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Regulation of cellulose synthesis in response to stress
Christopher Kesten\textsuperscript{a}, Alexandra Menna\textsuperscript{a} and Clara Sánchez-Rodríguez

The cell wall is a complex polysaccharide network that provides stability and protection to the plant and is one of the first layers of biotic and abiotic stimuli perception. A controlled remodeling of the primary cell wall is essential for the plant to adapt its growth to environmental stresses. Cellulose, the main component of plant cell walls is synthesized by plasma membrane-localized cellulose synthases moving along cortical microtubule tracks. Recent advancements demonstrate a tight regulation of cellulose synthesis at the primary cell wall by phytohormone networks. Stress-induced perturbations at the cell wall that modify cellulose synthesis and microtubule arrangement activate similar phytohormone-based stress response pathways. The integration of stress perception at the primary cell wall and downstream responses is likely to be tightly regulated by phytohormone signaling pathways in the context of cellulose synthesis and microtubule arrangement.

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Introduction
Plant growth adaptation to stress relies on precisely controlled changes in cell division and expansion. This is possible due to the flexibility of primary cell walls that are able to expand rapidly while restricting internal turgor pressure [1]. Secondary cell walls are deposited below primary walls in specialized, non-expanding cell types, that is, xylem vessels and woody tissues, providing mechanical support for the plant body [1]. Since this review is focused on cellulose modification in response to stress and therefore on actively growing tissue, we further concentrate on the primary cell wall.

The primary cell wall is composed of three different carbohydrate-based biopolymers, that is, cellulose [2], hemicelluloses and pectins [3,4], and cell wall remodeling proteins [5]. Cellulose, the main load-bearing polymer of the cell wall, is directly synthesized at the plasma membrane as \(\beta\)-1,4-linked d-glucose chains by mobile cellulose synthases (CesA) that are organized in rosette-shaped cellulose synthase complexes (CSCs) [2]. The current model of cellulose synthesis directly correlates the movement of CSCs at the plasma membrane (i.e. direction and speed) as a proxy for deposition of nascent cellulose microfibrils [6]. The tracks of moving CesAs co-align with the underlying cortical microtubules (MT), suggesting that these cytoskeletal fibrils guide the CSCs while producing cellulose [7,8]. This association is possible via the cellulose synthase interacting protein 1 (POM2/CSI1) that binds to both the CSC and cortical MTs [9–11]. The CSCs have also been localized in cytosolic microtubule-associated cellulose synthase compartments (MASCs) or small cellulose synthase compartments (SmaCCs), which over accumulate in response to stress [12,13]. This finding highlights the strong connection between CSCs and MTs that goes beyond their association during cellulose synthesis at the plasma membrane. Another MT-binding protein family involved in maintenance of MT-based guidance of CSC tracking are the cellulose-microtubule uncoupling proteins (CMU) that prevent the lateral diffusion of cortical MTs caused by the forces created by an active CSC [14]. The CSC-MT alignment typically rearranges during anisotropic cell elongation to follow a perpendicular orientation to the growth axis [8] and in response to certain stresses [12]. These studies confirm the importance of cortical MT integrity, stability and maintenance below the plasma membrane for correct guidance of the cellulose synthesis machinery. Therefore, integration of stress-induced changes in cellulose synthesis and MT reorganization must be tightly regulated to allow for optimal plant growth adaptation to the stimuli.

The plant cell wall seems to play an important role in stress perception by facilitating activation of signaling pathways and remodeling growth strategies in response to stresses. In the case of a microbe penetration attempt, the plant cell wall constitutes a physical barrier both as a preformed barricade and as an active barrier through wall reinforcement via callose deposition. The accumulation of this polysaccharide, composed of \(\beta\)-1,3-linked d-glucose, is a cell wall reinforcement mechanism involved in plant development and response to external stresses [15,16]. In addition, the plant cell wall acts as a source of signaling molecules to alert the plant immune system in the presence of potentially harmful intruders. Among these signals, the
plant responds to damage-associated molecular patterns (DAMPs) produced by microbe degradation of the plant cell wall [17]. Cellulose perturbations caused by microbe adhesion, but not degradation, can also be perceived by the plant as warning signals and are sufficient to trigger defense responses [18]. Despite the importance of a deep molecular understanding of the crosstalk between cellulose alterations, surveys of cell wall integrity (CWI) and downstream responses (e.g. rearrangement of the cortical MT network), our knowledge about these processes remains tenuous. Recently, comprehensive reviews concerning both CWI and cellulose synthesis have been published [2,19]. In this review, we will focus on integration of stress perception and downstream responses in the context of cellulose synthesis and MT networks.

**Perturbations in the cellulose synthase machinery affect plant tolerance to abiotic stress**

The essential function of the cell wall on providing mechanical strength to withstand turgor pressure might explain, at least partially, its contribution to abiotic stress tolerance, as most abiotic stresses affect the water equilibrium in the cell and therefore the turgor pressure. In addition, certain abiotic stresses impair cytoskeleton dynamics and this most probably alters the deposition of cell wall components [20]. Indeed, cellulose deficient mutant plants are typically more sensitive to abiotic stress than wild-type plants [20]. For example, lesions in *CESA6, POM2/GSII*, and the recently-discovered companion of cellulose synthase (CC) led to enhanced sensitivity to salt stress in *Arabidopsis* seedling roots [21,22**]. Lesions in *KORRIGAN1 (KOR1)*, a β-1,4-endoglucanase and integral part of the CSC [23], caused similar growth arrest in *Arabidopsis* roots upon salt stress [24]. In addition, the *hot2* allele of *CTL1*, a chitinase-like protein required for ordered cellulose deposition in *Arabidopsis* [25], showed enhanced sensitivity to both salt and osmotic stress [26]. The results indicate a prominent role of the cell wall and cell wall integrity in abiotic stress tolerance. Hence, these results point out an important role of the cellulose synthase machinery in abiotic stress responses. An extensive review on how cellulose synthesis is affected by abiotic factors was published recently [20], to which we refer for further information on this topic.

**Cellulose synthesis and integrity are important factors to counteract biotic stresses**

As one of the earliest structural barriers microbes encounter, the plant cell wall polysaccharides are largely targeted by microbes to establish their desired interaction with the host [27]. The so-called cell wall-degrading enzymes (CWDEs), like cellulases, have been shown to contribute directly to virulence. Pathogenic bacteria such as *Clostridium thermocellum* and fungi such as *Fusarium graminearum* possess numerous genes encoding for cellulases that are upregulated during plant infection [28–30]. Genomic analyses have demonstrated that symbiotic microorganisms also produce cellulases [31,32], indicating that structural weakening of the cell wall also facilitates access to symbiotic microbes. Indeed, a recent study showed that reduction of cellulose content in *Populus* by down-regulation of *KOR1*, results in significantly increased colonization by the beneficial fungal symbiont *Laccaria bicolor* [33]. Acetobixan, a novel cellulose biosynthesis inhibitor (CBI) secreted by the *Bacillus* *Bacillus* genus, was shown to reduce cellulose biosynthesis in *Arabidopsis* [34**]. Application of acetobixan causes clearing of CSC punctae from the PM, as shown previously with the CBI isoxaben [34**]. Therefore, this finding strongly suggests a role for microbe-derived compounds to weaken the cell wall by manipulating cellulose synthesis and/or trafficking of CSCs to facilitate pathogen entry.

As an evolutionary response to microbial attacks, plants may have adapted to recognize cellulose degradation as a warning signal or DAMP. This hypothesis is supported by the recent identification of cellulose-derived oligomers called cellulose as DAMPs [35**]. These β-1,4-glikened glucose dimers trigger similar signaling cascades to those activated by oligogalacturonans (OGs), DAMPs derived from microbial degradation of pectins [35**,36]. The cellulose-binding elicitor lectin (CBEL) secreted by the genus *Phytophtora* is perceived as a MAMPs/PAMPs (microbe-associated/pathogen-associated molecular patterns), since it induces immune responses and necrosis in several plants [18,37]. No CWI sensor has been reported to perceive changes in the cellulose structure upon microbe interaction. One candidate might be a receptor-like kinase THESEUS1 (THE). The *thesus1* (*the1*) mutant was identified as a partial suppressor of the stunted growth phenotype observed in the cellulose deficient mutant *procustel1* (*pro1-1*). Interestingly, *the1* was not able to compensate the low cellulose content of *pro1* plants. In addition, in the wild type background, *the1* mutants did not show any phenotype [38]. It is thus likely that THE is responsible for surveying cellulose synthesis integrity and likely to play a role in perceiving any of the above described cellulose modifications during defense response activation. The recently identified MIK2/LRR-KISS receptor is another strong candidate for DAMP perception as, together with THE1, regulates plant responses to chemical-induced cellulose synthesis inhibition. In addition, MIK2 might perceived DAMPs derived from pathogen attack, as it is required for resistance to *Fusarium oxysporum* [39]. The mechanosensitive channel proteins MCA1/2 function in perception of mechanical stress and are also likely to be involved in perception of microbe-induced perturbations of the cellulose [40]. One of the common defense outputs associated with DAMPs and MAMPs/PAMPs perception is the reinforcement of the cell wall by increasing the cross-linking of cell wall material and by local deposition of polysaccharides [16].
This local reinforcement of the cell wall at infection sites, known as papillae, is initiated in response to penetration attempts by biotrophic and hemibiotrophic microbes [41,42]. Recent studies showed that, in addition to callose, cellulose is also involved in papillae formation upon infection with powdery mildew fungi, such as Blumeria graminis f. sp. Hordei in barley and Goloeinomyces cichoracearum in Arabidopsis [43,44]. Interestingly, low cellulose leads to low callose deposition in the papillae, resulting in increased susceptibility to biotrophic pathogens [45,46]. Impairment in primary cellulose synthesis, either chemically or genetically induced, results in transcriptional activation of stress response mechanisms, including ectopic lignification accompanied by increased production of ethylene (ET) and jasmonic acid (JA), reminiscent of the response to pathogenic infection. Consequently, these mutations have varying effects on susceptibility to pathogens, depending on the colonization strategy of the microbe [47–49]. Taken together, cellulose is of broad importance in the defense against pathogens; as a structural barrier in the cell wall, as a target of MAMP/PAMP and as a source of DAMPs that lead to downstream modifications in hormone-signaling pathways, and in pathogen-induced papillae formation (Figure 1a).

As discussed in the introduction, the cellulose synthesis machinery is tightly connected with and its function relies on the cortical MT. Interestingly, rearrangement of the cortical MT network has been observed both during pathogenic attack and symbiotic interaction with beneficial microbes [50]. During rhizobia nodule formation in pea and Medicago truncatula, cortical MTs rearrange around bacterial entry points, and the pattern of reorganization corresponded to specific stages in development of the host–rhizobia interaction [51]. Due to their essential role in vesicle trafficking and cellular organization, MTs represent a logical virulence target for pathogens to block the secretion of antimicrobial compounds to the apoplast. For example, various Pseudomonas syringae type III secreted effectors, such as HopZ1a and HopE1, have been reported to manipulate the MT array and thereby to increase the host’s susceptibility [52,53]. Some studies suggest that the microbes also manipulate the MT–cellulose connection. CMU2 has been shown to interact with the HaRxL79 effector secreted by the oomycete biotroph HyaIarhomonospora arabidopsidis in a yeast-two-hybrid screening [54]. The authors confirmed that the ccm2 mutant (named klc in their work) is impaired in resistance to this microbe. They also reported the interaction of CMU2/KLC with several other oomycete effectors and one bacterial effector [54]. Therefore, it can be hypothesized that, by binding to CMUs, some pathogens alter the CSC guidance at the plasma membrane leading to impaired cellulose deposition and thus weakening the cell wall (Figure 1b). Also, the CBI acetoxiban produced by Bacillus might affect the MT pattern [34**]; Further experiments need to be done to evaluate the mode of action of these and other microbe effectors and CBIs.

**Nexus in the influence of abiotic and biotic stress on cellulose**

Plants coordinate growth and stress responses by integrating certain phytohormone pathways, MT array status and cellulose synthesis. The Brassinosteroids (BR) signaling cascade is one of these players, involved in both abiotic and biotic stresses [55]. The plasma membrane receptor kinase BRASSINOSTEROID INSENSITIVE 1 (BR1) binds to its co-receptor BAK1 upon BR recognition [56]. Subsequently, BRI1-EMS SUPPRESSOR 1 (BES1) and BRASSINAZOLE-RESISTANT 1 (BZR1) transcription factors [56] are activated leading to expression of BR-responsive genes. BES1/BZR1 are negatively regulated by the GSK3-like kinase BR-INSENSITIVE 2 (BIN2), an integral part of BR related signaling [57]. Hence, in the absence of BR, BIN2 is constitutively activated, which leads to constant phosphorylation and deactivation of BES1/BZR1 and consequently to target gene repression [57]. In general, BR mediated signaling is of great importance for plant stress signaling [58]. Notably, BAK1 acts as a dual co-receptor of BRI1 and various LRR-RLPs involved in MAMP/PAMP and DAMP recognition. Thus, BAK1 is an important player in the plant growth and immunity balance [59]. Overexpression of BR biosynthetic genes leads to alteration of biotic stress tolerance [60]. AVR2, an RXLR effector secreted by the potato blight pathogen Phytophthora infestans, has been reported to hijack the BR signaling pathway keeping BIN2 active to down-regulate host defense responses [61*]. Additionally, BAK1 seems to be required for plant immune response induced by the above mentioned CBEL secreted by the genus Phytophthora [37]. Thus, a more direct role of BR signaling in defense responses seems plausible (Figure 1b). The molecular regulation of BRs signaling in abiotic stress responses has recently been uncovered by the identification of the ubiquitin binding protein DOMINANT SUPPRESSOR OF KAR 2 (DSK2) [62*]. Upon abiotic stress, BES1 directly interacts with DSK2 and is targeted for degradation by the autophagosomal pathway [62*]. In addition, DSK2 was shown to be a direct phosphorylation target of BIN2 leading to enhanced degradation of BES1 [62*] (Figure 1b). Lesions in DSK2 lead to an accumulation of BES1 and enhanced sensitivity to both osmotic and drought stress. It might be quite possible that DSK2 also participates in the transcriptional repression of the BR cascade caused by pathogen effectors like AVR2 (Figure 1b). At the same time, BR has a clear impact in plant growth by regulating essential cell wall-related genes, including the CESAs [63,64]. Intriguingly, BIN2 was recently shown to negatively regulate cellulose synthesis via direct phosphorylation of CES1 resulting in reduced CSC activity [65**], proving a direct regulation of cellulose synthesis via the BR cascade [65**] (Figure 1b). BRs are also involved in
Environmental stresses influence the plant growth by altering the cellulose synthesis machinery at the primary cell wall. (a) Overview of the primary cell wall cellulose synthesis machinery and possible influences of biotic invaders. Cellulose is produced at the plasma membrane by cellulose synthase complexes (CSCs). The CSCs are guided by cortical microtubules (MTs) while excreting cellulose into the apoplast. Certain fungi can degrade the cell wall leading to the release of damage-associated molecular patterns (DAMPs), like cellulose. This putative building block of cellulose is perceived as a DAMP by the host. The oomycete *Phytophthora* secretes a cellulose-binding elicitor lectin (CBEL) that is sensed as a microbe-/pathogen-associated molecular patterns (MAMP/PAMP). Both DAMPs and MAMP/PAMPs might be perceived by membrane-based pattern-recognition receptors (PRR) that activate downstream defense mechanisms and potentially influence both cellulose synthesis and MT arrangement as a response to the biotic stress. Microbes secrete several effectors that influence molecular mechanisms inside the plant cell. For example, the *Pseudomonas syringae* effector HopE1 can directly bind MAP65-1 resulting in a breakup of MT bundles, which should alter the cellulose synthesis pattern. Also, the *Phytophthora* effector AVR2 can hijack the BR-signaling cascade (see panel B), which most probably also influences CSC activity. (b) Zoom into the possible influence of environmental stress on cellulose synthesis and the BR-signaling cascade. Upregulation of brassinosteroid (BR) related genes modifies plant defense responses. The cellulose-binding elicitor lectin (CBEL) is perceived in a BAK1-dependent manner, the co-receptor of BR signaling. AVR2 manipulates the BR-signaling cascade to keep BIN2 active. Abiotic stress also leads to BIN2 activation that in turn phosphorylates DSK2. Consequently, the transcription factor BES1 is degraded, leading to an enhancement of

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**Figure 1**

![Image of the diagram](https://www.sciencedirect.com)
cell elongation by directly affecting MT patterns. BZR1 has been shown to upregulate the microtubule destabilizing protein (MDP40), involved in MT reorientation and cell elongation [66]. These studies reveal a tight connection between the general plant stress response, cell wall modification during plant growth and BR signaling, suggesting an important role of BR as a general regulator of cellulose synthesis during abiotic and biotic stress (Figure 1b).

More evidence that MTs might serve as direct mediator of stress-related signals at the plasma membrane can be inferred from previous studies [67,68]. The importance of a well-established cortical MT-plasma membrane-cell wall connection was recently underpinned by the discovery of the CMUs, which were previously discussed as targets of cellulose synthesis impairment during pathogenesis [14*]. Cortical MTs are well known to coordinate the differential growth of neighboring cells. The mechanical stress that two neighboring cells apply to each other is regulated by MT reorientation perpendicular to the applied stress [67,68]. This mechanism consequently compensates the stress and restricts growth towards the neighboring cell through directed cellulose synthesis, resulting in two differentially, but coordinated, growing cells. These studies used laser ablation to induce stress, which causes a mechanical manipulation at the plasma membrane similar to abiotic (e.g. protoplast shrinkage due to osmotic or salt stress) and biotic stress (e.g. the applied pressure of a microbe to a cell). Indeed, upon salt stress cortical MTs undergo a well-coordinated de-polymerization and re-polymerization cycle [69] coordinated with modifications in the cellulose synthesis machinery.

Recently, the CG proteins have been shown to be required for this MT-cellulose harmonized response to salt stress [22]. The CGs co-localize with the CSC at the plasma membrane and bind directly to cortical MTs. The cytosolic N-terminus of the CGs was shown to be indispensable for salt resistance of plant cells as it binds directly to MTs and promotes their dynamics upon salt stress. Consequently, alea2 mutant plants were not able to recover a cortical MT array after salt stress as observed in WT plants [22,69]. As a consequence, these mutants were also unable to recover localization of CSCs at the plasma membrane supporting that a salt-adjusted cortical MT array is highly important for general plant growth adaptation to stress [8,13,24]. The CG proteins therefore present a direct link between plant growth and salt stress response in planta and might also be involved in the cortical MT response to biotic stress.

**Conclusion and future directions**

In plants, the ability to integrate information from external stimuli and balance stress-induced responses with optimal development is crucial. Activation of stress response signaling is energetically costly, and as such these signaling pathways must be tightly regulated. Both CSCs and cortical MTs undergo drastic re-organization upon perception and response to abiotic and biotic stresses. It remains to be described which process responds to perceived stimuli first: is CSC reorganization a consequence of stress perception and alteration in MT arrangement, or vice versa? The role of the CG proteins in salt stress response suggests a strong case for MTs as stress sensors, but it is unclear how perception of stress signals by MTs can be relayed to the CSCs and further through the cell wall. Receptors at the cell wall surface implicated in CWI are also likely to play an important role in stress response. It remains unclear if CSCs can directly perceive stress stimuli which are then transmitted downstream, or if receptors perceive and transmit information to the CSCs to alter cellulose synthesis and re-distribute energy resources during defense responses. Negative regulation of cellulose synthesis mediated by direct phosphorylation of CESAI by BIN2 demonstrates a direct connection between phytohormone regulation of cellulose synthesis. Furthermore, it is apparent that downstream signaling pathways following perception of abiotic and biotic stress-induced modification of cellulose synthesis and MTs are likely to overlap.

In the future, further investigation to fully understand mechanisms modulating trade-offs between plant growth, stress responsiveness and CSC-MT organization are necessary. Recently, a novel nucleotide-binding leucine-rich repeat (NLR) locus (group 1 ACQOS) has been implicated in the trade-off between abiotic and biotic stress adaptation [70**]. NLRs are well-known intracellular receptors involved in effector recognition, both in animals and plants [71]. This finding demonstrates not only a tight regulation of immune responsiveness via phytohormone networks, but also evidence of an evolutionary strategy toward balancing immunity with growth. In this review, we have summarized firm examples demonstrating modulation of cellulose synthesis and MT organization,
highlighting the current direction in which the field should move towards understanding stress perception at the cell surface and identifying processes necessary for growth under adverse conditions.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


This work demonstrates how microtubules can withstand the forces generated by moving cellulose synthase complexes and further establishes the importance of correct microtubule organization during cellulose synthesis.


In this paper, Endler et al. identify a new integral part of the cellulose synthase complex that aids in the re-establishment of the cortical microtubule network upon salt stress.


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This study identifies a novel cellulose biosynthesis-inhibitor secreted by Bacillus, providing evidence that microorganisms directly modify cellulose synthesis of plants to fit their needs.


This study identifies cellulosic as a novel DAMP, thus directly linking cellulose degradation to immunity response activation at the cell wall.


This study provides the first evidence of cellulose in papillae that form upon penetration attempts from microbes, confirming the importance of cellulose as a structural barrier to pathogens.


In this paper, Sahni et al. show that overexpression of brassinosteroid biosynthetic genes leads to enhanced stress tolerance in plants, further establishing a strong involvement of brassinosteroid signaling in adaptation to stress.


This study demonstrates that an oomycete-can directly hijack plant hormonal networks through a secreted effector and thereby modulate host immune responses.


In this outstanding work, Nolan et al. describe the active downregulation of the brassinosteroid signaling cascade by BIN2 in response to abiotic stress.


This study establishes a direct link between brassinosteroid signaling and cellulose synthesis, showing that CESA1 is phosphorylated and thereby negatively regulated by BIN2, the central kinase in the brassinosteroid signaling cascade.


In this work, Ariga et al. not only demonstrate a tight regulation of immune responses via phytohormone networks but also how plants balance immunity and growth.