Tansley review

Sentinels at the wall: cell wall receptors and sensors

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Contents

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Summary

The emerging view of the plant cell wall is of a dynamic and responsive structure that exists as part of a continuum with the plasma membrane and cytoskeleton. This continuum must be responsive and adaptable to normal processes of growth as well as to stresses such as wounding, attack from pathogens and mechanical stimuli. Cell expansion involving wall loosening, deposition of new materials, and subsequent rigidification must be tightly regulated to allow the maintenance of cell wall integrity and co-ordination of development. Similarly, sensing and feedback are necessary for the plant to respond to mechanical stress or pathogen attack. Currently, understanding of the sensing and feedback mechanisms utilized by plants to regulate these processes is limited, although we can learn from yeast, where the signalling pathways have been more clearly defined. Plant cell walls possess a unique and complicated structure, but it is the protein components of the wall that are likely to play a crucial role at the forefront of perception, and these are likely to include a variety of sensor and receptor systems. Recent plant research has yielded a number of interesting candidates for cell wall sensors and receptors, and we are beginning to understand the role that they may play in this crucial aspect of plant biology.

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I. Introduction

The plant cell wall is an important structural element that distinguishes plant cells from other eukaryotic cells. Cell walls provide more than just mechanical support because, together with the process of cell division, they are largely responsible for controlling plant and tissue morphology. It was recognized early on that cell walls impart both a structural and a functional continuum to the whole plant body – the apoplast; however, the notion that cell walls constitute the dead space surrounding the living protoplast has since been abandoned. Instead, our current view of the cell wall is of a highly dynamic, responsive structure which not only is associated with a variety of developmental events but is also important in relaying information from external stimuli (Pilling & Höfte, 2003). From this point of view, the cell wall continuum is extended to the plasma membrane and underlying cytoskeleton (Wyatt & Carpita, 1993; Baluška *et al.*, 2003; Paradez *et al.*, 2006) so that the external and the internal environments are linked. If this view is correct, then cell wall structure and composition will dictate the nature of interactions that exist between plant cells and their external environment.

The dynamic nature of the wall can only be explained by the existence of systems for sensing, signalling and feedback in the cell wall continuum, yet surprisingly there is a real scarcity of experimental evidence and our understanding of these systems is in its infancy. Until recently, much of the focus of plant cell wall research has been on the biochemistry and synthesis of cell wall polymers, but for the purposes of understanding sensing and feedback, this review will focus on the protein components of the wall.

II. Cell expansion and plant growth

The plant cell wall is interpreted to be a complex, composite material composed predominantly of polysaccharide networks consisting of cellulose, hemicellulose and pectin, with a small, albeit functionally significant contribution from protein (illustrated in Fig. 1; Table 1). It might not be surprising that, given its multifarious nature, it is not yet clear how the cell wall is assembled. Nor is it clear how the process of assembly is co-ordinated with the normal processes of growth and development. Cell expansion in particular is a complex process initiated by increases in turgor pressure followed by controlled loosening of the cell wall and simultaneous deposition of new wall material (Cosgrove, 1993; Refrégier *et al.*, 2004). In addition to wall loosening, wall rigidification must also be tightly co-ordinated. These processes can be contrasted to those that are associated with maintaining cell wall integrity, which are discussed in sections III and IV. Although the signals that elicit cell wall deformation and extension during growth are not well defined, they are presumably different from those that are associated with fortifying cell walls in response to various external stresses. On

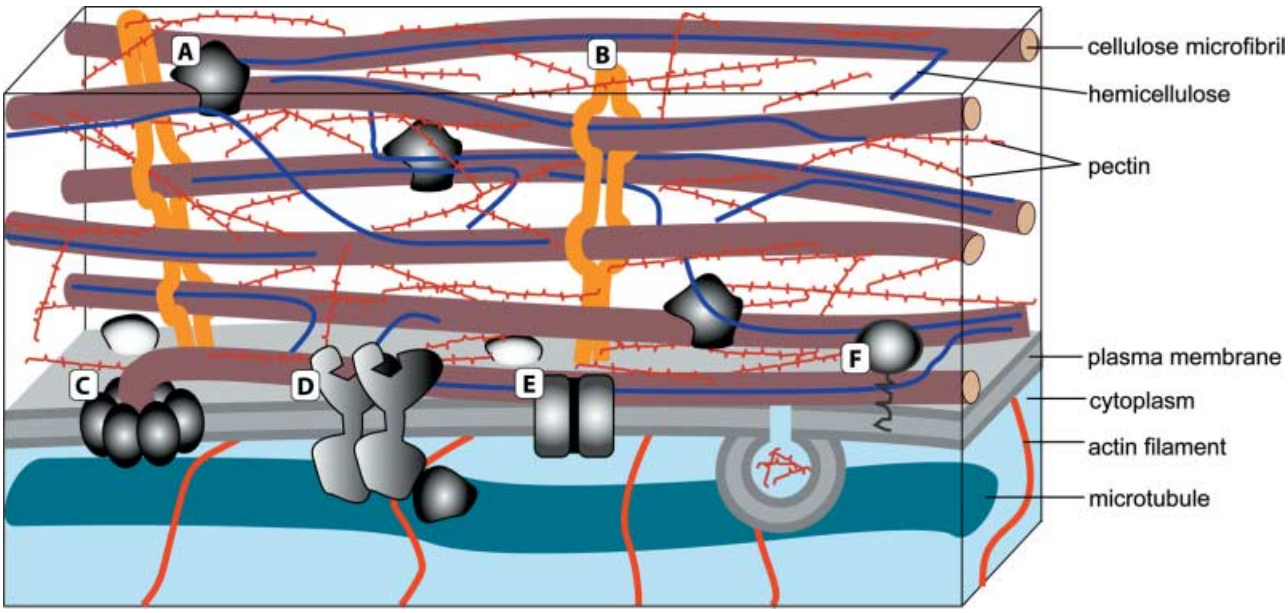

Fig. 1 Model of the cell wall–plasma membrane–cytoskeleton continuum illustrating the main polysaccharide and protein components. The wall consists of cellulose microfibrils, cross-linked by hemicelluloses, and embedded in a pectin matrix as well as numerous protein components such as (A) expansins, (B) extensins and (F) glycosylphosphatidylinositol (GPI)-anchored proteins which are heavily glycosylated and associated with the extensive polysaccharide network. Various plasma membrane proteins such as the (C) cellulose synthase complex, (D) receptor kinases, (E) ion channels, and (F) GPI-anchored proteins interact with the wall matrix as well as with internal cytoplasmic proteins, and the actin and tubulin cytokeleton.

Table 1 Plant cell wall protein mutants in Arabidopsis, including proteins implicated in signalling and feedback across the cell wall–plasma membrane–cytoskeleton continuum

Mutant	Gene identity	Locus	Phenotype	Reference
arabinogalactan protein 19	Arabinogalactan protein	At1g68725	Reduced height, altered leaf shape and size, lighter colour	Yang *et al*. (2007)
expansin 10	Expansin	At1g26770	Smaller cells. Overexpression: larger cells	Cho & Cosgrove (2000)
cobra	GPI-anchored protein	At5g60920	Disruption of orientation of cell expansion, reduced crystalline cellulose	Schindelman *et al*. (2001)
fragile fiber 1	Kinesin	At5g47820	Fragile fibres, altered microfibril orientation	Zhong *et al*. (2002)
gnom/embryo defective 30	Small G-protein exchange factor	At1g13980	Embryo defective, abnormal cell adhesion, defective cell walls, interrupted auxin transport	Shevell *et al*. (2000); Geldner *et al*. (2003)
kobito/abscisic acid insensitive 8	Unknown	At3g08550	Dwarf, cellulose deficiency, abscisic acid-insensitive	Pagant *et al*. (2002); Brocard-Gifford *et al*. (2004)
korrigan	Endo-1,4-β-glucanase	At1g01510	Cellulose deficiency, irregular xylem, root swelling, extreme dwarf	Nicol *et al*. (1998)
leucine-rich repeat/extensin 1	Leucine-rich repeat extensin protein	At1g12040	Abnormal root hairs	Baumberger *et al*. (2001)
mid1 complementing activity 1	Stretch-activated Ca^{2+} channel	At4g35920	Inability of roots to penetrate hard medium. Overexpression: browned hypocotyls, shortened stems, small rosettes, no petals	Nakagawa *et al*. (2007)
proline-rich extensin-like receptor kinase 13	Receptor kinase	At1g70460	Reduced cell elongation in roots	T. V. Humphrey *et al*. (unpublished)
petit 1	Unknown	?	Reduced cell elongation, aberrant cell wall structure	Kurata & Yamamoto (1998)
root epidermal bulgar 1/root hair defective 1	UDP-D-glucose 4-epimerase	At1g64440	Reduced root elongation, epidermal cell bulging, disordered microtubules, reduced expression of arabinogalactan proteins	Nguema-Ona *et al*. (2006)
root-shoot-hypocotyl defective/extensin 3	Extensin	At1g21310	Embryo defective, seedling lethal, irregular cell shape and size, loss of cell elongation	Hall & Cannon (2002)
sku 5	GPI-anchored protein	At4g12420	Skewed root growth	Sedbrook *et al*. (2002)
salt overly sensitive 5	Fasciclin-like arabinogalactan protein	At3g46550	Salt hypersensitivity, thinner cell walls, abnormal cell expansion	Shi *et al*. (2003)
tetraspore/nack 2	Kinesin	At3g43210	Failure of cytokinesis in pollen, ectopic internal wall formation, aberrant wall patterning	Spielman *et al*. (1997); Tanaka *et al*. (2004)
theseus 1	Receptor kinase	At5g54380	Attenuation of shortened hypocotyls in *cesa6* mutant	Hématy *et al*. (2007)
wall associated kinase 4	Receptor kinase	At1g21210	Dwarf, sterile, reduced cell elongation	Lally *et al*. (2001)

the one hand, growth can be considered a long-term developmental response, while on the other hand maintenance of wall integrity can be thought of as a short-term stress-related response.

Cell wall loosening requires the disruption of the molecular interactions between various cell wall components and may occur via a range of mechanisms including cleavage of the matrix polymer backbone, weakening of the noncovalent bonding between polysaccharides, and breakage of cross-links between matrix polymers (Cosgrove, 2005). A variety of agents can mediate wall loosening, including the expansins, xyloglucan endotransglycolase/hydrolases, endo-(1,4)-β-d-glucanases, yieldin and hydroxyl radicals, and there may even be direct induction by the secretion of new cell wall polymers, although it seems likely that a combination of different processes controls extension *in vivo* (Okamoto-Nakazato *et al.*, 2000; Darley *et al.*, 2001; Cosgrove, 2005).

One of the main agents responsible for controlling cell wall loosening is the expansins, which are small secreted proteins found at relatively low abundance in the cell wall. Arabidopsis contains 36 expansins which can be further classified into four different subfamilies based on sequence identities (Sampedro & Cosgrove, 2005). Expansins have been shown to directly bind to cellulose and are thought to induce cell wall loosening by disrupting the noncovalent bonds between cellulose and matrix polysaccharides (McQueen-Mason & Cosgrove, 1995). Expansin protein activity is stimulated by the decrease in pH associated with proton pumping into the extracellular matrix which occurs as a response to a number of different biological stimuli including light (Vanvolkenburgh & Cleland, 1980), auxins (Cleland, 1973) and the fungal elicitor fusicoccin (Cleland, 1976). Expansin activity is also controlled at the level of gene expression, as several studies have reported tight spatial and temporal regulation of basal expression, as well as induction of expansin expression by hormones such as auxin, cytokinins and ethylene (Downes *et al.*, 2001; Cho & Cosgrove, 2002). Knockout mutations in a number of different expansin genes have been identified, although most display obvious phenotypic defects, suggesting considerable genetic redundancy between members of this family (Cosgrove *et al.*, 2002; Li *et al.*, 2003). One exception is the *Petunia hybrida* alpha expansin gene, *PhEXP1*, down-regulation of which resulted in a dramatic reduction in petal size which was correlated with a reduced epidermal cell area (Zenoni *et al.*, 2004). By contrast, overexpression of expansin genes has been reported to increase growth (Cho & Cosgrove, 2000; Choi *et al.*, 2003; Lee *et al.*, 2003), and exogenous application or localized induction of expansin has also been demonstrated to cause initiation of leaf primordia (Fleming *et al.*, 1997; Pien *et al.*, 2001). Paradoxically, strong, constitutive overexpression of expansins has resulted in severely stunted or infertile plants (Cho & Cosgrove, 2000; Rochange *et al.*, 2001).

In addition to expansins, the xyloglucan endotransglycosylases, which function by cleaving and re-grafting xyloglucans, have also been suggested to have an important function in wall loosening. This restructuring of the xyloglucan network has the potential to alter wall properties and has been implicated in the physiological response to mechanical stimuli and auxin-mediated growth. There is also evidence that xyloglucan endotransglycosylases play a role in both wall loosening and strengthening (Fry *et al.*, 1992; Talbott & Ray, 1992; Antosiewicz *et al.*, 1997).

In order to maintain wall integrity in the long term, wall loosening must be accompanied by subsequent rigidification and deposition of new wall materials. When wall loosening occurs, the cellulose microfibrils separate, allowing deposition of new wall materials and cell elongation. The alignment of cellulose microfibrils provides a major physical constraint on the direction of cell expansion, as, without an ordered alignment, all cells would tend to form spheres through isotropic expansion in all directions. Most cells, however, elongate or show anisotropic growth, and in these cells, cellulose microfibrils are aligned perpendicularly to the axis of elongation. One cell wall protein that has been implicated in control of cell shape is COBRA, which is encoded by one of a 12-member multigene family (Brady *et al.*, 2007). A weak allele of *COBRA* was first identified in a mutant exhibiting abnormal cell expansion in roots and displaying reduced amounts of crystalline cellulose (Schindelman *et al.*, 2001). In null allele mutants, the phenotype was even more dramatic, with severe cellulose deficiency and extreme dwarfism (Roudier *et al.*, 2005). The COBRA protein is targeted to the apoplast and attached to the plasma membrane by means of a glycophosphatidylinositol anchor (Brady *et al.*, 2007). In the plant root, this protein was found to accumulate predominantly in the load-bearing outer walls of epidermal cells in a banding pattern that could be disrupted by drugs interfering with microtubule organization (Schindelman *et al.*, 2001; Roudier *et al.*, 2005). COBRA has been proposed to regulate the orientation of cell expansion by influencing the way in which cellulose microfibrils are laid down (Roudier *et al.*, 2005). By controlling the newly forming cell wall in this way, it defines the regions resistant to expansion and thus regulates the shape of the elongating cell. Thus, although a direct connection can only be inferred at this stage, it seems possible that COBRA could be a critical factor in the cell wall–plasma membrane–cytoskeleton continuum.

Once all of the wall components have been laid down and cell expansion has ceased, extensive cross-linking occurs between polysaccharide and protein components, resulting in rigidification of the wall. Hydrogen bonding, calcium ionic bonding, covalent ester linkages, and van der Waals interactions can all be utilized to form these intra- and intermolecular cross-links within the wall. Cell wall-located peroxidases can oxidize various substrates within the cell wall, forming cross-links between cell wall polymers and proteins (reviewed in Passardi *et al.*, 2004). One of the key components known to be responsible for cell wall rigidification is a group of rod-shaped cell wall proteins, the extensins. Extensins are

characterized by a series of $Ser(Hyp)_4$ that become arabinosylated, although their physical properties are highly variable as a result of specific glycosylation, hydroxylation, cross-linking with other cell wall components and in some cases attachment of glycosylphosphatidylinositol (GPI) anchors (Kieliszewski & Lamport, 1994; Borner *et al.*, 2002). Insolubilization of extensins has been correlated with increased tensile strength in cell walls, but it has also been demonstrated to be an inducible phenomenon occurring in response to wounding or elicitor treatment (Bradley *et al.*, 1992). Extensins become insolubilized in the wall matrix through the peroxidase-mediated formation of intra- and intermolecular cross-links involving tyrosine residues (Brady *et al.*, 1998; Held *et al.*, 2004). The importance of extensins for regular growth has been demonstrated in the extensin mutant root-shoot-hypocotyl defective (*rsh*), which has a severely defective embryo phenotype and is incapable of surviving for more than 3 wk (Hall & Cannon, 2002). In addition, overexpression of an Arabidopsis extensin led to stem thickening and height reduction as well as reduced lesion development after infection with *Pseudomonas syringae* (Roberts & Shirsat, 2006; Wei & Shirsat, 2006), suggesting that extensins may be especially important under conditions of stress from mechanical stimuli or pathogenesis.

III. Cell wall responses to stress

When not actively growing, the cell wall continues to play a pivotal role in mediating responses to external stimuli. Its responsive nature is highlighted by observations that perturbation of wall components, by either mutation or mechanical or chemical treatment, often leads to responses that are generally associated with abiotic and biotic stresses (Cheong *et al.*, 2002; Ellis *et al.*, 2002; Manfield *et al.*, 2004; Chen *et al.*, 2005). Because cellulose is the main load-bearing component of the wall, changes in cellulose content often lead to obvious consequences in either compensatory or integrity responses. For example, reductions in cellulose are generally associated with long-term compensatory changes in cell wall components, indicating that the cell wall can not only perceive, but also adjust for physical changes in its structure. For instance, loss-of-function alleles of cellulose synthase 3 (*CESA3*), encoding one of the catalytic subunits of primary cell wall cellulose synthases, can result in production of lignin in response to the reduction in cell wall cellulose (Caño-Delgado *et al.*, 2003). This seems to be a general characteristic of many cellulose deficiencies that are created either by mutation or by inhibitor treatments (Suzuki *et al.*, 1992; Taylor *et al.*, 1992; Zhong, RQ *et al.*, 2002; Cano-Delgado *et al.*, 2003; Rogers *et al.*, 2005). Another well-characterized compensatory response associated with cellulose deficiency is the production of excess pectin (Peng *et al.*, 2000; His *et al.*, 2001; Vaughn & Turley, 2001; Manfield *et al.*, 2004).

Reductions in cellulose content also feed back on responses that are associated with biotic and abiotic stress. For example, *CESA3* mutations or treatment with inhibitors such as isoxaben, which also leads to decreases in the cellulose content of the wall, cause constitutive expression of genes that are normally linked to jasmonate (JA) or ethylene signalling (Ellis *et al.*, 2002); hormones whose synthesis is most frequently associated with pathogens, wounding and drought (Creelman *et al.*, 1992; Creelman & Mullet, 1995; Penninckx *et al.*, 1998). Similarly, mutations affecting *CESA8*/irregular xylem 1 (*IRX1*), *CESA7*/*IRX3* or *CESA4*/*IRX5* lead to resistance to both pathogenic bacteria and fungi (Hernandez-Blanco *et al.*, 2007). Plants can also be made more tolerant to drought, salt and osmotic stresses by mutations at *CESA8*/*IRX1* (Chen *et al.*, 2005), indicating that this is probably a general consequence of *CESA* loss-of-function. Abscisic acid (ABA)-inducible genes such as responsive to dessication (*RD29A*) and pyrroline-5-carboxylate synthase (*P5CS*), and an ABA synthesis-related gene, alcohol dehydrogenase/reductase (*SDR1*), are constitutively expressed in an *irx1* mutant background (Chen *et al.*, 2005). Some cell wall-related genes, such as *KOBITO1* (Pagant *et al.*, 2002; Lertpiriyapong & Sung, 2003), have also been isolated through ABA-insensitive screens (Brocard-Gifford *et al.*, 2004), further highlighting the overlap between cell wall-related responses and hormonal ones. These observations might not be surprising considering that pathogen attack, wounding, and ionic and drought stresses all presumably damage or alter the cell wall in some way. Is any breach in cell wall integrity, then, even an endogenous breach caused by reduced cellulose, interpreted in a similar way? At minimum it seems that, at some level, the signalling pathways associated with cell wall integrity do converge, regardless of whether they are compositional or associated with pathogens, wounding or drought.

IV. Pathogen attack and mechanical stimuli

The cell wall must necessarily be responsive to external stresses from pathogen attack, wounding or mechanical stimuli. This is because the cell wall represents the first barrier to an invading pathogen and, if ingress can be stopped at this stage, cellular damage can be minimized and further defensive actions rendered unnecessary. Pathogen-secreted or endogenous plant polygalacturonases or pectate lyases cause enzymatic degradation of pectin in the plant cell wall, releasing oligogalacturonides, which can act as a signal to trigger defence responses (reviewed in Cote & Hahn, 1994; Mattei *et al.*, 2005). A typical reaction of an attacked plant is the build up of callose (a β-1,3-glucan) papillae on the inner side of epidermal cell walls directly below the entry point of a pathogen. Callose production is induced not only by pathogen attack but also by treatment with the cellulose synthase inhibitor dichlobenil (Nickle & Meinke, 1998), which again is suggestive of a feedback mechanism involving sensors of cell wall integrity. Callose synthase mutants display reduced papilla formation although, surprisingly, this has

resulted in enhanced pathogen resistance as a result of activation of the salicylic acid defence pathway (Jacobs *et al.*, 2003; Nishimura *et al.*, 2003). The production of callose has therefore been proposed to be an induced response which then acts as a negative regulator to limit further, potentially damaging defence responses (Nishimura *et al.*, 2003), although the signalling mechanism has yet to be determined.

Mechanical stimuli can include wind, touch and gravity (and the associated weight of plant structures), and induce such responses as thigmotropism, reaction wood formation and gravitropism. Although only some components of the sensing mechanism are understood, the mechano-sensing network is generally accepted to be located within the cell wall–plasma membrane–cytoplasm continuum (Jaffe *et al.*, 2002; Braam, 2005). Mechanical stimulation induces a rapid and transient increase in cytosolic Ca^{2+} concentration, which has been put forward as evidence of the involvement of stretch-activated calcium channels (Knight *et al.*, 1991; Legue *et al.*, 1997) although, until recently, their identification had been elusive. In animal systems, where mechanical processes are more clearly understood, one of the key players is the integrins, which are cell surface adhesion receptors that bind proteins from the extracellular matrix or counter-receptors on adjacent cells. Integrins also serve as transmembrane mechanical links from those extracellular contacts to the actin cytoskeleton inside cells. Many of the extracellular proteins that interact with integrins contain a characteristic RGD (arg-gly-asp) motif and RGD-containing peptides have been shown to directly activate integrins (Hynes, 2002). Neither fungi nor plants contain true integrin homologues, although there have been a few reports of integrin-like sequences, and RGD peptides have been shown to induce a variety of responses in plants (Jaffe *et al.*, 2002). Interestingly, one of the responses to RGD peptides is the disruption of Hechtian strands, which link the cell wall to the plasma membrane and appear during plasmolysis (Canut *et al.*, 1998; Mellersh & Heath, 2001). The strands contain actin filaments and microtubules and have been proposed to have an important role in cell-to-cell communication and signal transduction from the cell wall.

Currently, it is not understood how integrity or mechanical differences in the plant cell wall might be perceived, nor is it known how signalling pathways leading to either stress responses or compensatory adjustments might be elicited. Taking cues from what has been learned in other systems, in particular *Saccharomyces cerevisiae*, the simplest explanation could be that some receptor or cell wall sensor could provide the primary signal which would feed into multiple signal transduction pathways.

V. Lessons from yeast

Although quite different in composition and organization, the yeast cell wall provides a useful parallel to compare with plant cell walls. Some of the responses in yeast that are related to maintaining wall integrity are associated with developmental processes, such as growth and mating, while many others are associated with stress (e.g. temperature), osmolarity, and chemical disruption. Characterization of these processes has identified clear mechanisms involving cell wall-associated sensors which monitor the status of the wall and lead to remediation of any potential damage. Although plants and yeast have very different life histories, they must both deal with constant attacks from their external environment and respond appropriately to reduce any damage. Notwithstanding obvious organismal differences, the mechanisms of cell wall integrity in yeast provide instructive examples that can be used to define similar processes in plants.

In contrast to the plant cell wall, the yeast cell wall is composed of an inner, load-bearing, polysaccharide layer consisting mostly of β-1,3-glucan (80–90%), β-1,6-glucan (8–18%) and chitin (1–2%) and a protective outer layer which is rich in mannoproteins (Smits *et al.*, 1999). Like plant cell walls, yeast cell walls must resist the turgor pressure, created by the differential internal and external osmolarities, which is the ultimate driving force for cell expansion. Experimentally, the integrity of the wall can be disrupted by inhibiting or mutating genes involved in the synthesis of cell wall polymers such as β-1,3-glucan; by treatment with cell wall-digesting β-1,3-glucanases such as zymolyase; by adding chemical dyes such as Calcofluor white or Congo red, which bind different wall polymers; by using anionic detergents which destabilize the wall; or by growing cells at elevated temperatures which changes plasma membrane fluidity and presumably membrane enzyme activity (Levin, 2005). In all cases, these treatments are sufficient to trigger a signalling cascade that leads to a response which stimulates the cell wall biosynthetic machinery or activates a compensatory mechanism. These might include the activation of β-glucan synthesis-, cell wall synthesis-related glycosyltransferases and regulators, cytoskeleton reorganization, and the secretion of cell wall components. Although the full details are not known, a rough picture has started to emerge of how the status of the wall is relayed to the inside of the cell, and is summarized in Fig. 2 (Popolo *et al.*, 2001; Levin, 2005).

The pathway that has received the greatest attention with respect to cell wall integrity has been one of a number of mitogen-activated protein kinase (MAPK) cascades existing in yeast. Mutations affecting components of the protein kinase C (PKC1)–MAPK cascade lead to cell lysis defects which can be remedied by adding sorbitol to the medium. This phenotype suggests that the pathway is required for cell wall synthesis and integrity and thus has been referred to as the cell wall integrity (CWI) pathway (Levin, 2005). Indeed, the expression of essential cell wall-related genes, such as the glucan synthase *FKS1*, depends on a functional CWI pathway (Igual *et al.*, 1996). In general, the CWI pathway is activated by conditions that either cause cell wall damage or require cell wall remodelling. These conditions include high temperature,

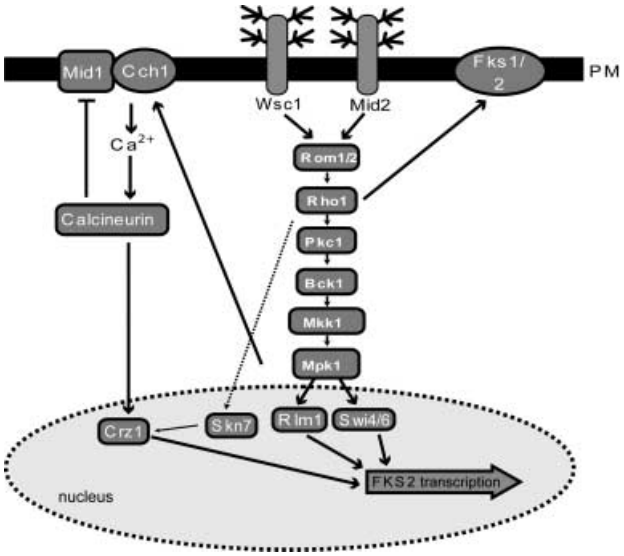

Fig. 2 Yeast cell wall integrity signalling. The model, adapted from Levin (2005), shows how both cell wall stress and calcium signalling can be integrated. Signals are initiated at the plasma membrane through the cell wall sensors Wsc1 and Mid2. Additional sensors located at the cell surface, such as Wsc2, Wsc3 and Mtl1, are not shown. The extracellular domains of Wsc1 and Mid2 are highly glycosylated, and, upon detection of cell wall stresses, the sensors stimulate nucleotide exchange on Rho1 through Rom1/2. Rom1/2 are recruited to the plasma membrane via phosphoinositide signalling (not shown). Rho1 activates, among others, a number of effectors including β1,3-glucan synthase (FKS1/2), protein kinase C1 (Pkc1), and the transcription factor Skn7. Activation of Pkc1 stimulates the mitogen-activated protein (MAP) kinase cascade which includes Bck1, Mkk1 and Mpk1. Two transcription factors, Rlm1 and Swi4/6, are among the targets of Mpk1, and these transcription factors stimulate the expression of *FKS2*, along with other cell wall-related genes. The Mid1–Cch1 channel can be stimulated by Mpk1, hypo-osmolarity, pheromones, or heat shock, and this leads to the stimulation of the Ca^{2+}/calmodulin-dependent protein phosphatase calcineurin. Calcineurin dephosphorylates the transcription factor Crz1, which in its unphosphorylated form enters the nucleus. Activation of Skn7 by Rho1 might help to stabilize Crz1, stimulating the transcription of FKS2. Additional regulatory inputs for Rho1 and Mpk1 exist but are not shown (see Levin, 2005 for more details). Bck, bypass of C kinase; Cch, calcium channel; Crz, calcineurin responsive zinc finger; FKS, FK506 sensitivity; Mid, mating induced death; MKK, MAP kinase kinase; Mpk, MAP kinase; Mtl, mid two-like; Rho, ras homology; Rlm, resistance to lethality of MKKIP386 overexpression; Rom, Rho 1 multicopy suppressor; Skn, suppressor of Kre null; Swl, switching deficient; Wsc, cell wall integrity and stress response component.

osmotic shock, mating pheromone response, and pseudohyphal growth (Gustin *et al.*, 1998; Heinisch *et al.*, 1999). Activation of the pathway is made constitutive either by mutation of genes such as *FK506* sensitive 1 (*FKS1*) or by treatment with cell wall-perturbing agents such as Calcofluor white or zymolyase (de Nobel *et al.*, 2000).

At least two hypotheses have been proposed to explain how the state of the wall is relayed to intracellular signalling (Rajavel *et al.*, 1999; Philip & Levin, 2001; Popolo *et al.*, 2001; Levin, 2005). The premise for the first hypothesis is that a weakened cell wall, which is now unable to resist turgor, would lead to responses that are similar to osmotic shock, as this causes the plasma membrane to stretch. In this situation, the initial signal would be a stretch-activated calcium pulse (Batiza *et al.*, 1996), which would in turn activate, through calcineurin, genes associated with cell wall integrity. An example of a situation in which cell wall deformation leads to ion flux changes is the response to mating pheromones. The mating factor causes an influx of calcium through a calcium channel complex consisting of calcium channel (Cch)1p, a voltage-gated calcium channel, and mating induced death (Mid)1p, which is associated with Cch1p, and is thought to relay stretch activation to Cch1p (Paidhungat & Garrett, 1997; Locke *et al.*, 2000). Mid1p is a glycosylated, integral membrane protein capable of conferring stretch-activated calcium influx in both yeast and heterologous systems (Iida *et al.*, 1994; Kanzaki *et al.*, 1999). Its activity is reduced by specific inhibitors, such as gadolinium, which target stretch-activated cation channels (Kanzaki *et al.*, 1999), indicating that Mid1 is a *bona fide* stretch-activated channel.

An alternative pathway depends on small cell surface receptors, which would act as mechano-sensors, and relate the state of the wall to the CWI pathway. The proteins thought to belong to this group of sensors are Mid2p (Ono *et al.*, 1994) and cell wall integrity and stress response component (Wsc)1p (Gray *et al.*, 1997; Verna *et al.*, 1997; Jacoby *et al.*, 1998) and their homologues mid two-like (Mtl)1p and Wsc2-4p (Verna & Ballester, 1999). The shared features of these sensors are that they are all membrane proteins characterized by a single transmembrane domain, which separates a small C-terminal domain from a large periplasmic domain rich in Ser/Thr residues. These residues are the sites of mannose addition, which are believed to make the protein more rigid and cause it to extend out into the surrounding wall (Ketela *et al.*, 1999; Rajavel *et al.*, 1999; Philip & Levin, 2001). However, whether this type of arrangement would place the external domain in close association with the cell wall polymers, so that it could essentially act as a probe for mechano-structural changes, is still a matter of speculation. However, evidence that supports this type of scenario is that the glycosylation status of the extracellular domains of either Wsc1p or Mid2p is apparently essential for function, as inhibition of their o-mannosylation weakens the Mid2p-sensor function (Philip & Levin, 2001).

Both sensors have been positioned upstream of the CWI Pkc1–MAPK pathway where they transmit a signal to the GTPase ras homology (Rho)1, via interaction with the guanine nucleotide exchange factors rho multicopy suppressor (Rom)1/2. The signal is then amplified through the CWI Pkc1-mediated MAPK cascade. A reduction in the amount of either Mid2p or Wsc1p protein causes a reduction in the phosphorylation events associated with cell wall stress responses (Ketela *et al.*, 1999; de Nobel *et al.*, 2000). This effect is associated with the transition of Rho1p from an inactive, GDP-bound form to an

active, GTP-bound form regulated by Rom1p and Rom2p (Martin *et al.*, 2000). As the C-terminal domains of both Wsc1p and Mid2p have been shown to interact with Rom2p (Philip & Levin, 2001), this suggests that they mediate the Rom2p activity for Rho1p. Indeed, in a *wsc1*Δ background, there is a 50% reduction in guanine nucleotide exchange for Rho1p and a similar 20% reduction in a *mid2*Δ background (Philip & Levin, 2001). However, synthetic interaction analysis has shown that Wsc1p is capable of eliciting downstream events, such as activation of Fks1p glucan synthase, through Rom2p independently of Mid2p (Green *et al.*, 2003).

VI. Candidate sensors and receptors in plants

Compared with yeast, the processes of cell wall sensing and signalling in plants remain a mysterious black box. The genetic approaches that have been so powerful in dissecting these signalling pathways in yeast have not been as fruitful or as well utilized in plants. One reason for this may be that the morphological and life strategy differences between yeast and plants have led to genetic redundancy and mechanisms of feedback and compensation that are more complicated and difficult to define. The specific sensors and receptors utilized by plant cells to relay cell wall-stimulated signals will undoubtedly be different from those in yeast cells, although similar strategies may have been used and it is quite possible that downstream signalling pathways are also similar. Evidence of classic MAPK cascades involved in pathogen, wound or stress responses (Brodersen *et al.*, 2006; Ichimura *et al.*, 2006; Meszaros *et al.*, 2006; Katou *et al.*, 2007), and intracellular calcium fluxes have been implicated in mechanical stimulation (Knight *et al.*, 1992; Haley *et al.*, 1995), implying similarities to yeast signalling. The most direct parallel with yeast wall integrity sensing has been brought to light recently by the identification of a stretch-activated calcium channel in Arabidopsis (Nakagawa *et al.*, 2007). These results provide a promising lead for further investigation and an opening to test whether additional components are similar between plants and yeast. Plants, however, also have developed a rich diversity of receptor serine/threonine kinases that might also fulfil many wall sensing and signalling roles (Shiu & Bleecker, 2003), and it is perhaps not surprising that several have been implicated in cell wall integrity sensing. In addition, the leucine-rich extensin (LRX) proteins and arabinogalactan proteins (AGPs) have also been identified as potential cell wall sensors.

1. Mechanosensing calcium channel

The yeast protein MID1 is a Ca^{2+}-permeable, stretch-activated channel that mediates responses to mechanical stimulation (Kanzaki *et al.*, 1999). By functional complementation of the lethal effect of a *MID1* mutation, Nakagawa *et al.* were able to identify an Arabidopsis gene, *MID1* complementing activity 1 (*MCA1*), which, like its counterpart in yeast, is localized to the plasma membrane and promotes calcium influx upon mechanical stimulation (Nakagawa *et al.*, 2007). Despite the functional similarity, MCA1 is structurally and mechanistically very different from the yeast MID1. Amino acid alignment shows only 10% identity and 41% similarity between the two proteins, and MCA1 has no significant similarity to any other protein characterized as an ion channel. In addition, MID1 requires another Ca^{2+} channel subunit, CCH1, for full functional activity whereas MCA1 appears to have functional activity on its own and could even complement the *mid1/cch1* yeast double mutant.

Physiological analyses of *mca1*-null and *MCA1*-overexpressing Arabidopsis mutants suggested that MCA1 does indeed mediate Ca^{2+} uptake across the plasma membrane in response to mechanical stimulation. The overexpressing lines accumulated higher concentrations of Ca^{2+} and displayed developmental defects of varying severity depending on the expression levels, ranging from short stems, small rosettes and reduced fertility to browning of hypocotyls and lethality. The *mca1*-null mutant had a wild-type phenotype under normal growth conditions, although the roots displayed an inability to penetrate a harder growth medium, demonstrating an important role for MCA1 in mechano-sensing.

2. Receptor kinases

Wall-associated kinases (WAKs) The WAKs are the best characterized of the potential cell wall receptors. Positioned at the plasma membrane with an external domain embedded within the wall and an intracellular kinase domain, they are ideally situated for sensing and signalling from the cell wall (Anderson *et al.*, 2001). The presence of WAKs in the cell wall was confirmed by immunolocalization, and biochemical analyses indicated that WAK1 was tightly associated with the insoluble cell wall fraction (He *et al.*, 1996). Further biochemical and immunological analysis suggested that WAKs bind directly to pectins (Wagner & Kohorn, 2001) and a pectin-binding subdomain of the extracellular region has since been identified and shown to bind to pectins in a noncovalent, calcium-dependent fashion (Decreux & Messiaen, 2005).

The WAKs are encoded by five highly similar genes, although there have been a further 22 WAK-like genes (*WAKLs*) identified based on sequence similarity (Verica & He, 2002). Like the *WAKs* themselves, most of the *WAKLs* are predicted to encode a transmembrane protein with a cytoplasmic Ser/Thr kinase domain and an extracellular region with similarity to vertebrate epidermal growth factor (EGF)-like domains. The exception is five of the *WAKLs* which are predicted to encode abbreviated proteins that lack the transmembrane domain and are predicted to be secreted to the extracellular matrix (ECM), although it remains possible that they are merely nonfunctional isoforms of the *WAKLs* (Verica & He, 2002).

The *WAKs* are expressed in leaves, meristems and cells undergoing expansion, although mRNA expression is also induced by pathogens, aluminium toxicity, wounding and numerous other stresses (He *et al.*, 1998; Wagner & Kohorn, 2001; Sivaguru *et al.*, 2003). Importantly, reduction of *WAK* expression causes a decrease in cell expansion, leading to a dwarf phenotype (Lally *et al.*, 2001; Wagner & Kohorn, 2001), and emerging data are beginning to shed light on the mechanism behind this. In loss-of-function *wak2* mutant plants, growth was dependent on the concentration of sugars in the growing medium, which suggested that WAKs may be involved in the control of sugar metabolism. When this was investigated further, it was found that there was a significant reduction in the activity of vacuolar invertase, which is involved in modulating solute concentrations within the cell. This means that the cells may be compromised in their ability to increase turgor pressure to the extent necessary for cell expansion (Kohorn *et al.*, 2006). Kohorn's group has therefore proposed a model whereby the WAKs may sense cell wall expansion by their attachment to pectin and signal via influencing the activity of vacuolar invertase, thus controlling turgor during cell expansion.

In addition to the binding of pectins to the WAK extracellular domain, there has been another report indicating binding to a glycine-rich secreted cell wall protein. A yeast two-hybrid screen was conducted using the extracellular domain of WAK1, which identified a strong interaction with Arabidopsis glycine-rich protein 3 (AtGRP3), and this was also confirmed *in vitro* (Park *et al.*, 2001). The authors propose that AtGRP3 could be the ligand for the WAK1 receptor and provide evidence for involvement in pathogenesis-related processes. Evidence regarding the downstream components of WAK signalling is limited, but includes interactions with the kinase-associated protein phosphatise (KAPP) and a chloroplast oxygen-evolving enhancer protein (Park *et al.*, 2001; Yang *et al.*, 2003). As yet it is not clear how or even if these interactions relate to the observed effect of WAK2 on vacuolar invertase activity, and this will be an interesting focus for future studies.

Lectin receptor kinases (LecRKs) Lectins are proteins that bind to but do not alter carbohydrates, and a large family of receptor kinases have been identified which contain an extracellular lectin-like domain, the lectin receptor kinases (LecRKs; Herve *et al.*, 1999). Their ability to bind carbohydrates, combined with a receptor function, makes them ideal candidates for monitoring cell wall integrity, and indeed they have been found to be activated by pectin oligomers (Riou *et al.*, 2002). Recently, a subset of these receptors was identified in studies of plasma membrane–cell wall adhesions which can be visualized upon tissue plasmolysis (Gouget *et al.*, 2006). Cell wall–plasma membrane adhesion sites can be disrupted by binding of a protein from the plant pathogen *Phytophthora infestans* that contains the RGD (arginine-glycine-aspartic acid) tripeptide sequence, a characteristic cell adhesion motif in mammals (Senchou *et al.*, 2004). Phage display was used to identify peptide sequences that bind the RGD motif and, from these sequences, 12 candidates were identified as natural RGD-binding proteins. Eight of these were receptor kinases, four of which contain a lectin-like extracellular domain, which was shown to be responsible for protein–protein interactions in binding to the RGD motif as well as having potential for binding carbohydrates (Gouget *et al.*, 2006). Disruption of plasma membrane–cell wall adhesion is caused by a number of biotrophic plant pathogens which may use this as a means of disrupting the induction of nonspecific defence responses which require communication between cytoplasm and cell wall components (Mellersh & Heath, 2001). In animals, ECM proteins containing RGD motifs interact with integrins which span the plasma membrane and couple to actin-binding proteins in the cytoplasm. Plant cells do not contain true integrin homologues, although it is conceivable that, by binding to endogenous cell wall RGD proteins, the LecRKs could fulfil a similar function.

THESEUS1 (*The1*) An interesting new candidate for a cell wall integrity sensor is the receptor kinase THESEUS1, identified recently by Herman Höfte's group (Hématy *et al.*, 2007). Arabidopsis THE1 is one of 17 members of the *Catharanthus roseus* receptor-like kinase 1 (CrRLK1) subfamily of plasma membrane-bound receptor-like kinases, all with undetermined functions. The predicted plasma membrane location was confirmed by localization of a green fluorescent protein (GFP) fusion and promoter:GUS analysis revealed expression primarily in expanding cells and vascular tissue.

THE1 was identified as a result of a suppressor screen of the cellulose synthase subunit 6 mutant *cesa6*. When grown in the dark, *cesa6* mutants are cellulose deficient, have shortened hypocotyls, and accumulate ectopic lignin and callose (Desnos *et al.*, 1996; Fagard *et al.*, 2000). Some of these pleiotropic effects were attenuated by *the1*, although it did not rescue the cellulose synthesis defect. The *the1* mutant partially restored the hypocotyl elongation defect of the *cesa6* mutant as well as that of other cellulose-deficient mutants including *cesa1*, *cesa3* and *pompom1*. Mutations in *THE1* and overexpression of a functional THE1-GFP fusion protein did not affect wild-type plants, indicating that the *the1* mutant phenotype is only revealed under conditions of defective cellulose synthesis. Therefore, THE1 appears to be a mediator of the cellular response to perturbed cellulose synthesis, and, hopefully, future studies will shed light on the mechanism for sensing these perturbations. Interestingly, another member of the CrRLK1 family was identified as containing an RGD-binding motif in its extracellular domain and thus, similar to the LecRKs, has been implicated in mediating cell wall–plasma membrane contacts (Gouget *et al.*, 2006).

Proline-rich extensin-like receptor kinases (*PERKs*) The *PERK* gene family of receptor kinases contains 15 members, all of which encode proteins containing a proline-rich,

extracellular domain similar to that of extensins (Nakhamchik *et al.*, 2004). PERK1 has been shown to be located at the plasma membrane (Silva & Goring, 2002) and it seems likely that the extracellular domain is embedded in the cell wall in a similar manner to that of the WAKs, perhaps cross-linked to extensin proteins. Analysis of microarray data reveals two predominant types of *PERK* genes with different patterns of expression, those that are more or less ubiquitously expressed throughout all plant tissues and those that are expressed specifically in the pollen (Nakhamchik *et al.*, 2004). Antisense down-regulation of *PERK* expression in Arabidopsis resulted in growth and floral organ defects, indicating the importance of this gene family in plant development (Haffani *et al.*, 2006). Analysis of individual Arabidopsis T-DNA knockout lines has, for the most part, not revealed any specific mutant phenotypes, indicating considerable genetic redundancy between family members. The exception is the *perk13* mutant, which displays decreased cell elongation in the roots, an effect that is amplified with the application of the actin-depolymerizing drug latrunculin B and the vesicle transport inhibitor brefeldin A. The *perk8,9,10* triple mutant also displays a slight decrease in cell elongation in the roots, which is amplified in the presence of latrunculin B, but not brefeldin A (T. V. Humphrey *et al.*, unpublished). Unlike *the1*, the *perk* mutant plants are not affected by cellulose synthesis inhibitors such as isoxaben. A clear function for the PERKs has not yet been determined although they, along with the WAKs and THE1, appear to affect cell expansion, and are looking like good candidates for cell wall integrity receptors.

3. Leucine-rich extensin proteins

The leucine-rich extensin (*LRX*) gene family encodes 11 chimeric proteins consisting of an N-terminal leucine-rich repeat (LRR) domain and a C-terminal extensin-like domain which are insolubilized in the cell wall (Rubinstein *et al.*, 1995; Baumberger *et al.*, 2001). LRR domains are important for protein–protein interactions and, in plants, are commonly found in signalling proteins such as LRR-receptor kinases, nucleotide binding site (NBS)-LRR proteins, and GTPase-activating proteins (Kobe & Kajava, 2001). The LRR domain in the LRX proteins suggests the importance of protein–protein interactions and places them in a possible regulatory or signalling role. As extensins are normally insolubilized within the cell wall, the extensin domain in the LRX proteins may have an anchoring function, establishing a specific localization to subdomains in the cell wall, as was shown for *Zea mays* pollen extensins (ZmPEX1/ZmPEX2) (Rubinstein *et al.*, 1995).

Phylogenetic and expression analysis has enabled the *LRX* genes to be subdivided into two groups, those that are expressed specifically in the pollen (the *PEX* genes), and those expressed in vegetative tissues (Baumberger *et al.*, 2003a). The Arabidopsis *LRX1* and *LRX2* genes are both expressed predominantly in root hairs and are likely to have a role in cell wall formation there. The *atlrx1* mutant displays an aberrant root hair phenotype which is enhanced in the *atlrx1/atlrx2* double mutant, where root hairs frequently rupture soon after initiation. AtLRX1 and AtLRX2 appear to be involved in cell wall assembly, as the ultrastructure of the cell wall in the double mutant is severely affected and weakened to the point where it cannot resist the turgor pressure exerted by the protoplast (Baumberger *et al.*, 2003b). The role of LRX1 in cell wall formation in root hairs has been further delineated by the results of a suppressor screen which identified a rhamnose biosynthesis gene, *RHM1*, involved in the synthesis of cell wall pectins (Diet *et al.*, 2006).

4. Arabinogalactan proteins and glycosylphosphatidylinositol-anchored proteins

Many cell wall proteins are secreted to the outer face of the plasma membrane by virtue of their GPI anchors, which are added to the protein post-translationally. As the GPI anchors may be cleaved by phospolipase C or D (Sherrier *et al.*, 1999; Borner *et al.*, 2003), it is possible for GPI-anchored proteins (GAPs) to be liberated from the plasma membrane into the cell walls. Over 200 GAPs have been identified in Arabidopsis and may play a role in cell surface processes such as signalling, adhesion, matrix remodelling and pathogen response (Borner *et al.*, 2002).

One group of GAPs that has been implicated in cell wall sensing and signalling is the AGPs. As the name implies, this group of proteins is highly glycosylated; predominantly with arabinose and galactose, but sometimes also with glucuronic acid units. These sugars decorate the protein core at multiple sites as polysaccharide units which vary in size from 30 to 150 sugar residues (Showalter, 2001). AGPs are not membrane proteins; however, by virtue of GPI anchors which are added to the protein post-translationally, many are secreted to the outer face of the plasma membrane (Cullen *et al.*, 2000; Schultz *et al.*, 2000; Gaspar *et al.*, 2001). In this context, it is interesting that some AGPs bind cell wall pectins (Iraki *et al.*, 1989; Serpe & Nothnagel, 1995), so it is possible that they could effectively act as integrity sensors.

Studies investigating AGP function have exploited the use of Yariv reagent, a phenylazoglycoside dye, which specifically binds the carbohydrates on AGPs (Yariv *et al.*, 1962; Yariv *et al.*, 1967). Treatment of Arabidopsis roots with Yariv reagent is thought to cross-link AGPs and causes cells to become isotropic and to swell (Willats & Knox, 1996; Ding & Zhu, 1997), indicating that AGPs have a functional role in permitting cell elongation and maintaining cell wall integrity. This phenotype is echoed in loss-of-function alleles of genes such as salt overly sensitive 5 (*SOS5*) (a predicted GPI-anchored, fasciclin-like AGP), which result in thinner cell walls and reduced cell expansion (Shi *et al.*, 2003). GPI-anchored AGPs located at the cell surface have also been implicated in control of cell shape via a connection with the cytoskeleton, as they have

been shown to be involved in orienting cortical microtubules (Andeme-Onzighi *et al.*, 2002; Sardar *et al.*, 2006; Yang *et al.*, 2007). AGPs have also been implicated in wall integrity mechanisms because they can be induced by ionic changes (Lamport *et al.*, 2006) and mechanical stimulation (Lee *et al.*, 2005), which implies that the primary function of these AGPs is to act as cell wall reinforcement and not as sensors. It is possible that a subset of AGPs will turn out to function as wall integrity sensors that either directly or indirectly affect downstream signal transduction; however, at this point these arguments are mostly speculative.

5. Formins

In animals, formins are cytoplasmic proteins that function in the organization of the actin cytoskeleton. Plant formins are decidedly different in structure and function, in particular those of class I, which contain a transmembrane domain near the N terminus (Deeks *et al.*, 2002). The C-terminal domain was predicted to be extracellular and contain similarity to proline-rich extensins, and for this reason they have been suggested to play a role in the cell wall–cytoplasm continuum (Deeks *et al.*, 2002; Baluška *et al.*, 2003). However, more recent data (Michelot *et al.*, 2005; Yi *et al.*, 2005) have predicted the opposite orientation and identified domains in the C-terminal region that function in actin binding which, by definition, must occur on the cytoplasmic side of the protein. Therefore, the initial structural predictions and cell wall connection need to be reconsidered, although it remains possible that the short extracellular N terminus may be involved in sensing or interaction with cell wall components.

VII. Conclusions

The plant cell wall is no longer perceived as a rigid and static structure providing merely mechanical support; rather, the emerging view is of a dynamic and responsive wall that exists as part of a continuum with the plasma membrane and cytoskeleton. A plant cell must perceive changes associated with normal growth as well as stresses such as wounding or attack from pathogens, and the wall must be responsive and adaptable enough to maintain its integrity and allow co-ordinated growth and development. The protein components of the wall are likely to play a crucial role at the forefront of perception and are likely to include a variety of sensor and receptor systems, as has been seen in yeast. In plants, we can define a cell wall sensor as perceiving mechanical stresses such as the newly described stretch-activated calcium channel, MCA1, while a receptor would have a more biochemical function in binding specific molecular ligands such as polysaccharide fragments or pathogen elicitors. There is likely to be considerable overlap between the functions of sensors and receptors, as both are likely to involve interactions with matrix polymers and other proteins and by definition require the initiation of some sort of signalling cascade. There are currently a number of interesting candidates that may fulfil either sensor or receptor roles, but we are still a long way from delineating signalling pathways and defining mechanism.

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