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REVIEW PAPER

Hormone activities and the cell cycle machinery in immunity-triggered growth inhibition

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Abstract

Biotic stress and diseases caused by pathogen attack pose threats in crop production and significantly reduce crop yields. Enhancing immunity against pathogens is therefore of outstanding importance in crop breeding. However, this must be balanced, as immune activation inhibits plant growth. This immunity-coupled growth trade-off does not support resistance but is postulated to reflect the reallocation of resources to drive immunity. There is, however, increasing evidence that growth–immunity trade-offs are based on the reconfiguration of hormone pathways, shared by growth and immunity signalling. Studies in roots revealed the role of hormones in orchestrating growth across different cell types, with some hormones showing a defined cell type-specific activity. This is apparently highly relevant for the regulation of the cell cycle machinery and might be part of the growth–immunity cross-talk. Since plants are constantly exposed to Immuno-activating microbes under agricultural conditions, the transition from a growth to an immunity operating mode can significantly reduce crop yield and can conflict our efforts to generate next-generation crops with improved yield under climate change conditions. By focusing on roots, we outline the current knowledge of hormone signalling on the cell cycle machinery to explain growth trade-offs induced by immunity. By referring to abiotic stress studies, we further introduce how root cell type-specific hormone activities might contribute to growth under immunity and discuss the feasibility of uncoupling the growth–immunity cross-talk.

Key words: Cell cycle, cell identity, cell type specificity, growth under stress, hormone signalling, immunity, root apical meristem, root development, stress adaptation.

Introduction

As sessile organisms, plants are repeatedly challenged as their environment changes during their lifetime. The ability of plants to perceive and respond to these changes in an adaptive way facilitates survival and reproduction. Environmental stresses are highly variable in their temporal occurrence and physical nature (e.g. abiotic or biotic) while their intensity (e.g. amplitude and complexity) defines the stress severity on plants. Among the regular and thus predictable re-occurring changes is the day–night cycle and the different seasons in temperate climates. Plants have evolved adaptive systems such as the circadian clock (e.g. to integrate the day–night cycle), which are part of developmental programmes (e.g. senescence or vernalization) to adjust growth and reproduction accordingly (Huijser and Schmid, 2011; Hsu and Harmer, 2014). Plants have also evolved morphogenetic traits to overcome or avoid stress. For instance, roots sense nutrient and water content in the soil and actively reorganize root architecture to access areas with superior resource availabilities (Gifford *et al.*, 2013; Bao *et al.*, 2014). Biotic stress induced by pathogen or herbivore attack, in contrast, is unpredictable, and plants must immediately activate immune pathways to ward off the invader. It is a significant challenge for plants to sense biotic stress severity adequately and respond appropriately. Any failure would allow invaders to feed on plants, resulting in plant disease and plant death. On the other hand, activation of immunity

is also associated with trade-offs that can significantly affect growth and yield.

Plant immunity defines plant responses to stop pathogen invasion and is based on highly sensitive receptor-based perception systems activating antimicrobial signalling cascades. Pathogens such as bacteria and fungi are generally recognized by plasma membrane-localized or intracellular receptors that initiate signalling cascades to activate transcription factors in order to induce stress-adaptive genes (Boller and Felix, 2009; Stergiopoulos and de Wit, 2009; Bernoux *et al.*, 2011; Heidrich *et al.*, 2012). More precisely, plant immunity is turned on upon the recognition of conserved microbial molecules known as microbe-associated molecular patterns (MAMPs), such as bacterial flg22 and elf18 (active epitopes of bacterial flagellin and elongation factor-Tu, respectively) or fungal chitin. Plasma membrane-localized pattern recognition receptors (PRRs) specifically recognize these MAMPs to trigger immune responses (Gómez-Gómez *et al.*, 1999; Kunze *et al.*, 2004; Wan *et al.*, 2008; Petutschnig *et al.*, 2010). This so-called pattern-triggered immunity (PTI) includes different immune pathways such as the rapid apoplastic production of reactive oxygen species (termed the ROS burst) and the phosphorylation of mitogen-activated protein kinases (MAPKs) and Ca^{2+}-mediated activation of Ca^{2+}-dependent protein kinases (CDPKs) that activate transcription factors to induce defence genes (Felix *et al.*, 1999; Asai *et al.*, 2002; Boudsocq *et al.*, 2010; Macho *et al.*, 2012). The modular composition of immune signalling basically consisting of receptors, signalling cascades, and gene expression is highly effective as it rapidly integrates different signalling streams. Based on this signalling concept, plant immunity provides protection against the majority of pathogens (Jones and Dangl, 2006; Boller and Felix, 2009).

PTI signalling is based on the concerted action of synergistically and antagonistically interacting pathways that add to the robustness and effectivity of immunity (Tsuda *et al.*, 2009; Pieterse *et al.*, 2012). The MAPK and CDPK pathways, for instance, independently and synergistically activate defence genes (Boudsocq *et al.*, 2011). Hormones significantly contribute to plant immunity and can synergistically or antagonistically activate defence genes. For instance, immunity against necrotrophic pathogens crucially depends on the synergistic interaction of jasmonate (JA) and ethylene (ET) or JA and abscisic acid (ABA) pathways, respectively. In turn, salicylic acid (SA), as part of the immunity to stop biotrophic pathogens, involves the suppression of JA signalling (Pieterse *et al.*, 2009, 2012).

Though immunity is highly effective in protecting plants, it antagonizes plant growth (Bowling *et al.*, 1994; Gómez-Gómez *et al.*, 1999; Jirage *et al.*, 2001; Kunze *et al.*, 2004). Biotic stress induces a redistribution of resources such as energy currents and signalling processes to activate immunity (Navarro *et al.*, 2004; Bolton, 2009; Tsuda *et al.*, 2009; Pieterse *et al.*, 2012) that might account for the inhibition of growth. In this review, we will introduce our current understanding of the growth–immunity antagonism and propose current models to explain this conflict. In addition to the energy reallocation hypothesis which considers growth suppression by immunity as a resource trade-off (Smedegaard-Petersen and Tolstrup, 1985), we will discuss the observed growth inhibition as a function of conflictive cross-talk of hormone signalling pathways participating in immunity and growth-associated cell cycle regulation. By focusing on roots, we will finally consider how immunity affects the spatio-temporal function of hormones in root growth and development. Since plants are constantly attacked by microbes under both agricultural and natural conditions, this switch from a 'growth' to a 'stress' operating mode can prevent crops from harnessing their full genetic yield potential (Brown, 2002). As well as the economic impacts on crop production, this growth to stress switch also bears conflictive potential in view of our efforts to generate next-generation crops with improved stress resistance and yield under climate change conditions.

What is plant growth and how is it regulated?

Plant growth is the result of the well-co-ordinated interaction of cell cycle and cell growth in shoots and roots (Sablowski and Carnier Dornelas, 2014). In the root apical meristematic zone (MZ), the cell cycle continuously delivers new cells through mitotic activity to maintain root growth (Fig. 1). Above the MZ, in the elongation zone (EZ), cells stop dividing and instead undergo rapid cell elongation via the endocycle, a cell cycle variant under which cells replicate their DNA without entering mitosis. This enhances cell ploidy and associates the endocycle with cell growth, which is characterized by cell expansion and dependent on vacuole-mediated cell turgor and of cytoplasmic growth driven by anabolic metabolism and protein synthesis in the EZ (Breuer *et al.*, 2014; Edgar *et al.*, 2014; Sablowski and Carnier Dornelas, 2014). The MZ and EZ are separated by a short transition zone (TZ). Here, cells show slight elongation, while some mitotic activity can still be found (Fig. 1). Thus, root growth is a succession of processes (e.g. cell division, endocycle) taking place at different root zones. Though hormones play an essential role in regulating growth via the cell cycle, its molecular basis is only partly understood (Fig. 1).

The cell cycle regulates cell proliferation via four defined phases to organize DNA synthesis and mitosis. Cell cycle progression is mainly mediated by two classes of cyclin-dependent kinases (CDKs) that function and gain specificity in complex with various cyclins (Cycs) (De Veylder *et al.*, 2007; Van Leene *et al.*, 2010; Nowack *et al.*, 2012). The formation of CDK–Cyc complexes is supported by the induction of different *Cyc* and *CDK* genes by auxin (*CYCA2;3*, *CYCB1;1*, and *CDKB2;1*), cytokinin (CK; *CYCD*), and brassinosteroid (BR; *CYCB1*) (Riou-Khamlichi *et al.*, 1999; González-García *et al.*, 2011; Wang and Ruan, 2013). DNA synthesis is initiated after CDKA in complex with CycD and CYCA3 phosphorylates and thus inactivates retinoblastoma-related (RBR) protein (De Veylder *et al.*, 2007). RBR inactivation allows E2Fa-DPa and E2Fb-DPb transcription factor dimer formation to regulate genes involved in DNA replication and chromatin remodelling (De Veylder *et al.*, 2002;

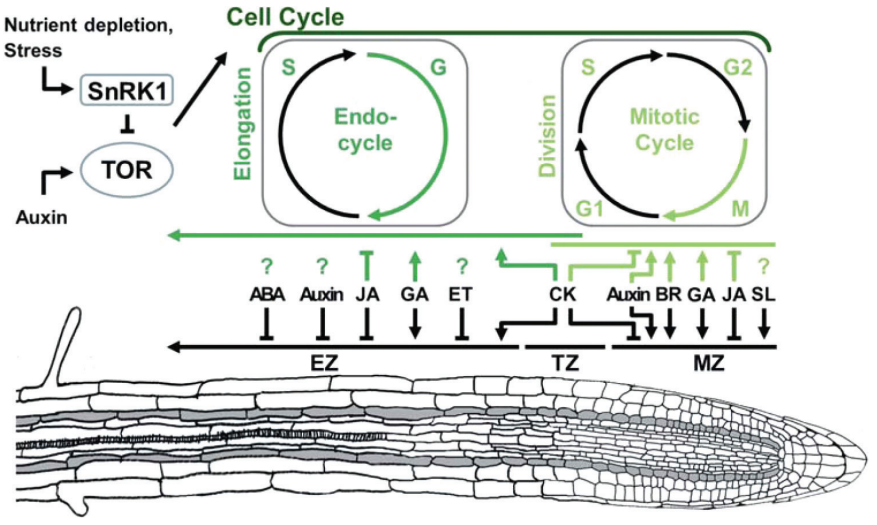

Fig. 1. Hormone function in root growth. Indicated are the supportive or inhibitory effects of the different hormones on growth in the meristematic zone (MZ), transition zone (TZ), and elongation zone (EZ). The effect of these hormones on cell division in the MZ and endoreplication via the endocycle is unknown for most hormones (?). ABA, abscisic acid; AUX, auxin; BR, brassinosteroids; CK, cytokinins; ET, ethylene; GA, gibberellins; JA, jasmonates; SA, salicylic acid; SL, strigolactone; TOR, target of rapamycin; SNRK1, Snf1-related AMP-activated kinase.

Ramirez-Parra *et al.*, 2003; Vandepoele *et al.*, 2005; Magyar *et al.*, 2012). Auxin has been identified to support this step further by stabilizing E2Fb (Magyar *et al.*, 2005). At the time that cells enter mitosis, CDKA–CycB1/CycD3 and CDKB–CycB/CycA2 complexes have activated Myb3R transcription factors to regulate genes involved in vesicular trafficking and other processes mediating mitosis and cytokinesis (Ito *et al.*, 2001; Araki *et al.*, 2004).

KIP-related proteins (KRPs) that are conserved in all eukaryotes function in concert with plant-specific Siamese (SIM) and Siamese-related (SMR) proteins as CDK inhibitors. Auxin and gibberellic acid (GA) suppress KRP2 and SIM, thereby supporting cell division, while ABA enhances *KRP1* expression (Wang *et al.*, 1998). In addition, the Cullin-ring finger E3 ligase anaphase-promoting complex/cyclosome (APC/C) blocks the entry into mitosis to maintain the endocycle. To achieve this, cell division cycle 20 (CDC20) and cell cycle switch 52 (CCS52) interact and thus activate APC/C to degrade Cycs such as CycA2;3. In complex with CDKB1, these interactions negatively regulate the endocycle (Cebolla *et al.*, 1999; Boudolf *et al.*, 2009). CKs assist the endocycle by inducing CCS52a1 through ARR2 in the TZ (Takahashi *et al.*, 2013). The endocycle E2F transcription factors are suppressors of the endocycle. DP-E2F-like 1 (DEL1)/E2Fe, for instance, interferes with endocycle entry by misregulating *CCS52a1* expression (Lammens *et al.*, 2008), and E2Fa interacts with RBR to form a transcriptional repressor complex that binds to the promoter of *CCS52a1* and *CCS52a2* to prevent endocycle entry (Magyar *et al.*, 2012).

In addition to hormonal control, the cell cycle is a function of the energy status of the plant. Plant organs possess a developmental and growth plasticity to cope with fluctuations in internal resources (e.g. nutrient availability) and external (e.g. environmental stress) conditions. This plasticity is partly anchored in the cell cycle as plant organs compensate disturbances in cell proliferation by the adaptation of cell sizes, to maintain overall organ size (Sablowski and Carnier Dornelas, 2014). However, conditions that ultimately trigger cell growth cessation also impair cell proliferation and elongation (Henriques *et al.*, 2014). In contrast to the low energy input process of turgor-driven cell elongation, cytoplasmic growth (and thus cell growth) depends on available cellular energy and nutrient resources. Plants therefore require a sensing and integration system that translates cellular energy/nutrient status into appropriate growth and cell cycle outputs, also taking into account cellular and environmental changes. As in other eukaryotes, target of rapamycin (TOR) kinase and Snf1-related AMP-activated kinase (SNRK1) signalling pathways in plants control cell growth by integrating energy availability and environmental stimuli (Baena-González *et al.*, 2007; Robaglia *et al.*, 2012). SNRK1 monitors the nutrient and stress status of cells and reduces anabolic processes to enable energy homeostasis and sustain growth under unfavourable conditions (Baena-González and Sheen, 2008). TOR, in turn, is directly involved in the regulation of translational processes as well as in growth-promoting transcription (Xiong *et al.*, 2013; Henriques *et al.*, 2014). This indicates an opposite effect of SNRK1 and TOR signalling pathways on growth. Moreover, SNRK1 negatively regulates TOR under stress or nutrient depletion (Fig. 1). It is currently unclear how TOR and SNRK1 perceive cellular energy/nutrient status and environmental stress and how this is communicated to the cell cycle programme. A recent study, however, revealed that, driven by photosynthesis-derived glucose, TOR induces primary metabolism genes including protein and cell wall anabolism in roots and also phosphorylates E2Fa to activate cell cycle S phase in the root apical meristem (RAM). It indicates a direct connection of TOR and plant growth by an alternative activation of cell proliferation and anabolic pathways (Xiong *et al.*, 2013). Intriguingly, auxin is able to activate TOR (Schepetilnikov *et al.*, 2013) (Fig. 1). How this interaction is associated with other known auxin activities on cell cycle regulation is currently unknown.

Biotic stress and immunity inhibit plant growth

If not lethal, biotic stress and plant disease as a result of pathogen colonization inhibit growth of affected plants. The reason for these symptoms is thought to reflect energy and nutrient undersupply. In addition to altering plant primary metabolism to recruit nutrients to foster their own reproduction, plant pathogens disturb root system architecture during infection, which can affect root function and hence the capacities for water and nutrient acquisition. This suggests that disease symptoms such as stunted growth are a direct consequence of nutrient and energy depletion.

Immune elicitors (MAMPs) of pathogens affect shoot and root growth to a degree that can be very similar to disease symptoms. Studies with the MAMPs flg22 and elf18 or with plants constitutively expressing resistance genes indicated that an activated immune system interferes with plant growth and development (Gómez-Gómez *et al.*, 1999; Jirage *et al.*, 2001; Kunze *et al.*, 2004). This indicates that a highly sensitive or hyperactive immune system can activate traits that are highly disadvantageous for crop growth and thus yield. In fact, field studies with barley indicated that even a regular PTI activation by microbes of the phyllosphere and rhizosphere reduces crop yield by ~10% (Smedegaard-Petersen and Tolstrup, 1985). The potential of such an immunity trade-off is obvious in *Arabidopsis* mutants with constitutively activated immunity, which show up to 90% yield reduction (Jirage *et al.*, 2001; Bartels *et al.*, 2009). Considering the impact of immunity on growth and yield raises the question of the molecular origin of this trade-off.

Why does immunity inhibit plant growth?

The effectiveness of immunity depends on different strategies in which the reallocation of resources for the *de novo* synthesis of stress-adaptive proteins and secondary metabolites as well as the reconfiguration of cell signalling by hormones are of critical importance (Bolton, 2009; Robert-Seilaniantz, 2011; Pieterse *et al.*, 2012; Neilson *et al.*, 2013; Henriques *et al.*, 2014) (Fig. 2). Biotic stress integration obviously requires a co-ordinated redirection of cell processes in which stress is prioritized over growth signalling. As a consequence, energy and nutrient resources are allocated to a diverse set of stress-adaptive responses. The observed growth inhibition under stress is therefore believed to reflect a competition for energy and nutrient resources, as both growth and stress adaption demands cannot be covered at the same time (Smedegaard-Petersen and Tolstrup, 1985; Purrington, 2000; Heil and Baldwin, 2002).

This hypothesis of competition for limited resources is, however, challenged by other studies. Hormones are essential for the regulation of growth and immunity. Obviously, hormone signalling networks substantially differ depending on whether cells operate under a growth or immunity mode (Pieterse *et al.*, 2009; Wolters and Jürgens, 2009; Bennett and Scheres, 2010; Vanstraelen and Benková, 2012; Jung and McCouch, 2013; Huot *et al.*, 2014) (Fig. 2). Although data presented in Fig. 2 display hormone growth networks in whole roots in comparison with immunity networks in whole plants, they suggest a close link between the alteration of hormone interactions and the growth–immunity cross-talk. Consistent with this hypothesis, growth-inhibiting MAMP treatments suppress signalling of the growth hormone auxin (Wang *et al.*, 2007; Navarro *et al.*, 2008) and the mutually inhibitory cross-talk of JA and GA in different plants (e.g. rice) (Hou *et al.*, 2010; Wild *et al.*, 2012; Yang *et al.*, 2012; Heinrich *et al.*, 2013). However, the growth–immunity cross-talk is not unidirectional. Recent studies indicated that growth suppresses PTI responses by interfering with BR signalling (Albrecht *et al.*, 2012; Belkhadir and Jaillais, 2012; Lozano-Duran *et al.*, 2013; Shi *et al.*, 2013; Fan *et al.*, 2014; Malinovsky *et al.*, 2014). Importantly, immunity-triggered growth inhibition might be explained by JA- and SA-mediated inhibition of the cell cycle. Chen *et al.* (2011) demonstrated that JA suppressed *CDKA;1* and *CYCB1;1*. Moreover, the transcription factor MYC2, a positive regulator of JA signalling, was found to bind to the promoter of *Plethora 1* (*PLT1*) and *PLT2* (Chen *et al.* 2011). Together with auxin, PLTs are essential for stem cell

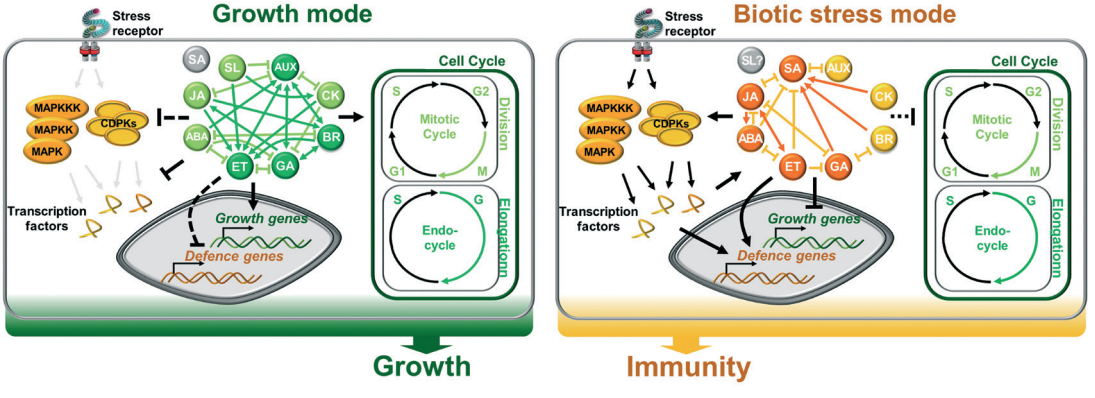

Fig. 2. Schematic overview of hormone signalling in growth and immunity. The cell cycle is central to plant growth and is affected by hormone signalling. Upon biotic stress, stress receptors activate immune signalling and cells operate in a stress mode. Immune signalling rewires hormone signalling in order to substantiate immunity. Under the stress mode, immuno-associated hormone signalling is postulated to suppress growth at the transcriptional and post-translational level. Under growth conditions, AUX, BR, ET, and GA show the highest interconnections, in contrast to ABA, ET, GA, JA, and SA under biotic stress. Dashed lines, predicted link. MAPK, mitogen-activated protein kinase; CDPK, Ca^{2+}-dependent protein kinase; ABA, abscisic acid; AUX, auxin; BR, brassinosteroids; CK, cytokinins; ET, ethylene; GA, gibberellins; JA, jasmonates; SA, salicylic acid; SL, strigolactone.

maintenance, root meristem activity, and root zone patterning (Mähönen *et al.*, 2014). Recent studies further suggested the stabilization of DELLAs by JA signalling (Yang *et al.*, 2012). DELLAs are inhibitors of GA signalling that also induce the CDKA and CDKB inhibitors *KRP2*, *SIM*, and *SMR* (Achard *et al.*, 2009). The growth inhibitory activity of SA, in turn, might be based on a cross-talk with auxin signalling as SA treatment stabilized auxin-inhibiting AUX/IAA proteins (Wang *et al.*, 2007). However, an antagonistic effect of SA on auxin-mediated cell cycle regulation is currently unknown.

Remarkably, despite this highly complex interdependence of intertwined or conflictive hormone signalling networks (Denance *et al.*, 2013; Huot *et al.*, 2014), the growth–immunity cross-talk appears to be detachable. Studies of the mutualistic fungus *Piriformospora indica* showed that the growth–immunity cross-talk is separated in JA mutants (Jacobs *et al.*, 2011). While the fungus suppressed flg22-triggered growth inhibition, flg22-triggered immune signalling (e.g. ROS burst) was unimpaired. This therefore negates an immuno-relevant function of signalling processes underlying growth inhibition. Moreover, chitin is equally as potent as flg22 or elf18 as an activator of immunity in plants (Wan *et al.*, 2008; Petutschnig *et al.*, 2010). Although these three MAMPs share signalling pathways and trigger highly similar immune responses (e.g. oxidative burst, callose deposition, immunity gene induction) chitin does not inhibit growth. In addition, Luna *et al.* (2014) recently identified the molecular nature of growth suppression by the chemical immuno-activating agent α-aminobutyric acid (BABA). BABA induces immunity by binding to the aspartyl-tRNA synthetase IMPAIRED IN BABA-INDUCED IMMUNITY 1 (IBI1). This interaction blocks aspartyl-tRNA synthesis by IBI1 and results in the accumulation of uncharged $tRNA^{Asp}$. It was shown that the protein kinase GCN2 recognizes these uncharged tRNAs and phosphorylates the translation initiation factor eIF2α to stop protein synthesis, resulting in plant growth inhibition. Interestingly, BABA was still able to induce immunity but did not inhibit growth in the *gcn2* mutant (Luna *et al.*, 2014). Considering the importance of GCN2 for cell growth, this study further suggests that the observed hormone-induced growth trade-offs under stress might be based on an impairment of protein synthesis.

Taken together, energy and nutrient distribution must be rearranged upon stress in order to achieve stress resistance (Bolton, 2009). However, the observed growth arrest upon stress is apparently not a consequence of the reallocation of nutrient and energy resources. Rather, the hormone signalling network is redirected. Since hormones appear to have defined spatio-temporal functions in root growth, root cell type-specific studies can help us to elucidate the redirection of hormone signalling during the growth–immunity cross-talk.

Cell type specificities of hormonal growth pathways

Root growth needs to be highly regulated in order to ensure proper establishment and maintenance of the different developmental zones as well as co-ordinated cell expansion along the longitudinal and radial axis (Fig. 3A, B). If we hypothesize that immunity–growth cross-talk can be uncoupled in roots, it will be crucial to understand the underlying regulatory mechanisms of growth under immunity at the developmental and cell type level. Hormones are prime candidates when looking for a starting point to manipulate such trade-offs. They are known to act in interdependent networks, linking growth and development to immunity (Wolters and Jürgens, 2009; Robert-Seilaniantz, 2011; Depuydt and Hardtke, 2011; Pieterse *et al.*, 2012). As discussed above, cell cycle progression is also directly influenced by hormones (Gutierrez, 2009; Takatsuka and Umeda, 2014).

Over the last years, hormone signalling was found to be greatly influenced by cellular context (Dello Ioio *et al.*, 2007, 2008; Dinneny *et al.*, 2008; Gifford *et al.*, 2008; Ubeda-Tomás *et al.*, 2008, 2009; Hacham *et al.*, 2011; Iyer-Pascuzzi *et al.*, 2011; Bargmann *et al.*, 2013; Duan *et al.*, 2013; Geng *et al.*, 2013; Fridman *et al.*, 2014). This offers the fascinating possibility to manipulate subsets of hormone functions by specifically targeting signalling components in distinct cell types. So far, most information about this topic comes from studies on root tips, where hormone signalling was either activated or disrupted in distinct cell types. Although these studies focused on growth and development, the generated mutant lines will prove extremely useful for investigating cell context-dependent hormone responses during immune activation. Furthermore, this research provides valuable insights into the emerging concepts of cell type-specific hormone signalling, that need to be understood to decipher growth–immunity trade-offs.

Auxin and cytokinin: concentration gradient and activity in a defined root zone

The auxin–CK circuit constitutes the main hormonal regulator of RAM size, which is modified by the activities of other hormones. While auxin was shown to promote stem cell maintenance and cell division, CK supports cell differentiation (Blilou *et al.*, 2005; Dello Ioio *et al.*, 2007, 2008; Ruzicka *et al.*, 2009; Petricka *et al.*, 2012; Vanstraelen and Benková, 2012; Moubayidin *et al.*, 2013).

The distribution of auxin, both longitudinally and radially, strongly influences root patterning (Kieffer *et al.*, 2010). Recent research has refined our understanding of cellular specificities of auxin distribution and signalling in the root tip (Petersson *et al.*, 2009; Brunoud *et al.*, 2012; Bargmann *et al.*, 2013) (Fig. 3C). Quantification of auxin levels in different cell types showed a gradient, with a maximum in the quiescent centre (QC), high levels in the stele, endodermis and cortex, and low levels in the epidermis (Petersson *et al.*, 2009). This map of auxin distribution was largely confirmed by use of the highly sensitive auxin sensor DII-VENUS (Brunoud *et al.*, 2012). In addition, Bargmann *et al.* (2013) found transcription of most auxin-regulated genes to be cell context dependent. This means that the identity of a given cell, which is determined by cell type, developmental status, and the combination of both, can intersect with auxin signalling and modify the auxin response. A cell response to auxin is therefore determined by its internal composition and the concentration of the hormone, which is actively regulated by the plant.

In contrast to auxin, CK was shown to exert its control over meristem size specifically through signalling in the TZ

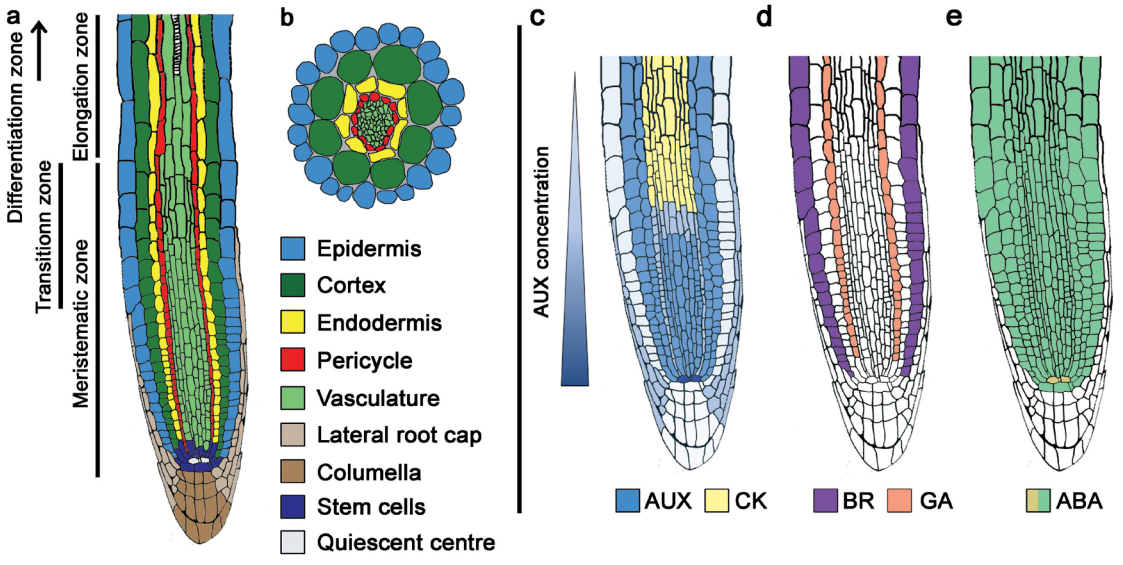

Fig. 3. Root organization and cell type specificities of hormone signalling. (a) Developmental zones and cell types of *Arabidopsis* roots. The pericycle and the cell types of the vasculature form the root stele. The quiescent centre (QC) plus surrounding stem cells build the stem cell niche (SCN). (b) Cross-section of a mature root showing the concentric arrangement of root cell types. (c–e) Different modes of cell context-specific hormone signalling. (c) AUX distribution (blue) is a main regulator of root patterning and meristem function (Blilou *et al.*, 2005; Kieffer *et al.*, 2010). AUX shows a general basipetal gradient across the root tip (Petersson *et al.*, 2009; Brunoud *et al.*, 2012). CK (yellow) acts in the TZ vasculature to promote cell differentiation (Dello Ioio *et al.*, 2007). (d) Epidermal BR signalling (grey) regulates cell division and cell size (Hacham *et al.*, 2011; Fridman *et al.*, 2014). GA (red) exerts control over meristem development and cell elongation through the endodermis (Ubeda-Tomás *et al.*, 2008, 2009). (e) ABA inhibits cell division in the RAM (Zhang *et al.*, 2010). While QC maintenance positively affects root growth (beige), it is negatively influenced by inhibition of cell division in the remaining meristem (green).

stele (Dello Ioio *et al.*, 2007) (Fig. 3C). The regulation of cell differentiation in the whole TZ requires vascular CK signalling through the ARABIDOPSIS HISTIDINE KINASE 3 (AHK3) receptor and the response regulators ARR1 and ARR12 (Dello Ioio *et al.*, 2007, 2008). ARR1 indirectly influences cell cycle progression through SHORT HYPOCOTYL 2 (SHY2), an AUX/IAA protein expressed in the vasculature of the TZ (Weijers *et al.*, 2005; Dello Ioio *et al.*, 2008). AUX/IAA proteins are negative regulators of auxin signalling and are degraded in the presence of auxin (Mockaitis and Estelle, 2008). Increased SHY2 protein levels in the vasculature cause redistribution of auxin (Dello Ioio *et al.*, 2008). As a result, the auxin–CK balance is shifted towards CK, therefore favouring cell differentiation instead of proliferation in all tissues of the TZ (Dello Ioio *et al.*, 2008).

CK also provides a good example for another level of complexity in hormone signalling. Bishopp *et al.* (2011) investigated the basipetal transport of shoot CK in the root phloem. Specific depletion of this CK element had no effect on root meristem size, but altered root vasculature patterning. Therefore, hormones produced in different source tissues appear to determine distinct developmental functions. This raises the question of whether it will be possible to manipulate subsets of plant growth and stress responses by interfering with hormone biosynthesis in specific tissues.

Brassinosteroids and gibberellic acid: distinct cell type-specific activities

In contrast to the broader activity of auxin and CK, BR and GA promote root growth through distinct cell types (Ubeda-Tomás *et al.*, 2008, 2009; Hacham *et al.*, 2011; Fridman *et al.*, 2014) (Fig. 3D). BR regulates cell proliferation and elongation in the root via the epidermis (González-García *et al.*, 2011; Hacham *et al.*, 2011; Fridman *et al.*, 2014) (Fig. 3D). In mutant studies, balanced BR signalling was found to be necessary for optimal meristem development, as both reduced and increased BR signalling led to a reduction in root meristem size (González-García *et al.*, 2011; Hacham *et al.*, 2011). Expression of the BR receptor *BRI1* in non-hair epidermal cells of the *bri1* mutant was sufficient to restore meristem size (Hacham *et al.*, 2011). Thus, BRI1 signalling in the epidermis is sufficient to control meristematic cell expansion and activity. Moreover, BR signalling was found to have opposing effects on cell elongation, depending on the relative abundance of BRI1 in non-hair compared with hair epidermal cells (Fridman *et al.*, 2014).

GA signalling occurs via degradation of growth-repressing DELLA proteins (Peng *et al.*, 1997; Silverstone *et al.*, 1998, 2001; Olszewski *et al.*, 2002). In an elegant study, Ubeda-Tomas and colleagues (2008) identified the endodermis as the primary target site for GA-induced root cell elongation. Expression of the non-degradable DELLA protein variant *ga insensitive* (*gai*) (Peng *et al.*, 1997) exclusively in this tissue layer led to disrupted cell elongation, while *gai* expression in other cell layers had no effect on root growth (Ubeda-Tomás *et al.*, 2008). In addition to its effect on cell elongation, GA controls cell proliferation in the meristem (Achard *et al.*, 2009; Ubeda-Tomás *et al.*, 2009). Therefore, GA signalling reduces the expression of cell cycle inhibitors KRP2 and SIM, providing another direct link between hormone signalling and cell cycle control (Achard *et al.*, 2009). Regulation of meristem size further requires GA perception in the endodermis

(Ubeda-Tomás *et al.*, 2009). In 2013, Shani and colleagues observed the accumulation of fluorescently labelled GA in the root endodermis. Importantly, this also indicated the existence of an active GA transport mechanism in roots that is dependent on endodermal cell identity (Shani *et al.*, 2013).

Abscisic acid: versatile integrator in the meristem

ABA plays a central role in plant adaptation to various biotic and abiotic stresses, but has important developmental functions under homeostatic conditions as well (Raghavendra *et al.*, 2010; Finkelstein, 2013; Nakashima and Yamaguchi-Shinozaki, 2013). In the RAM and the lateral root meristem (LRM), ABA was shown to inhibit division of QC cells (Zhang *et al.*, 2010). Through this, ABA promotes maintenance of the stem cell niche and thus positively influences root growth. Inhibition of cell proliferation by ABA in the other parts of the root meristem, however, suppresses root growth. Thus, ABA is perceived throughout the RAM but has opposite effects on overall root growth by exerting the same regulatory function on different cell types within the meristem (Zhang *et al.*, 2010) (Fig. 3E). Recently, highly sensitive ABA sensors have been developed that will open up new possibilities in studying the roles of ABA at cell type and longitudinal resolution (Jones *et al.*, 2014; Waadt *et al.*, 2014).

Cell context-dependent abiotic stress signalling: what can we learn?

Is there a direct link between hormones, stress, cellular context, and root growth and development? Considering the importance of cell type-specific activities of hormones in root growth, it seems likely that the observed growth–immunity cross-talk will depend on a cell type-specific redirection of hormone signalling. Unfortunately, the question has not been addressed concerning biotic stress so far. This can, however, be postulated from various cell type-specific transcriptome studies of abiotic stress and nitrogen depletion (Gifford *et al.*, 2008; Dinneny *et al.*, 2008; Iyer-Pascuzzi *et al.*, 2011; Geng *et al.*, 2013). These studies revealed cell context-dependent hormone signalling to be crucial during adaptation to abiotic stress and changing environments.

ABA, for example, is known for its involvement in plant responses to various adverse environments (Raghavendra *et al.*, 2010; Finkelstein, 2013; Nakashima and Yamaguchi-Shinozaki, 2013). For several abiotic stresses, ABA signalling was shown to be directly linked to proteins controlling cell identity (Iyer-Pascuzzi *et al.*, 2011). Cell identity regulators have been defined as genes with a known function in the determination or maintenance of a cell type (Dinneny *et al.*, 2008; Iyer-Pascuzzi *et al.*, 2011; Bargmann *et al.*, 2013). Indeed, many of these genes showed differential expression during abiotic stress responses. One of the proteins that probably links stress responses and cell identity is SCARECROW (SCR) (Iyer-Pascuzzi *et al.*, 2011). SCR is a transcription factor expressed in the endodermis where it regulates the expression of cell cycle components to control ground tissue patterning (Scheres *et al.*, 1995; Di Laurenzio *et al.*, 1996; Sozzani *et al.*, 2010). Several ABA-responsive genes have been identified as direct targets of SCR (Iyer-Pascuzzi *et al.*, 2011; Cui *et al.*, 2012). In addition, in phosphate-limiting conditions, SCR levels depend on PDR2, a protein involved in inorganic phosphate sensing (Ticconi *et al.*, 2004, 2009). These studies exemplify the intricate interconnection between cell identity regulators and stress adaptation. Given their involvement in hormone signalling, development, and stress sensing, it can be expected that cell identity regulators also influence the immunity–growth cross-talk. Studies focusing on cell type-specific transcriptomics in *Arabidopsis* roots have uncovered core gene sets defining certain cell types, thus greatly widening the list of possible cell type regulators (Birnbaum *et al.*, 2003; Brady *et al.*, 2007; Gifford *et al.*, 2008; Dinneny *et al.*, 2008; Mustroph *et al.*, 2009; Iyer-Pascuzzi *et al.*, 2011; Bruex *et al.*, 2012; Bargmann *et al.*, 2013; Geng *et al.*, 2013; Lan *et al.*, 2013; Simon *et al.*, 2013). It is yet to be determined which of them are linked to immune signalling, but these findings open up an exciting opportunity to identify new links between growth and defence responses.

Concerning stress, hormonal signalling at cellular resolution has been best studied under high salinity conditions and revealed a redirection of hormone activities and salt stress-induced growth inhibition (Dinneny *et al.*, 2008; Duan *et al.*, 2013; Geng *et al.*, 2013). The response of primary root growth to high salt concentrations can be divided into several distinct phases (Geng *et al.*, 2013). Initial growth reduction leads to a quiescent period without growth. This is followed by a recovery phase in which growth is reinitiated and subsequently maintained at a lower rate in the homeostasis phase. Tissue-specific hormone signalling is crucial in governing these growth phases. For instance, profiling at cell type resolution allowed the identification of both broad (several cell types show the same response) and cell type-specific ABA responses. It also revealed the endodermis and pericycle as the main sites for ABA-dependent primary root growth recovery (Geng *et al.*, 2013). In lateral roots, the endodermis was found to be the primary site of ABA-mediated regulation of growth in response to salt treatment (Duan *et al.*, 2013).

Intriguingly, growth of the different root meristems (RAM and LRM) is affected quite differently by salt stress (Duan *et al.*, 2013; Geng *et al.*, 2013). In the primary root, the salt-induced quiescent phase lasts several hours and is associated with ABA-induced growth suppression (Geng *et al.*, 2013). The same effect has been observed for lateral roots, but here the meristem was found to be considerably more sensitive to ABA, resulting in a quiescent phase that lasted several days (Duan *et al.*, 2013). The findings raised the question of whether lateral roots are generally hypersusceptible to growth-inhibiting hormones. However, application of an ET precursor caused stronger growth reduction in the primary than in the lateral roots. Thus both root types seem to be equipped with a unique set of signalling components to interpret stress and hormone signalling, with a major impact on root system architecture (Duan *et al.*, 2013). These results should be taken into account when studying immunity–growth trade-offs in roots, since a sole focus on primary root

length or fresh weight might overlook more subtle effects that occur in individual meristems or cell types.

The classic defence hormone JA was identified to play a role in salt stress adaptation as well (Geng *et al.*, 2013). JA signalling was activated during salt stress and found to be involved in growth suppression (Geng *et al.*, 2013). While JA is a key regulator of many defence responses, it has recently been shown to inhibit root growth by regulating the expression of several cell cycle-related genes (Chen *et al.*, 2011; Pieterse *et al.*, 2012). The inhibitory effect of JA signalling on growth during salt stress occurred via the inner root tissues (Geng *et al.*, 2013). In contrast, induction of the JA signalling inhibitor *JAI3* was observed specifically in the epidermis, indicating cell type specificity of JA-related stress signalling. Intriguingly, genes associated with defence responses were enriched among the JA-induced genes (Geng *et al.*, 2013). This raises the question of whether these defence proteins play a role during salt adaptation. Alternatively, roots might activate JA signalling solely to adjust root growth patterns, and activation of JA-related defences might occur as an unspecific side effect. It will be most interesting to see if JA-associated growth suppression during salt stress can be decoupled from the observed activation of defence responses. This example also demonstrates how research on immunity–growth trade-offs can profit from studies addressing abiotic stress responses.

Conclusions

Immunity inhibits plant growth with potentially very negative impacts on crop yield. The effect of immunity cannot only be attributed to the reallocation of limited resources, but, rather, stress perception redirects cell signalling from a growth to a stress mode. Roots are a quintessential example of an organ whose diverse functions are orchestrated by the interaction of metabolically and functionally very different cell types. This orchestration across all cell types is mediated by hormones, with some hormones characterized by their strict cell type-specific activity. In addition to a synergistic or antagonistic interaction in the regulation of signalling (e.g. co-activation/suppression of transcription factors) within and across cell boundaries, hormones are anchored in cell cycle regulation. The cell type-specific localization of cell cycle genes and the known regulation of cell cycle modules or pathways by hormones might be part of the growth–immunity cross-talk. In fact, recent studies indicated a direct link of immunity proteins (e.g. CPR5) in the regulation of central cell cycle regulators as well as of the cell cycle on SA signalling (Bao and Hua, 2014; Chandran *et al.*, 2014; Wang *et al.*, 2014). This further underlines the importance of cell identity and developmental status in the hormonal regulation of root growth during immunity. Though recent studies have broadened our knowledge of root immunity (Millet *et al.*, 2010; Jacobs *et al.*, 2011; Beck *et al.*, 2014), high-resolution transcriptomic data would be needed to unveil underlying regulatory principles. Identifying the signalling pathways involved in regulating the growth–immunity cross-talk in combination with localizing their exact site of action would open up opportunities to adjust the growth–immunity trade-off and could enable researchers to uncouple immunity from growth or at least drastically mitigate its negative effects.

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