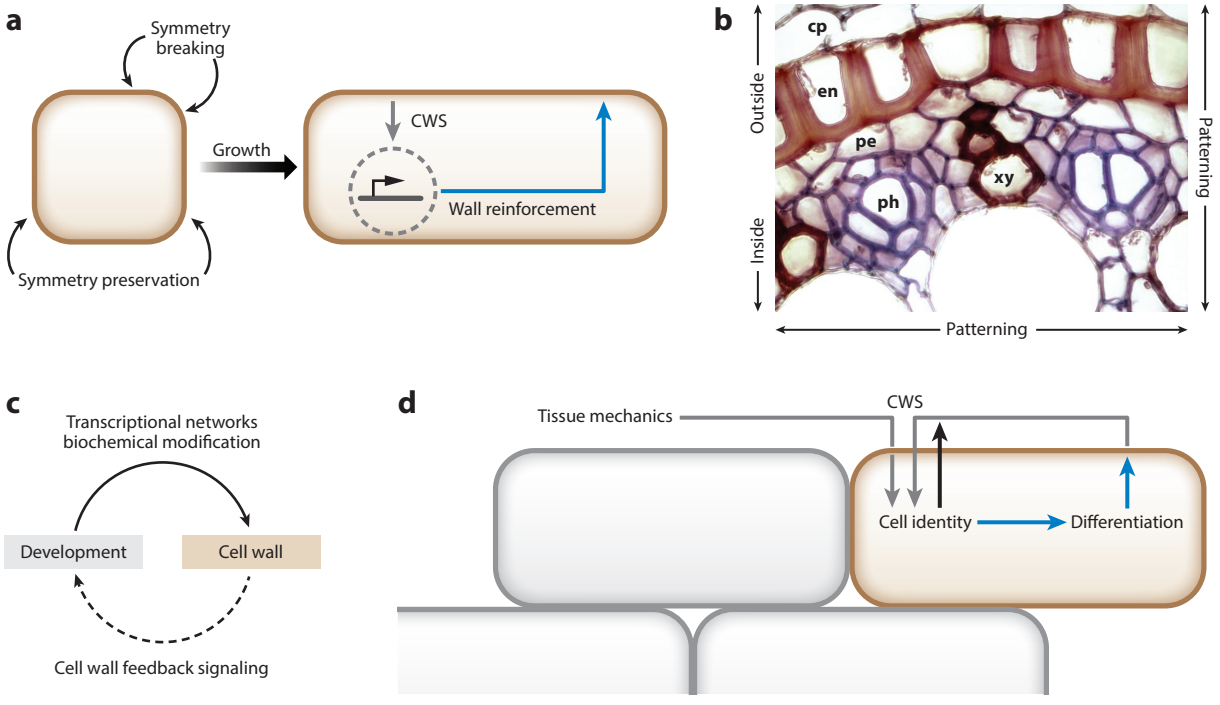

Figure 1

Conceptualized model of CWS in development. (*a*) Anisotropic growth typical for plants requires both symmetry breaking and symmetry preservation as an isodiametric cell undergoes turgor-driven, cell wall–controlled elongation. As growth requires an increase in cell wall extensibility and is often accompanied by cell wall thinning, it represents a challenge to cell wall integrity. In this scenario, CWS controls the growth process and ensures wall reinforcement. (*b*) Cell type–specific cell wall differentiation in a lily root cross section, stained with safranin and astral blue, showing the transition between the vascular cylinder (*bottom*) and cortex (*top*). (*c*) The cell wall is part of the differentiation program of each cell but can also provide feedback on the regulatory mechanisms of development. (*d*) Cell identity determines the specific cell wall differentiation program, but cell wall state might also impact cell identity maintenance both cell-autonomously and over long distances, for example, as a conduit for mechanical signals at the tissue level. Gray arrows in panels *a* and *d* indicate CWS; blue arrows indicate transcriptional rearrangements. Abbreviations: cp, cortex parenchyma; CWS, cell wall signaling; en, endodermis; pe, pericycle; ph, phloem, xy, xylem.

1.2. Brief Overview of Cell Wall Architecture

The cell wall is a complex, carbohydrate-rich structure enclosing all plant cells that remarkably combines the attributes of extreme tensile strength and extensibility. In most plant cells, the characteristic anisotropy of cell expansion is traditionally assumed to be conferred by the alignment of cellulose microfibrils, which restricts growth to the axis perpendicular to the net cellulose orientation (8, 158). Cellulose is synthesized by plasma membrane–spanning, hexameric cellulose synthase complexes (CSCs), which use cytosolic uridine diphosphate (UDP)-glucose to generate extracellular β-1,4-glucan chains that coalesce into a cellulose microfibril. The CSCs travel in the plasma membrane propelled by their own activity, which adds glucose subunits to the immobilized microfibril (90, 106, 144, 221). The trajectory of CSCs and, thus, the orientation of the newly deposited cellulose microfibril, which is so important for growth orientation, are determined by cortical microtubules, which CSCs track along, guided by adaptor proteins (24, 60, 89). Microtubules can align along mechanical stress patterns, providing a feedback mechanism that integrates mechanics and growth regulation (95, 97, 179).

Cellulose microfibrils are embedded in a hydrated matrix of pectin and hemicelluloses, which are both synthesized in the Golgi apparatus by glycosyltransferases and delivered to the cell wall by secretory vesicles (106, 121, 208). Hemicelluloses are a diverse group of polysaccharides that contain backbones of neutral sugars, linked mostly by β-1,4 glycosidic bonds (185). The backbone can be substituted as in the primary cell wall hemicellulose xyloglucan, which is composed of a glucan backbone decorated by xylose, galactose, and fucose residues in a characteristic pattern. The most abundant class of hemicelluloses is the xylans—characterized by xylose-containing backbones—which associate with cellulose in secondary cell walls of woody tissues (194). Pectins are acidic polysaccharides that are composed of backbones rich in galacturonic acid but can contain very complex side chains with a dazzling amount of different sugars and linkages (2). However, the most abundant type of pectin, homogalacturonan (HG), is relatively simple: It is a linear chain of galacturonic acid in which some of the individual subunits can contain acetyl- or methyl ester substitutions. In addition to the three main polysaccharide classes, structural proteins such as extensins (hydroproline-rich glycoproteins), proline-rich proteins, glycine-rich proteins, and arabinogalactan proteins (AGPs) critically contribute to the architecture of the cell wall by forming cross-linking connections with themselves and cell wall polysaccharides (19, 28, 193, 202, 211).

1.3. Connectivity of the Cell Wall

The structural cell wall components are interconnected through a variety of different linkages, the full extent and function of which are just beginning to emerge (39, 107). For example, matrix polysaccharides have been shown to associate with cellulose microfibrils to either provide cross-links or act as repellents to ensure microfibril spacing (38, 88, 194, 217). While cellulose alignment was once believed to be the sole determinant of cellular morphology, in recent years it has become apparent that remodeling of the cell wall matrix plays a key role in regulating cell wall mechanics and plant development. For example, xyloglucan, the most abundant hemicellulose in primary cell walls of dicots, forms load-bearing contact sites with cellulose (159, 160), and it is assumed that these contact sites are the targets of expansins (EXPs), an important class of cell wall–modifying enzymes (69). Xyloglucans are also targeted by xyloglucan endotransglucosylase/hydrolases (XTHs), a large and conserved group of cell wall–remodeling enzymes. Due to its importance in growth and development, pectin, arguably the most dynamic and complex cell wall polysaccharide, has garnered a lot of attention over the last few years. HG is synthesized in the Golgi apparatus in a highly methylesterified state (106). After delivery to the extracellular space, HG can be demethylesterified by pectin methylesterase (PME), leaving a free carboxylic acid

group on the pectin backbone, as well as yielding methanol and a proton. PME activity, in turn, is affected by interaction with PME inhibitor proteins. Depending on the pattern of carboxylic acid and methyl ester groups created by PME, the mechanical properties of the wall are dramatically altered, and the mechanism of this is not well understood (22, 72, 119, 161–163, 166, 177, 219). Even though all PMEs presumably catalyze the same basic reaction, the large number of isoforms differ in processivity, substrate, pH optimum, and ion preferences (188). Compounding the difficulties in understanding the consequences of PME activity, HG occurs in the wall as part of the proteoglycan ARABINOXYLAN PECTIN ARABINOGALACTAN PROTEIN1 (APAP1) (202) and as a copolymer with the less abundant pectin types rhamnogalacturonan I (RG-I) and rhamnogalacturonan II (RG-II) (2). Recently, it has emerged that cell wall polymers can undergo liquid–liquid phase separation, providing an alternative mechanism for cell wall patterning (169). In the case of pectin, volume changes in HG nanofilaments that transition from densely packed methylesterified pectin to less dense demethylesterified pectin have been proposed to drive cell morphogenesis without requiring turgor-driven growth (91, 92).

Virtually all plant cells are surrounded by the primary cell wall. After cessation of growth, some cell types deposit a secondary cell wall with varying composition. Most of what is known about secondary cell wall composition and assembly has been gleaned from secondary xylem cells, i.e., wood, the main driver of terrestrial biomass accumulation (7). Like primary cell walls, xylem secondary cell walls contain large amounts of cellulose but differ from the former by greatly reduced levels of pectin, the incorporation of xylans as the main hemicelluloses, and the addition of the irregular polyphenol lignin. Lignin simultaneously impregnates and hardens xylem cell walls to facilitate water transport and vertical growth, respectively, and concomitantly provides protection against enzymatic attack (241, 242).

2. CELL WALL SIGNALING

2.1. Cell Wall Signaling: The Concept

Faced with the challenge that growth is determined by cell wall components that are out of the reach of intracellular control mechanisms such as posttranslational modification, plants have evolved cell wall–monitoring systems to convey the status of the cell wall to the inside of the cell. Even though our knowledge of specific cell wall perception mechanisms is still limited (see below), it is incontrovertible that feedback signaling from the wall is incorporated into cellular decision making. Feedback from the cell wall might serve a number of different functions, some of which are listed here:

1. Plant cell wall functions depend on its composition and the connectivity between individual components. Thus, in growing and differentiating plant cells, the proportion of the respective cell wall components has to be carefully tuned, despite the fact that the cell wall is not preassembled inside the cell and different wall components are produced at different subcellular locations (106). Thus, the maintenance of cell wall homeostasis requires gathering information from the extracellular space.
2. Growth is itself a challenge for CWI and is often uncoupled from cell wall biosynthesis (40, 170); therefore, the state of the wall needs to be monitored in order to orchestrate compensatory responses (**Figure 1*b***).
3. Plants are multicellular organisms in which every cell is constrained by a wall whose existence predates multicellularity. Therefore, all cells are connected to neighboring cells through walls that were deposited during cell division. Intrinsic differences in growth rates of adjacent cells lead to tension and compression, but cells need to grow coordinately and

communicate with each other (150, 207). Cell walls are often punctured by channels called plasmodesmata, ensuring cytoplasmic connections between neighboring cells, although it is currently unknown to what extent communication through plasmodesmata contributes to growth coordination.

4. Each cell division creates a new cell wall, meaning that all of the walls of an individual cell have a different origin and life history. Yet some of the cell walls need to change their extensibility in a coordinated way, while others need to maintain similar extensibility (22, 163). Growth thus entails symmetry breaking and symmetry preservation in different walls of an individual cell, presumably requiring wall communication and feedback control (**Figure 1*a***).
5. Cell walls are the first line of defense against microbes and, hence, the primary target of most plant pathogens, which have a huge arsenal of cell wall–degrading enzymes and diverse mechanisms to mechanically breach CWI. In addition, a number of abiotic stress factors can alter the state of the wall. These wall alterations can serve as threat indicators and trigger stress responses (4, 67).

In accordance with the numerous potential functions of cell walls, the evidence for cell wall feedback signaling pathways is overwhelming, even if some of it is circumstantial, as outlined below. Most of the work has been carried out in *Arabidopsis*; therefore, what is described below refers to this species unless otherwise stated. Furthermore, *Arabidopsis* genes with known functions in CWS are listed in **Table 1**.

2.2. Cell Wall Signaling: The Evidence

It has long been known that the products of cell wall breakdown can lead to physiological responses that can only be explained by signaling (3, 93, 155). Cell wall fragments mainly act as danger-associated molecular patterns (DAMPS); i.e., they are perceived by the cell as signals for a loss of structural integrity and the presence of pathogen threats (4, 151). Consistent with the large arsenal of pathogen-derived cell wall–degrading enzymes targeting diverse cell wall components, signaling activity has been described for breakdown products of pectin (11, 43, 195, 214), cellulose (44, 118, 136), hemicellulose (6, 35, 84, 142, 143), and β-1,3-glucan (147, 220), as well as for the trisaccharide 31-β-D-Cellobiosyl-glucose and the tetrasaccharide 31-β-D-Cellotriosyl-glucose (233). However, cell wall fragments have also been implicated in development (12, 173, 240). The best-studied cell wall DAMPs are oligogalacturonides, breakdown products of pectin. Pectin is a preferred target of many invading pathogens (33) as it is much more susceptible to enzymatic degradation than cellulose. The strongest defense reactions are induced by oligogalacturonides with a chain length of 10–15 galacturonic acid residues derived from demethylesterified pectin (11, 68, 93, 152, 155, 156, 195). In addition, oligogalacturonide trimers and tetramers can also promote defense (43, 195). Both kinds of oligogalacturonides are also suspected to play a role in development, for example, by antagonizing auxin (10, 23) and by inhibiting photomorphogenesis (196). The production of the defense-active oligogalacturonides requires the activity of PME to remove methyl groups, which renders the demethylesterified HG susceptible to the hydrolytic activity of polygalacturonases (70, 216). Illustrating the arms race between plants and their pathogens, a recent study analyzing oligogalacturonide production in *Arabidopsis* leaves under attack by the necrotrophic fungus *Botrytis cinerea* revealed that successful pathogens can evade oligogalacturonide signaling by employing pectin lyase, an enzyme class not found in plants, which uses β-elimination to degrade highly methylesterified pectin, thus producing oligogalacturonides with very little signaling activity (214).

Table 1 *Arabidopsis* **genes with demonstrated function in cell wall signaling (CWS)**

Genes	Function in CWS context	Sites of action	Subcellular localization	Reference(s) for CWS function
***Catharanthus roseus* RECEPTOR-LIKE KINASE1-LIKE proteins**				
THESEUS1 (*THE1*)	Response to cellulose biosynthesis inhibition, receptor for RAPID ALKALINIZATION FACTOR 34 (RALF34)	Ubiquitous	Plasma membrane	83, 104, 139, 172
FERONIA (*FER*)	RALF receptor, immune receptor scaffolding, pectin sensing	Ubiquitous	Plasma membrane	56, 57, 66, 100, 112, 135, 176, 192, 200
ANXUR1 (*ANX1*), *ANX2*	RALF receptor, cell wall integrity maintenance	Pollen tube	Plasma membrane	17
ERULUS (*ERU*)	Cell wall integrity maintenance	Root hair	Plasma membrane	61
HERKULES1 (*HERK1*), *HERK2*	Cell wall integrity maintenance	Ubiquitous	Plasma membrane	61
BHUDDA'S PAPER SEAL1 (*BUPS1*), *BUPS2*	RALF receptor, cell wall integrity maintenance	Pollen tube	Plasma membrane	77, 78, 243
WALL-ASSOCIATED KINASES				
WALL-ASSOCIATED KINASE1 (*WAK1*), *WAK2*	Pectin and oligogalacturonide perception, regulation of growth and immune responses	Ubiquitous	Plasma membrane	25, 46, 47, 102, 123, 125, 129, 215
Leucine-rich repeat receptor-like kinases/receptor-like proteins				
FEI1, *FEI2* (*FEI1*, *FEI2*)	Response to cellulose biosynthesis inhibition	Ubiquitous	Plasma membrane	61, 232
MDIS1-INTERACTING RECEPTOR LIKE KINASE2 (*MIK2*)	Response to cellulose biosynthesis inhibition	Ubiquitous	Plasma membrane	209
STRUBBELIG (*SUB*)	Required for cell wall integrity response, root epidermal patterning, ovule development	Ubiquitous	Plasma membrane	31, 32, 34, 73, 128, 134, 198
RECEPTOR-LIKE PROTEIN44 (*RLP44*)–*BRASSINOSTEROID INSENSITIVE 1* (*BRI1*)	Response to pectate limitation, vascular cell–type specification, stress responses	Ubiquitous	Plasma membrane	110, 111, 224, 225
RECEPTOR-LIKE PROTEIN12 (*RLP12*)	Response to cellulose biosynthesis inhibition	Root, hypocotyl	Plasma membrane	5
PEP1 RECEPTOR 1 (*PEPR1*), *PEPR2*	Dampening of cell wall integrity	Ubiquitous	Plasma membrane	61

(*Continued*)

Table 1 (*Continued*)

Genes	Function in CWS context	Sites of action	Subcellular localization	Reference(s) for CWS function
Others				
MID1-COMPLEMENTING ACTIVITY1 (*MCA1*), *MCA2*	Response to cellulose biosynthesis inhibition	Ubiquitous	Plasma membrane	61
MECHANOSENSITIVE CHANNEL OF SMALL CONDUCTANCE-LIKE 2 (*MSL2*), *MSL3*	Response to cellulose biosynthesis inhibition	Ubiquitous	Chloroplast	61, 101
LEUCINE-RICH REPEAT EXTENSINS (*LRXs*)	Required for FER functions	Ubiquitous	Cell wall	57, 146, 238
MEDIATOR5a (*MED5a*), *MED5b*	Response to lignin perturbation	Ubiquitous	Nucleus	19
ARABIDOPSIS DEHISCENCE ZONE POLYGALACTURONASE 1 (*ADPG1*)	Generation of cell wall–derived signal upon lignin perturbation	Normally inflorescence but induced elsewhere upon lignin perturbation	Cell wall	75
LORELEI (*LRE*)/*LORELEI-LIKE GLYCOSYLPHOSPHATIDYLINOSITOL-ANCHORED PROTEINS* (*LLGs*)	Essential components of CrRLK1 signaling	Ubiquitous	Plasma membrane	78, 133, 230
NITRATE REDUCTASE1 (*NIA1*), *NIA2*	Response to cellulose biosynthesis inhibition	Various tissues	Cytosol	80

Apart from these cell wall–derived danger signals, it became clear as early as 1990 that plant cells must have mechanisms in place to perceive the state of their cell walls. Cell cultures habituated to grow in the presence of cellulose biosynthesis inhibitors developed a unique cell wall composition adapted to sustain integrity without the load-bearing capacity of cellulose microfibrils (190). A key discovery for the field was made in 2000, when Burton and coworkers (26) reported that virus-induced gene silencing of a cellulose synthase isoform in *Nicotiana benthamiana* resulted in a compensatory increase in pectin content and a specific enrichment of demethylesterified HG epitopes, unraveling the existence of feedback loops that ensure cell wall homeostasis. In the years that followed, evidence for compensatory changes in response to cell wall alterations accumulated (15, 29, 58, 59, 105, 139), and some of the molecular components involved in CWS, such as the receptor kinases FERONIA (FER) and THESEUS1 (THE1) (described below), were revealed.

As we are only beginning to understand the complexity of CWS, it is not clear how many pathways actually exist. This is partially due to the intrinsic problem that feedback pathways are difficult to reveal. Owing to the homeostatic nature of many of the pathways involved, the identification of CWS components can require brute force approaches to overmatch the homeostatic capacity of feedback loops and reveal phenotypes that can be scored or screened for. These initial brute force approaches, such as cellulose biosynthesis inhibition or overexpression of cell wall modifiers, often cannot simultaneously serve as good proxies for a physiological stress condition but rather should be viewed as tools to reveal new molecular players in CWS. The physiological roles of these components then have to be unraveled in a second step with loss-of-function approaches under more natural conditions. In line with this, the machinery

responsible for orchestrating the response to cellulose biosynthesis inhibition was later discovered to be important for the defense against pathogens that challenge CWI (167, 209) as well as for regulating normal plant morphogenesis (83).

Cell wall integrity signaling (CWI signaling): one type of cell wall signaling, responding to loss of wall integrity; sometimes used interchangeably with signaling in response to cellulose biosynthesis inhibition

2.3. Beyond Cell Wall Integrity

To accommodate the extensive evidence for wall-related signaling responses that go beyond the maintenance of CWI, I suggest the use of the term cell wall signaling (CWS) to indicate any signaling event that occurs in response to cues from the cell wall. The often-used term cell wall integrity signaling (CWI signaling) would then be reserved for a specific case of CWS (**Figure 2**). Within the boundaries of this definition, the cell wall can thus be both upstream and downstream of CWS events, but a pathway that merely maintains wall integrity without upstream input from the cell wall itself would not qualify. Overlaps between CWS and defense signaling exist, as illustrated by the perception of cell wall breakdown product as DAMPs and the frequently observed tight connection between cell wall alterations and defense activation. Thus, a sharp distinction between development- and immunity-related CWS is neither achievable nor necessary. Instead, CWS is a broad umbrella term, fitting for a field that is only beginning to appreciate the breadth and complexity of a multitude of signaling pathways (**Figure 2**).

2.4. Utility and Shortcomings of Comparisons to Other Models

From early on, the field of plant cell wall–associated signaling was heavily influenced by the more advanced research on perception of the yeast cell wall, including the adoption of the focus on CWI signaling. While this comparison with yeast was certainly helpful as a guiding light, only limited molecular similarities have been found (154). Yeast CWI signaling relies on a

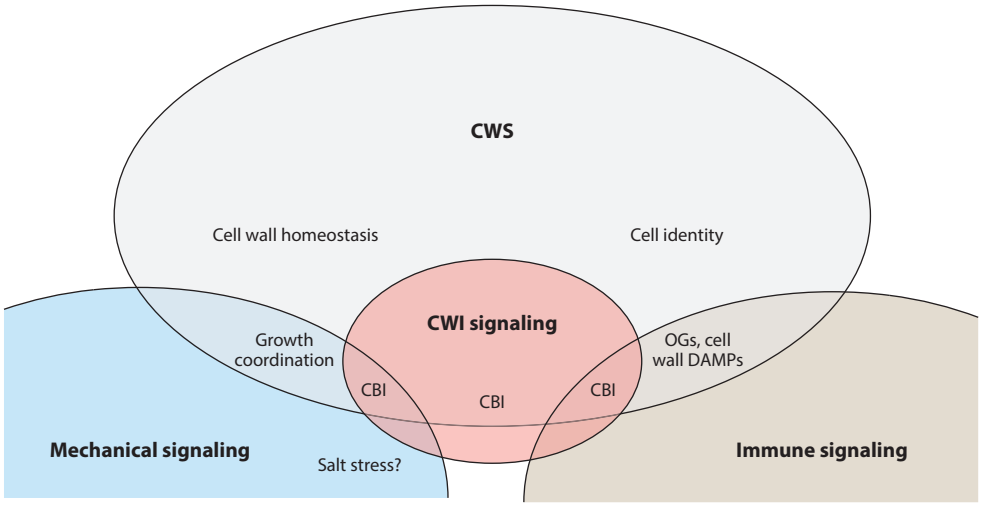

Figure 2

The relationship between cell wall, CWI, mechanical, and immune signaling. The commonly used term CWI signaling can be seen as categorizing a special case of CWS, which can have many additional roles besides the response to cell wall damage. Overlap with mechanical and immune signaling exists for both CWS and CWI signaling. Note that there is a sector of CWI signaling that does not overlap with CWS as defined here, in that it might control CWI and bursting but does not itself respond to cues from the cell wall. Abbreviations: CBI, cellulose biosynthesis inhibition; CWI, cell wall integrity; CWS, cell wall signaling; DAMP, danger-associated molecular pattern; OG, oligogalacturonide.

set of membrane-spanning nanosensors with spring-like extracellular regions (114). These sensors activate a signaling pathway involving the Rho1 GTPase and a mitogen-activated protein kinase (MAPK) cascade (132). However, this pathway can be triggered by a vast amount of other substances and cues and is not limited to signals from the wall (117). Moreover, one could argue that a too-strict adherence to the model of yeast CWI signaling could be impeding conceptual progress in the field as, after all, the potential roles of wall-associated signaling in multicellular plants greatly exceed those of unicellular organisms and also go significantly beyond the maintenance of structural integrity (see Sections 3 and 4). Conversely, maintaining CWI is vital for a unicellular organism, while arguably the structural integrity of many plant cells is expendable.

Another fruitful comparison can be drawn with the animal extracellular matrix (ECM), which plays important roles in a wide variety of signaling pathways. While the parallels are more conceptual than molecular [notwithstanding exceptions, such as the existence of a plant receptor recognizing animal adhesion peptide motifs (87)], the broad spectrum of functions can be liberating from the close confinements of CWI. For example, the stiffness of the animal ECM can be sensed by stretch-sensitive transmembrane protein complexes that link the ECM to the cytoskeleton (131, 210) but also by stretch-induced release of extracellular ligands (186, 191). In light of the multitude of cell wall–bound proteins (175, 180), it seems worthwhile to investigate whether similar indirect perception mechanisms exist in plants. Moreover, seminal work has shown that the ECM is an instructive part of the animal stem cell niche (113, 222), as biochemical signals present in the ECM, as well as its mechanical properties, govern cell fate decisions. For example, incubating mesenchymal stem cells on matrices with varying stiffness triggers acquisition of a wide range of progenitor fates (42, 62, 178). In addition, elastic matrices promote stem cell proliferation, whereas stiff matrices inhibit these processes (82, 109). Moreover, matrix tethering has a profound effect on stem cell differentiation independent of bulk tissue stiffness, demonstrating that the role of the ECM in governing cell fate is multifaceted (205).

It is certainly conceivable that similar mechanisms are available for plant CWS (**Figure 1*d***), such as conditional exposure of ligands depending on mechanical forces or conditional release of smaller ligands depending on changes in extracellular ion concentration or pH. It has already been shown that the cell wall affects the behavior of cell surface receptor proteins by restricting their mobility (140, 145). Furthermore, CWS components have been shown to affect cell identity (32, 110), similar to what has been described for brown algae (13). In the plant developmental patterning context, cell walls could serve as a persistent identity reinforcement signal when cells are no longer under the influence of hormone-mediated morphogenetic fields, for example, as cells get displaced from meristems. This role would be akin to what has been suggested for an epigenetic memory (14) and would accommodate the unique properties of plant patterning (**Figure 1*b*,*d***).

More generally, and consistent with these observations, it is now firmly established that development and patterning cannot be explained by biochemical gradients alone (63, 103, 150). The cell wall can act as a conduit for mechanical forces shaping development, and thus altered cell wall composition and properties presumably affect these mechanical signaling inputs (130, 212, 228) (**Figure 1*d***). However, the decoding of mechanical signals does not necessarily require cell wall–associated perception systems (36, 85, 86).

3. ROLES OF CELL WALL SIGNALING AND EXAMPLES IN RESPONSE TO THE DIFFERENT CELL WALL COMPONENTS

More and more evidence is accumulating that suggests that alterations in many, if not all, cell wall components can lead to a signaling response. The response to inhibition of cellulose biosynthesis is arguably the most studied case of cell wall–triggered signaling, but a specific response is also induced by interference with HG modification or biosynthesis (discussed in Section 3.2). Mutants

lacking discernible amounts of xyloglucan due to the genetic lesion of two xyloglucan xylosyltransferases (*xxt1 xxt2*) show altered cellulose content and changes in gene expression (229) that are assumed to compensate for the absence of the major *Arabidopsis* hemicellulose. Complex transcriptional rearrangements as well as loss of salt stress tolerance are also observed in arabinose-deficient mutants (187, 239). Furthermore, impairment of secondary cell wall biogenesis, such as in mutants with altered lignin content or composition but not in those with altered xylan biosynthesis (65), leads to substantial growth impairments that have been shown to depend on signaling-mediated rearrangement of developmental programs (18, 74, 75, 138). For example, genetic impairment of lignin biosynthesis can trigger defense signaling responses that negatively affect growth by elevating salicylic acid content (72). Conversely, inhibiting salicylic acid signaling restores growth despite the altered lignin composition, indicating that the morphological phenotype is due to a secondary response and not a direct effect of the cell wall properties.

Importantly, due to the connectivity of the various cell wall components and the lack of knowledge regarding sensing systems, it is at present unclear whether all cell wall components are under surveillance or whether some serve as proxies for the state of the wall as a whole and are guarded by sentinel receptors. Furthermore, derived and aggregate wall parameters, for example, membrane tension and mechanical stress, rather than or in addition to wall biochemistry might be sensed (96, 98, 101, 154). In fact, despite the wealth of evidence for cell wall–associated signaling events, in no instance was it revealed how exactly wall cues are perceived. Therefore, it is crucial to decipher cell wall–sensing mechanisms and determine their agonists. Corollary to these observations, it is difficult and risky to interpret mutant phenotypes with respect to the molecular function of the mutated gene product as long as putative response pathways are not understood. While this is possibly valid for any analysis of genetic diversity, cell wall–related mutants and their wall plasticity exemplify the notion in a particularly impressive manner: Severe growth impairments in lignin or cellulose biosynthetic mutants caused by defense and THE1-mediated signaling, respectively, and phytohormone signaling-induced morphology changes in response to pectin modification provide powerful examples (74, 104, 224), which are discussed in more detail below.

3.1. Cellulose-Triggered Cell Wall Signaling

It has long been known that genetic or pharmacological interference with cellulose biosynthesis triggers a wide variety of responses, including cell swelling, reduction of elongation growth, induction of defense gene expression, and phytohormone accumulation, as well as deposition of callose and lignin (29, 48, 58, 59, 80, 94, 206, 227). Unsurprisingly, such a complex response involves a number of cellular signaling pathways and compounds, including, for example, abscisic acid and jasmonate signaling, as well as the precursor of ethylene, 1-aminocyclopropane-1-carboxylic acid (ACC) (5, 206). Interestingly, cellulose biosynthesis inhibition causes a nitrate reductase–dependent disturbance of cytokinin homeostasis, resulting in altered cell cycle activity in root meristems (80). In addition, a recent study reports that cellulose biosynthesis inhibition also interferes with specification of hair and nonhair cells in the root epidermis (32).

A number of chemicals can be used to inhibit cellulose biosynthesis, and some of them have been used as herbicides. The best-studied cellulose synthase inhibitor is isoxaben, which upon application leads to a near-instantaneous relocalization of CSCs from the plasma membrane to intracellular compartments in *Arabidopsis* (41, 90, 158), whereas another cellulose biosynthesis inhibitor, 2,6-dichlorobenzonitrile, leads to stalling of CSCs in the plasma membrane (45). Some of the responses to cellulose biosynthesis inhibition induced by isoxaben, but not CSC internalization, can be suppressed by osmotic support (61, 80, 94). Thus, while the internalization or stalling of cellulose synthases is the primary effect of cellulose biosynthesis inhibitors (49, 184), the signaling-mediated response seems to depend on consequential cell wall alterations that can

be sensed by CWS systems and to be sensitive to treatment with osmoticum. In agreement with this, enzymatic cell wall degradation elicits similar, osmoticum-sensitive defects (61), indicating that the response to isoxaben is indeed a cell wall damage response, likely with the contribution of mechanoperception (96). This is corroborated by the observation that jasmonate-Ile accumulation in cellulose-deficient mutants likely depends on the mechanical pressure exerted by swollen cells and that the accumulation of the active hormone can be triggered by hypoosmotic treatment (149). Interestingly, cellulase alone is not sufficient to elicit cellulose biosynthesis inhibition–like phytohormone accumulation but requires the addition of pectin-degrading enzymes, indicating once again the highly connected network-like character of the cell wall (61). A number of factors required for the response to altered cellulose biosynthesis have been identified, such as the receptor-like kinases (RLKs) THE1 (104) and STRUBBELIG (SUB), also known as SCRAMBLED (31). A phenotypic clustering approach identified a number of genes required for the full cellulose biosynthesis inhibition response, including the RLKs *FEI2* and *MALE DISCOVERER1-INTERACTING RECEPTOR LIKE KINASE2* (*MIK2*) as well as the ion channels *MID1-COMPLEMENTING ACTIVITY1* (*MCA1*) and *MECHANOSENSITIVE CHANNEL OF SMALL CONDUCTANCE-LIKE 2* (*MSL2*)/*MSL3* (61), and confirmed THE1's proposed role as a key signaling element in the cellulose biosynthesis inhibition response and possible sensor of cell wall damage. Conversely, THE1, FER, and MIK2 were also shown to be involved in defense against *Fusarium oxysporum* (141, 209). However, pattern-triggered immunity components, such as the receptors for plant elicitor peptides PEPR1 and PEPR2, exert a dampening effect on the cellulose biosynthesis inhibition response, underlining the complex interlacing of CWI and defense signaling (61).

3.2. Pectin-Triggered Cell Wall Signaling

Pectin is the most dynamic and most charged cell wall component and is intimately connected to all other cell wall polysaccharides and a number of different cell wall proteins (217, 218, 235, 244, 245). Pectin and/or pectin fragments can apparently serve as indirect readouts for wall stress caused by other components, including lignin (75) and light signaling (196). Lignin, one of the prominent factors in limiting the accessibility of secondary cell wall biomass for enzymatic and nonenzymatic breakdown, is a key target for efforts to improve the exploitation of this renewable raw material. However, plants with reduced lignin content or altered lignin quality typically show growth defects that severely hamper their suitability for biomass production (18, 74). These growth defects can be caused by signaling events that result in salicylic acid accumulation, which, in turn, causes dwarfism (74). Recent evidence suggests that downstream of lignin perturbation, unknown CWS triggers compensatory cell wall adjustments and differential transcription of cell wall–related genes. The product encoded by one of these genes, the normally inflorescence-restricted polygalacturonase ARABIDOPSIS DEHISCENCE ZONE POLYGALACTURONASE 1 (ADPG1), releases pectic breakdown products that elicit defense responses including the growth-restricting salicylic acid accumulation (75, 76).

Genetic or pharmacological interference with PME-mediated pectin modification triggers an increase in the signaling strength of the growth-regulatory brassinosteroid (BR) signaling pathway (224). Among BR-regulated genes, cell wall biosynthesis and modifying enzymes are strongly overrepresented, and BR signaling has been shown to directly control cell wall properties (168, 181, 201, 231, 237). Thus, activation of BR signaling most likely represents a compensatory reaction to the interference with pectin modification. Consistent with this, inducible expression of a PME inhibitor protein results in only transient reduction of global PME activity, before BR-dependent transcriptional upregulation of pectin biosynthesis and PME genes mask this primary effect (224). While it remains to be seen how the state of pectin methylesterification is sensed

by the cell, the mechanism of BR signaling activation has been resolved. The pectin-triggered BR response critically depends on RECEPTOR-LIKE PROTEIN44 (RLP44), an evolutionarily conserved, broadly expressed transmembrane protein with an extracellular leucine-rich repeat (LRR) domain. RLP44 directly interacts with both the brassinosteroid receptor BRASSINOSTEROID INSENSITIVE 1 (BRI1) and its coreceptor BRI-ASSOCIATED RECEPTOR KINASE (BAK1) and acts as a scaffold promoting the association of receptor and coreceptor (110, 225), substituting for the extracellular ligand that induced heterooligomerization of LRR-RLK receptor complexes (108). Notably, the responses to pectin modification and to cellulose biosynthesis inhibition can be genetically separable, as RLP44 is required for the response to the former but completely dispensable for the latter (61). Apparently, more than one pectin-sensing pathway exists, as, for example, the FER-mediated response to salt stress seems to be initiated by pectin monitoring (described below) (66, 67), and, as mentioned in Section 2.2, pectin breakdown products act as elicitors for defense signaling.

Pectin is especially suited for surveillance as it is the most dynamic cell wall component, owing to the activity of PMEs and other pectin-modifying enzymes. Due to the multitude of epitopes, states, and interactions, pectin is presumably also the cell wall component that is most responsive to the environment, as interactions with ions and other charged molecules can alter its configuration and physical properties (27, 197, 236). Consistent with this, competition between Ca^{2+} and Na^{+} ions has been implicated in salt stress perception by FER (66), and THE1 mutant alleles show an altered growth adaptation to the presence of heavy metals, which are also assumed to interfere with Ca^{2+}-mediated cross-linking of pectate (unmethylesterified pectin) (172). LRR extensin (LRX) proteins are also required for salt stress response and associate with pectin (238). The recently discovered ability of pectin to undergo phase separation (64, 91, 92) further expands the functional landscape of this complex polymer. A comparison of pectin modification in different plant species suggests that pectin demethylesterification originated as a cell wall–consolidating mechanism. This wall-fortifying role of pectate can be observed, for example, in single-celled zygnematophycean green algae, believed to be the algal group most closely related to land plants (116, 171). Extensive studies on an extant member of this group, *Penium margaritaceum*, have shown that at the growing end of the alga, methylesterified pectin is deposited, which is later solidified by PME activity (51–53, 157). A similar mechanism is operative in pollen tubes, where highly methylesterified pectin is secreted at the growing tip, whereas demethylesterified pectin dominates at the stiffer shank. Accordingly, PME activity, spatially regulated by PME inhibitor proteins, is required for pollen tube integrity (20, 21, 115, 174, 226). Thus, in these isolated cellular contexts, the function of demethylesterified pectin is consistent with its gelling properties in the presence of calcium ions observed in vitro (213); i.e., demethylesterification leads to gelling and stiffening. In more complex, multicellular contexts, however, pectin seems to exert different functions beyond wall consolidation, and the simple relationship of methylesterified, soft pectin enabling growth and demethylesterified, rigid pectin conferring stability is broken (22, 161, 164, 166). On the contrary, in many tissues, pectin demethylesterification seems to be associated with growth and a more extensible wall (160–162). These in vivo effects of pectin, which are much less intuitive and more complex than what is observed in vitro, are therefore consistent with its proposed central role in CWS.

3.3. Response to Altered Lignin and Its Implications for Biotechnological Utilization of Biomass

As indicated above, polyphenolic lignin is the main reason for the recalcitrance of plant secondary cell wall biomass and is therefore a prime target for bioengineering. However, attempts to reduce

Cell wall recalcitrance: the resistance of cell walls, especially lignified secondary cell walls, towards enzymatic, chemical, or physical degradation

cell wall recalcitrance by altering lignin content or quality are often hampered by unfavorable growth responses of the plant, such as dwarfism. Initially assumed to reflect insufficient mechanical support caused by the lignin alterations, it is now clear that these growth trade-offs are caused by surveillance mechanisms and can be suppressed by interfering with the respective pathways. For example, growth of the *ref8* mutant, in which a mutation of a lignin biosynthetic gene leads to a favorable lignin quality and dwarfism, can be restored by a mutation in specific subunits of the mediator complex (18). The multisubunit mediator acts as a transcriptional coactivator in the RNA polymerase II preinitiation complex by connecting with transcription factors at promoter and enhancer elements. Thus, the mediator affects a plethora of transcripts, although it is currently not known how specific responses are generated or which signaling pathways converge on mediator subunits. Importantly, mutation of mediator subunits largely restores the vast transcriptional rearrangements in *ref8*, suggesting that the mediator complex is genuinely involved in the secondary response to lignin alteration. Notably, the growth-restoring mutation of the mediator subunits does not affect *ref8* lignin quality, underlining that the altered lignin with favorable properties can sustain growth without problems. Other lignin mutants can be rescued by interference with the accumulation of salicylic acid, which has been shown to be the main cause for dwarfism and represents a secondary effect of the cell wall alterations, indicating that secondary cell wall properties or composition is also under surveillance (74). These examples illustrate that successful tailoring of plant cell wall properties requires understanding of CWS.

4. CLASSES OF POTENTIAL CELL WALL RECEPTORS

Naturally, proteins that could potentially act as cell wall receptors have drawn the most attention in CWS studies. Some of these candidates are listed below and depicted in **Figure 3**. However, it should be noted that genetic involvement in a CWS pathway and belonging to a class of receptor proteins are not enough to constitute a cell wall receptor, as signaling pathways can be multilayered, and some of the receptors might be involved in signal-amplifying loops. Likewise, the binding to cell wall components might not be related to signaling but might serve as anchoring or regulate trafficking. A bona fide cell wall receptor, on the other hand, would have a cell wall agonist that demonstrably affects its signaling outputs. Arguably, so far, none of the receptor candidates, with the possible exception of FER (135), have met this criterion.

4.1. *Catharanthus roseus* RECEPTOR-LIKE KINASE1-LIKE Proteins

The *Catharanthus roseus* RECEPTOR-LIKE KINASE1-LIKE (CrRLK1L) protein family contains the best-studied group of CWS components so far (**Figure 3*a***). CrRLK1Ls carry a malectin-like extracellular domain that has been hypothesized to interact with cell wall carbohydrates based on the ability of animal malectin to interact with diglucose motifs (183). Indeed, cell wall association with CrRLK1L extracellular domains has been described (66, 135), but so far it has not been possible to unravel the binding mechanism (153), which seems to differ from that between malectin and diglucose (182). In addition, CrRLK1L proteins interact with LORELEI-LIKE GLYCOSYLPHOSPHATIDYLINOSITOL (GPI)-ANCHORED PROTEINS (LLGs) that are required for some, if not most, CrRLK1L functions (78, 133, 230). Intracellularly, CrRLK1Ls possess a kinase domain, although it is not clear which aspects of CrRLK1L function actually require kinase activity (120, 148). Signaling downstream of CrRLK1L has been shown to employ Rho-of-plants (ROP) GTPases, ROP-GUANINE NUCLEOTIDE EXCHANGE FACTORS (ROP-GEFs), and RECEPTOR-LIKE CYTOPLASMIC KINASES (RLCKs) (16, 54, 71, 135, 203). Domain swap experiments in which the extracellular domains of three CrRLK1Ls were exchanged have indicated that downstream signaling might be at least partially shared

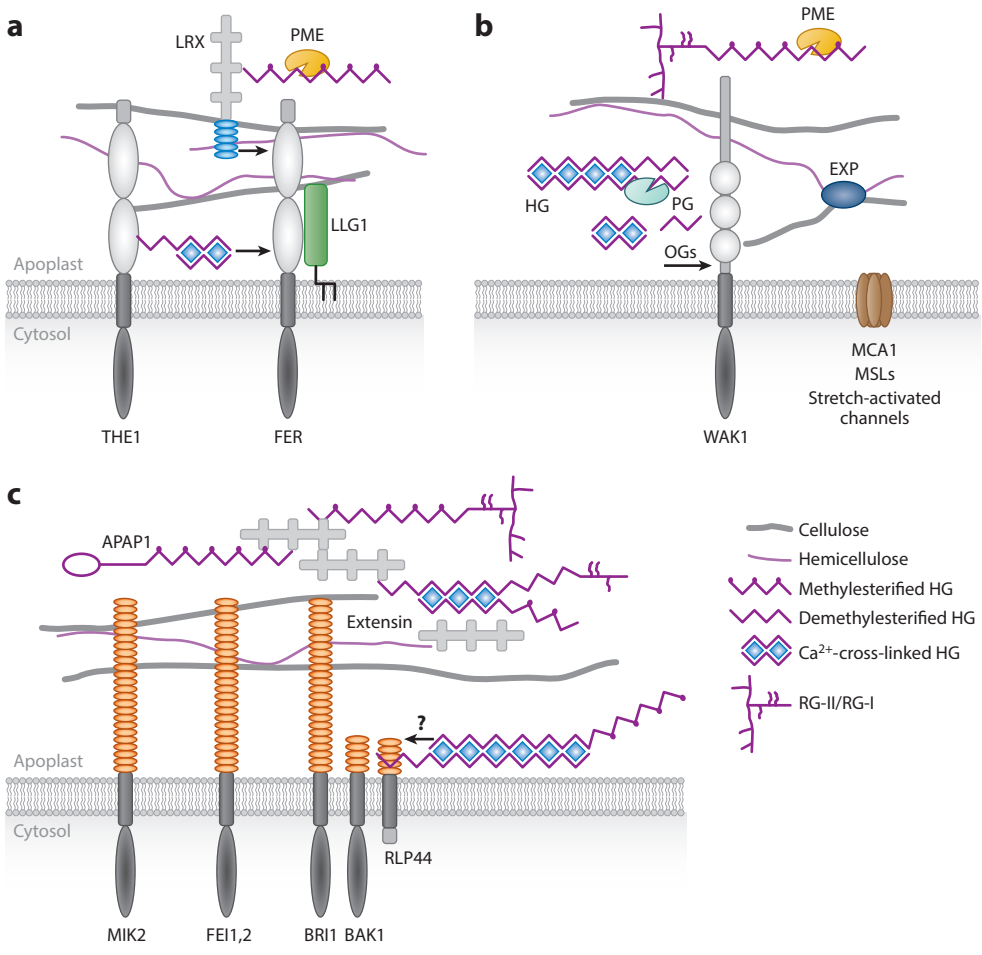

Figure 3

Overview of cell wall receptor candidates. The main structural cell wall components are indicated in a simplified format. Note that cell wall polysaccharides interact with each other in manners that are too complex and manifold to display. Putative wall receptors of the (*a*) CrRLK1L (THE1, FER), (*b*) WAK (WAK1), and (*c*) LRR-RLK/RLP (MIK2, RLP44) classes are indicated, together with channels that might play a role in detecting cell wall–derived cues. Abbreviations: APAP1, ARABINOXYLAN PECTIN ARABINOGALACTAN PROTEIN1; BAK1, BRI1-ASSOCIATED RECEPTOR KINASE; BRI1, BRASSINOSTERIOID INSENSITIVE 1; CrRLK1L, *Catharanthus roseus* RECEPTOR-LIKE KINASE1-LIKE; EXP, expansin; FER, FERONIA; HG, homogalacturonan; LLG1, LORELEI-LIKE GLYCOSYLPHOSPHATIDYLINOSITOL-ANCHORED PROTEIN 1; LRR, leucine-rich repeat; LRX, leucine-rich repeat extensin; MCA1, MID1-COMPLEMENTING ACTIVITY1; MIK2, MALE DISCOVERER1-INTERACTING RECEPTOR LIKE KINASE2; MSL, MECHANOSENSITIVE CHANNEL OF SMALL CONDUCTANCE-LIKE; OG, oligogalacturonide; PG, polygalacturonase; PME, pectin methylesterase; RG-I, rhamnogalacturonan I; RG-II, rhamnogalacturonan II; RLK, receptor-like kinase; RLP, RECEPTOR-LIKE PROTEIN; THE1, THESEUS1; WAK, WALL-ASSOCIATED KINASE.

between CrRLK1Ls (120), whereas specificity is conferred by the extracellular region. In line with this, several CrRLK1L proteins have been shown to activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, resulting in extracellular reactive oxygen species bursts (17, 48, 55).

The best-characterized CrRLK1L, FER, was originally identified as a female determinant of pollen tube discharge (112, 176) and later was revealed to play multifaceted roles in development and immunity. FER is the receptor for peptides of the RAPID ALKALINIZATION FACTOR (RALF) class, such as RALF1 and RALF23, and acts as a scaffold that promotes the interaction of other receptor-like kinases (100, 200). As a receptor for RALF1, FER is required for RALF-induced growth inhibition and cytosolic calcium spikes (100). Another FER ligand, RALF23, has a negative effect on immunity by reducing the formation of FER-scaffolded immune receptor complexes, whereas RALF17 activates immunity in a FER-dependent manner. In addition to these already complex functions as a growth and immunity integrator, FER has been linked to the cell wall by a number of studies. First, FER interacts with members of the LRX family of cell wall– (pectin-)interacting proteins (**Figure 3*a***), and mediates vacuolar expansion in response to cell wall cues (57). The vacuole occupies 30–40% of the cell volume in meristematic root cells but 80–90% in fully elongated cells. This increase in vacuole size can be triggered by cell wall acidification before the developmentally regulated onset of elongation. Conversely, interfering with pectin demethylesterification inhibits vacuolar expansion, indicating that this growth-accompanying process responds to inputs from the cell wall. This inhibition of vacuole expansion depends on both FER and the cell wall–binding of LRXs, suggesting that LRXs link the cell wall and plasma membrane by interacting with FER (57).

Increased salinity causes a reduction of root growth accompanied and most likely caused by a loss of cell anisotropy and reduction in cell wall stiffness. After a brief recovery period, cell wall stiffness is regained and growth resumes (66, 79). This growth and cell wall recovery critically depend on FER, and mutant plants fail to maintain CWI, experiencing bursting of epidermal cells. Notably, the *murus1* mutant, which has an impaired synthesis of GDP-L-fucose and thus is defective in fucose-mediated borate cross-linking of RG-II, shows similar defects, indicating that the ability to form pectin cross-links is critically required for salt tolerance. Supporting this notion, the *fer* mutant can be rescued by elevated calcium and borate in the medium, consistent with the idea that HG and RG-II cross-links are attacked by monovalent cations, and the ensuing reduction in wall stiffness of the altered pectin conformation is sensed by a CWS pathway involving FER. Further supporting a central role of the cell wall in the perception of salinity, *lrx* mutants show a phenotype similar to that of *fer* with respect to salt sensitivity (238), as independently observed in the context of cell wall–mediated inhibition of vacuolar expansion (57). Notably, FER has been reported to associate with pectin in vitro (66, 135), supporting a potential role as a cell wall receptor. A recent study demonstrated that FER controls demethylesterified pectin accumulation at the filiform apparatus, the cell wall–rich structure at the entrance to the female gametophyte in the ovule (56). Pollen tube arrival triggers the accumulation of nitric oxide in the filiform apparatus, which, in turn, switches off the activity of chemical attractants for other pollen tubes. Astonishingly, nitric oxide release depends on the presence of both FER and demethylesterified pectin and can be triggered by fragmented pectate in a FER-dependent manner (56).

Furthermore, FER is also involved in the response to mechanical stress induced by the root substrate. Compressive strain results in a biphasic elevation of intracellular calcium, accompanied by an alkalinization of the root meristem extracellular space (192). Part of this response is dependent on FER, and the erratic expansion patterns in *fer* root meristems would be consistent with a role for mechanical feedback, sensed by FER, in growth coordination. It should be noted that *fer* mutants themselves have an altered cell wall composition (234) and, thus, presumably altered mechanical properties and that it is currently unknown whether the cell wall–associated

roles of FER involve the RALF peptides. However, an attractive hypothesis is that RALF availability might be modified by the state and/or composition of the cell wall, reminiscent of the interaction of growth factors and the animal ECM. Finally, pectin perception by FER has been implicated in regulating the morphogenesis of leaf epidermal pavement cells (135, 203). Notably, the publication by Lin et al. (135) is the first report of a non-DAMP cell wall agonist (pectin) activating a receptor (FER), leading to a measurable downstream response (Rho GTPase activation). It also should be noted that this CWS pathway seems to regulate development and does not seem to constitute a cell wall damage response.

THE1 was the first receptor implicated in CWS (**Figure 3*a***), as it is genetically required to mediate growth inhibition, ectopic lignification, and defense gene activation in response to a lesion in primary cell wall cellulose synthases (104). Besides the central role of THE1 in the response to cellulose biosynthesis inhibition, it has been recently shown to be a receptor for an extracellular peptide of the RALF family, RALF34 (83). Interestingly, the RALF34-THE1 signaling module is important for the tuning of lateral root initiation, reminiscent of the role of the yeast CWI pathway in bud formation. Remarkably, the RALF34-THE1 interaction is susceptible to acidic pH, suggesting the existence of an amplification loop due to the alkalinizing activity of RALF34 (83). Interestingly, RALF34 can also be perceived by pollen tube CrRLK1Ls ANXUR1/ANXUR2 and BUPS1/BUPS2. In the context of fertilization, ovule-expressed RALF34 induces pollen tube rupture and sperm cell release; i.e., it dramatically reduces pollen tube CWI (77). RALF34 competes with pollen tube–expressed RALF4 and RALF19, the perception of which depends on the aforementioned pollen tube CrRLK1Ls, LRXs, and LLG2 and LLG3, forming an autocrine CWI maintenance signaling module (77, 78, 146, 243). Further work needs to unravel to what extent this CWI maintenance mechanism is also responsive to cell wall cues or whether the RALF-CrRLK1L module instead acts as a kind of dead man's switch primed to be triggered by the competing ovule-derived RALF4 upon arrival of the pollen tube at its destination. It has been noted that binding to LRX proteins exposes a highly basic surface patch in RALFs, which could mediate interaction with charged cell wall components (153), but, clearly, more work is needed to unravel the intricacies of this enigmatic signaling module.

4.2. Wall-Associated Kinases

Members of the WALL-ASSOCIATED KINASE (WAK) family have been identified as potential CWS components due to the tight interaction of WAK1 with pectin and its role in cell elongation (102, 125, 129, 215). Biochemical characterization of WAK1 revealed that the N-terminal part of the extracellular domain can associate with demethylesterified pectin or polygalacturonic acid, whereas the epidermal growth factor (EGF)-like repeats are not involved in cell wall binding (46, 47, 123) (**Figure 3*b***). The WAK1 extracellular domain shows a clear preference for pectate in the Ca^{2+}-cross-linked configuration, and binding is greatly diminished by methylesterification (46). Shorter fragments of HG and oligogalacturonides are also bound, but not monomeric galacturonic acid or other types of pectin (123). The interaction seems to be charge-based and is mediated by patches of basic amino acids (47), as described for the interaction between the LRR protein POLYGALACTURONASE INHIBITING PROTEIN1 (PGIP1) (199) and peroxidases (30, 189). These ionic interactions are markedly different from the binding mechanism of carbohydrate-binding modules (CBM) that are found, for example, in microbial cell wall–degrading enzymes or malectin and that act through hydrophobic stacking between aromatic residues and the sugar rings (81, 182). This type of pectate interaction should be sensitive to the ionic conditions and would thus provide a means to detect changes in the environment. However, pectins have been reported to be bound extremely tightly to the WAK extracellular domains in vivo (100, 213). Apart from the firmly established interaction with pectin, WAK signaling has been

shown to be responsive to HG in the case of WAK2 (123) and to oligogalacturonides in the case of WAK1 (25), regulating cell expansion and defense responses, respectively (124, 127). Thus, WAKs seem to be CWS receptors regulating both development and defense, and competition between longer HG fragments and oligogalacturonides has been proposed to tilt the balance toward either development or defense (122, 126). Relatives of WAKs have been implicated in the response to pathogens, such as *Fusarium* (50). However, it is not known whether cell wall perception plays any role in these defense responses.

4.3. Leucine-Rich Repeat Receptor-Like Kinases and Receptor-Like Proteins

LRR-RLKs form the largest class of RLKs in land plants and are capable of forming a complex interaction network that is further elaborated by LRR-RLPs, proteins similar to LRR-RLKs but lacking the kinase domain (**Figure 3*c***). Among the LRR-RLKs implicated in CWS are FEI1 and FEI2, which are required for cellulose synthesis and controlled cell elongation under elevated sugar conditions (232) as well as for proper organization of seed coat mucilage (99). FEI1 and FEI2 have been genetically linked to SALT OVERLY SENSITIVE 5 (SOS5), an AGP, which is also required for functions regulated by FEI1/FEI2 (9). While the nature of the biochemical thread from the cell wall to the FEI/SOS5 pathway remains to be shown, FEI2 has recently been demonstrated to act downstream of THE1 in the response to cellulose biosynthesis inhibition (61), confirming a role in CWS for the FEIs but rendering a role as cell wall sensor unlikely.

Another LRR-RLK linked to THE1 is MIK2, which is required for the response to cellulose biosynthesis inhibition but is also involved in combatting abiotic and biotic stress (209). Salt stress induces biomass reduction and left-handed root skewing in *mik2* loss-of-function mutants, phenotypes that depend on the presence of THE1. Independently of THE1, MIK2 is also required for the response to the fungal pathogen *F. oxysporum* (209), suggesting that MIK2 is a possible integrator of development and stress.

A newly discovered player in CWS is the atypical LRR-RLK SUB. SUB is a well-known developmental regulator, critically important for the specification of epidermal cell fate patterning, floral morphogenesis, and integument outgrowth (34, 73, 128, 134, 198). A recent study revealed that SUB not only participates in the response to cellulose biosynthesis inhibition independently from THE1 and MIK2 (31) but also has activity that is regulated by the cell wall, and cellulose synthesis inhibition can phenocopy *sub* loss-of-function mutants with respect to misspecification of epidermal cell fate and ovule morphology (32). Conversely, these results show that the state of the cell wall can determine cell fate, reminiscent of the role of the ECM in animals. Cell fate maintenance is also controlled by RLP44, which conveys the state of the cell wall to BR signaling (described in Section 3.2). Remarkably, RLP44 is required for maintaining procambial cell identity in the root, as *rlp44* mutants show ectopic xylem in place of procambial cells (110). It is not yet clear which role the cell wall plays, if any, in RLP44-mediated cell identity maintenance, and it remains to be determined whether RLP44 directly senses changes in the wall. Conceivably, RLP44 might occupy pectate epitopes, which might become limiting under certain conditions, releasing RLP44 to interact with the BR receptor complex and thus conferring responsiveness to wall state (**Figure 3*c***). Alternatively, RLP44 might only be the last link in a longer chain of cell wall perception components. However, cell identity maintenance downstream of RLP44 was revealed to occur through the receptor complex for the phytosulfokine (PSK) peptide, while BRI1 only plays an indirect role. As observed with the BR receptor heterodimer, RLP44 promotes association of the PSK receptor with its coreceptor. Genetic and biochemical evidence indicates that the BR and PSK receptor complexes compete for RLP44, and that RLP44 availability can be limiting, at least for PSK signaling (111), indicating how complex the integration of CWS and developmental networks can be.

5. CONCLUSIONS

Due to exciting recent discoveries, feedback signaling from the cell wall has drawn a lot of interest from diverse fields such as developmental biology and plant–pathogen interaction. Today, it is firmly established that CWS pathways are in place to monitor the state of the cell wall and that information obtained this way is integrated with an increasing variety of signaling networks. However, much remains to be deciphered in the near future. For example, an obvious and persistent shortcoming in the field is that a plausible perception mechanism is not known for any of the putative cell wall receptor proteins. Resolving this issue for any CWS pathway would constitute a major breakthrough for the field. Moreover, the full breadth of how the state of the cell wall is conveyed to the cell interior is not understood. While it is conceivable that cell wall molecules are sensed through biochemical interactions, and while evidence for cell wall association of proteins is abundant, the complexity of carbohydrate biochemistry and the difficulty of obtaining or producing pure and defined cell wall fragments have severely hampered progress. Groundbreaking work in the chemical synthesis of defined carbohydrate oligomers (165) is a major step toward resolving the structure of receptors in their glycan-bound state, especially if these efforts succeed in producing GalA-based fragments (i.e., pectic oligomers). Future research should also address whether the cell wall state can be inferred indirectly, for example, by sensing membrane tension or by the influence the cell wall has on proteins involved in signaling or, potentially, their ligands.

As outlined above, research on CWS processes is justifiably focused on plasma membrane proteins that could be involved in sensing. However, not much is known about the integration of feedback from the cell wall with intracellular signaling networks controlling development. If ECM signaling in other kingdoms bears any similarity to plant CWS, a huge intracellular landscape of cell wall–associated signaling may await discovery.

One underdeveloped field of research is how the cell wall is connected to cellular metabolism. Cell wall biosynthesis has attracted a lot of attention, and impressive progress has been achieved in our understanding of cell wall biosynthetic enzymes and sugar conversion pathways. However, how the state of the wall, the cell's primary carbon sink, feeds back on cellular metabolism, potentially involving cell wall salvage pathways, is largely unknown. In this respect, it is interesting to note that many cell wall–associated mutants are hypersensitive to elevated sugar concentrations in their surroundings, but this common response is not understood. Thus, CWS research is not short on future tasks but can capitalize on the considerable progress achieved during the last decade (223).

SUMMARY POINTS

1. Plants are able to sense the state of the cell wall and integrate this feedback signaling into cellular decision making.
2. Diverse cell wall components are under surveillance, and their alterations trigger compensatory responses, often including cell wall modifications.
3. Feedback signaling from the plant cell wall through an ever-expanding repertoire of cell wall signaling pathways is involved in a multitude of cellular processes including cell wall homeostasis, cell morphogenesis, and cell identity maintenance.
4. Cell wall signaling, defined as signaling triggered by cell wall–derived cues, encompasses and goes significantly beyond cell wall integrity signaling.

5. The cell wall is a primary battleground of plants and pathogens, and products of cell wall breakdown can be perceived as danger signals, underlining the close connection of cell wall signaling and immunity.
6. A number of plasma membrane–localized receptor proteins involved in various cell wall signaling pathways have been identified, but the precise nature of the respective cell wall signals remains to be revealed.
7. Recent studies have begun to reveal how cell wall signaling might be integrated into regulatory networks controlling development and defense responses.

FUTURE ISSUES

1. Despite an expanding list of cell wall receptor candidates and recent advances regarding the perception of pectin in particular, a mechanistic understanding of cell wall perception is still missing.
2. Compared to that of proteins and nucleic acids, analysis of carbohydrates is challenging, particularly at cellular resolution. In addition, obtaining pure preparations of defined cell wall material and potential carbohydrate ligands is a constant bottleneck for the biochemical and structural characterization of protein–cell wall interactions. Thus, further development of chemical carbohydrate synthesis would represent a major breakthrough for the field.
3. In addition to the identification of cell wall perception mechanisms, unraveling how cell wall cues are processed and integrated with the regulatory networks of development, defense, and stress responses remains an important field for future studies.
4. The full complexity of cell wall signaling pathways is unknown, but the available data suggest that many different cell wall components are sensed by a multitude of different pathways, and more might await discovery. In this context, an interesting question is whether some of these pathways converge on the same targets and responses, as is the case for signaling in response to extracellular pathogen elicitors.
5. Recent evidence points toward a role of cell wall perception in cell identity determination, analogous to extracellular matrix signaling in animals. Future studies will hopefully be able to follow up on these promising results.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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