To Divide and to Rule; Regulating Cell Division in Roots During Post-embryonic Growth

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Contents

Abstract Post-embryonic cell proliferation allows for the development of an extensive root system. Recent genetic analysis in *Arabidopsis thaliana* has revealed several mechanisms involved cell proliferation control during root development, including hormone signaling and regulatory loops. Furthermore, cell division responds to changes in redox status induced by environmental stresses, and we explore putative connections to the pathways that regulate cell proliferation.

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1 Introduction

The regulation of cell division in roots is tightly linked to the development of the root system. Over the past years, intensive genetic analysis in *Arabidopsis* and other species has revealed key developmental regulatory pathways which mediate cell proliferation during development and growth. Here we review our knowledge of the pathways involved in the regulation of the cell cycle in the different tissues of the root apical meristem and during lateral root initiation and formation and explore the connections to the mechanisms involved in cell cycle progression while focusing on observations in *Arabidopsis*.

2 The Cell Cycle in Roots and the Core Components

For the evolution of land plants, the development of vascularized roots was crucial and allowed for the progression toward larger plants such as ferns, horsetails, and seed plants. Post germination, root growth enables plants to explore their substrate and hence to extract nutrients and water from larger areas and from greater depths whilst also providing anchorage to the substrate. Furthermore, roots provide a niche for symbiotic organisms, and in several species roots have evolved so they can store nutrients, while in others they are a major vehicle of asexual propagation.

In seed plants, the root consists of concentric cylinders of different tissues in the radial dimension, a pattern which is set up during embryogenesis by formative cell divisions. The outside tissue layer or epidermis encloses the other root tissues and contains the trichoblast lineage, a cell lineage with a specific cell identity, which gives rises to root hairs by tip growth. These root hairs enhance the surface area for uptake and aid in anchoring the root. The cortical cell layers provide protection and mechanical support, whereas the endodermis, with its secondary thickening of the cell wall, forms a selective barrier for ions. Inside the endodermis, the cells in the pericycle maintain meristematic properties that can give rise to lateral root primordia, and during secondary root growth the progeny of this cell layer can contribute to vascular tissues or diverge into cork cambium in some species. The vascular tissue originates from the procambium and can differentiate into the two types of conductive tissue in plants, phloem and xylem, and these tissues can be organized in different patterns in different taxa (Elo et al. 2009). Once again, these patterns are set up during embryogenesis in a series of asymmetric and formative divisions, resulting in well-defined cells layers with distinct cellular identities.

The forward growth of the root is achieved by a combination of cell wall biosynthesis and cell divisions perpendicular to the growth axis in a region at the tip of the root. In the root tip of seed plants (Fig. 1), the root cell files, apart from the epidermis and the lateral root cap tissues, originate around a region that in *Arabidopsis* consists of three to four cells which proliferate slowly. This quiescent center (QC) plays a major role in organizing the meristem and is required to maintain the stem cell identity

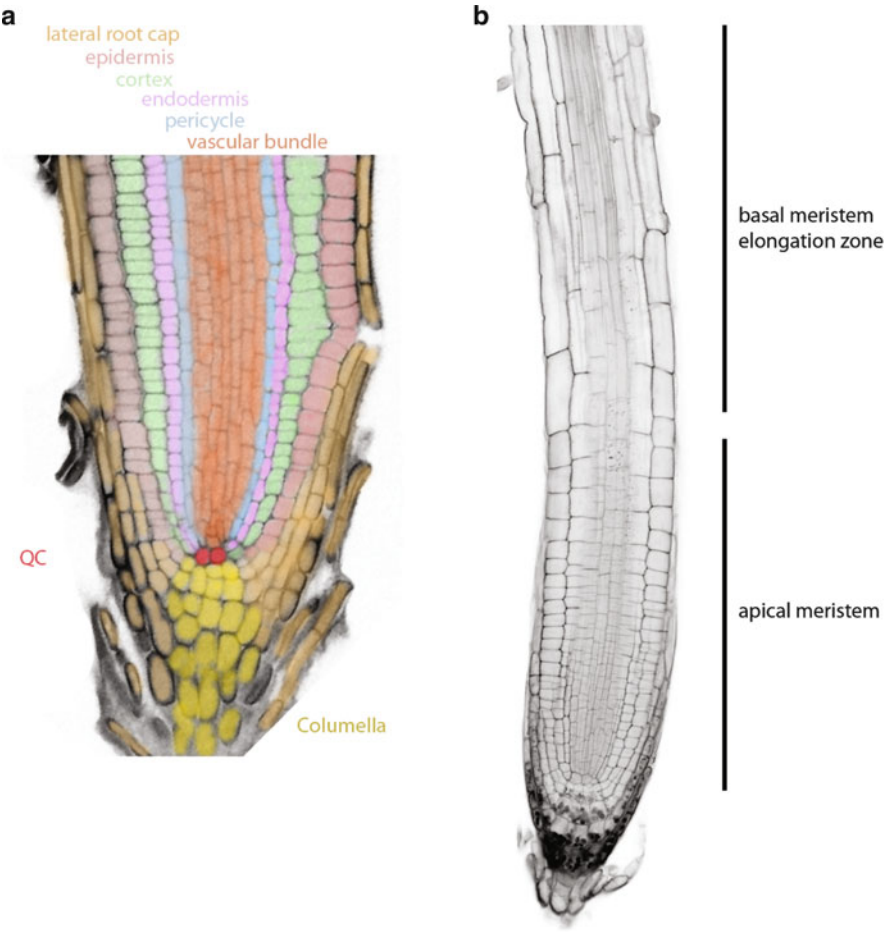

Fig. 1 Organization of the *Arabidopsis* root apex. (**a**) The different tissues of the root apical meristem. (**b**) Micrograph of a cleared root tip, revealing the apical meristem and the basal meristem with the onset of cellular elongation

of the neighboring cells, the initials, which abut on the QC. Remarkably, this organization seems to have a high degree of autoregulation, as removal of the QC, either surgically (Feldman and Torrey 1977) or by laser ablation (Van den Berg et al. 1997), results in the de novo formation of new quiescent center with flanking initials. The stem cells flanking the cortex–endodermis stem cell on the outside give rise to the initials of the epidermis and the lateral root cap (Pernas et al. 2010). Cells above the QC form the proximal meristem, and cells below are referred to as the distal meristem. The progeny of the distal meristem will form the central root cap cells. Within the different tissues of the meristematic region, cells grow and divide at a relatively small yet constant size resulting in forward movement of the tip. Cells that reach a threshold distance from the actual tip gradually start to elongate, and it is still

unclear whether they divide at a large cell size, or whether division activity arrests before elongation rate increases (Fig. 1). Higher up the root, cell division arrests and cells rapidly elongate. In many tissues, cell elongation is associated with endoreduplication, a shunted cell cycle that allows for DNA replication without intervening mitosis, resulting in a logarithmic accumulation of genome copies in each nucleus. Unfortunately, at this point in time, we do not have a full map of nuclear ploidy in the different tissues and cell types at our disposal, and it would be interesting to establish the relationship between cell elongation and DNA ploidy in the different tissues. What we do know is that both pericycle and cambium cells away from the root tip maintain the potential to reinitiate division.

Pericycle cells at the xylem poles can be primed to become lateral root progenitors or founder cells in the transition zone of the meristem, and currently two mechanisms have been put forward. A local alternating pulse of auxin, or localized auxin response, has been proposed to be the major component of pericycle cell priming (De Smet et al. 2007; Dubrovsky et al. 2008). However, recently another mechanism based on endogenous and autonomous oscillations of gene expression was put forward (Moreno-Risueno et al. 2010). Primed cells have the potential to resume cell division and to create a de novo lateral root primordium with the same cellular and tissue organization as the primary root apex by a well-characterized sequence of transverse, anticlinal, and periclinal cell divisions (Casimiro et al. 2003). Intriguingly, while pericycle cells at the phloem pole remain in G_1, pericycle cells at the xylem poles have the capacity to progress to G_2 (Beeckman et al. 2001).

Periclinal divisions of the cambium cells give rise to additional cells, which differentiate into phloem or xylem and contribute to thickening of the root.

Hence, conceptually, cell division in the growing root is associated with three major processes: cell division in the apical root meristem provides cells during longitudinal growth, cell cycle reactivation activation of the pericycle results in the formation of lateral primordia for the ramification of the root system, and activation of the cell cycle in the cambium and the pericycle provide cells for secondary radial development.

A challenge lies in understanding how key growth and developmental pathways which mediate cell proliferation in the different root tissues interface and coordinate with the core cell cycle mechanisms. Cell cycle progression in eukaryotes is driven by the ordered consecutive action of different cyclin-dependent kinase (CDK) complexes (Inze and De Veylder 2006). Genome sequencing has revealed a significant number of core cell cycle regulators in higher plants (Renaudin et al. 1994; Vandepoele et al. 2002). The different cyclins and cyclin-dependent kinases are regulated post-translationally. This involves post-translational regulation by interactions with scaffolding proteins, inhibitors, and activating or inhibiting phosphorylation by regulatory kinases (Inze and De Veylder 2006). Hence, there is an extensive tool set for regulation of the cell cycle, and we are still exploring the composition (Van Leene et al. 2010) and function of the different complexes.

Apart from the CDKAs which are conserved in animals (CDKs) and yeast (CDK1/cdc2+/cdc28), plants have a unique family of CDKB cyclin-dependent kinases composed of two subfamilies. The CDKB1 and CDKB2 kinase activity is maximum during G2/M and mitosis, respectively (Inze and De Veylder 2006).

In *Arabidopsis*, the single CDKA is essential (Nowack et al. 2006), but in other species with more then one CDKA gene (e.g., rice) there might be a level of functional redundancy and specificity.

D-type cyclins were postulated to be important for the G1/S transition by controlling the activity of retinoblastoma-related proteins (RBRs) by phosphorylation. In higher plants, the CYCD gene family has several members, which can be classified into seven conserved families (CYCD1–CYCD7) (Menges et al. 2007). Indeed, in plants a subset of D-type cyclin genes respond transcriptionally to mitogenic signaling (Riou-Khamlichi et al. 1999; Oakenfull et al. 2002) and CYCD/CDKA kinases are able to hyperphosphorylate the RBR protein (Nakagami et al. 2002). This in turn renders RBR unable to suppress transcription factors such as E2F/DP which promote S-phase progression. Furthermore, loss of function of the three members of the CYCD3 gene family and CYCD3;1 ectopic overexpression indicated that CYCD3 genes are rate limiting for cell proliferation in aerial organs (Dewitte et al. 2003, 2007). Nevertheless, given the multiple CYCD genes (*Arabidopsis* has ten CYCD genes), it is feasible that some CYCDs interact with different CDKs, and other or additional functions can be anticipated for the different CYCD/CDK kinases.

A-type cyclins (CYCAs) are subdivided into three types (CYCA1–CYCA3) and the different members seem to have acquired quite different functions. The expression of a few members of the CYCA3 family peaks at the G_1/S transition, and those CYCAs are able to form active kinase complexes with CDKA which have activity toward RBR, making it not unlikely that they act in concert with CYCD complexes during the G_1/S transition (Menges et al. 2005; Takahashi et al. 2010). CYCA2;3 was found in a complex with CDKB1;1, and its prolonged expression inhibits the onset of endoreduplication, indicating that the CYCA2;3/CDKB plays an active role at the G_2/M boundary (Boudolf et al. 2009). Another member of the CYCA group, CYCA1;2, plays a crucial role in the two cell-cycle transitions of meiosis (Erfurth et al. 2010).

There are 11 CYCBs in *Arabidopsis* and they are divided into three different subgroups (CYCB1–CYCB3) (Menges et al. 2005). Transcript analysis in synchronized *Arabidopsis* cell cultures shows that transcripts of most B-type cyclins show a common regulation, with a distinct peak in G2 and early mitosis. The main exception is *CYCB1;1*, which is activated from early S phase in synchronized cells and does not significantly increase further during G2 phase (Menges et al. 2005). In *Arabidopsis* plants, the accumulation of the *CYCB1;1* transcript is correlated with meristematic tissues (Ferreira et al. 1994). Detailed analysis of the CYCB1;1 promoter identified cis-acting elements and regulatory proteins involved in the regulation of *AtCycB1;1* gene transcription (Ito 2000; Planchais et al. 2002). B-type cyclins proteins are also a subject of cell cycle-dependent proteolysis, and their protein levels follow the transcriptional regulation. Interestingly, CYCB1;1 accumulates in several backgrounds that are defective in genome structure and chromatin maintenance (Wu et al. 2010) or in response to DNA damage (De Schutter et al. 2007). In all these backgrounds, the accumulation of CYCB1;1 is associated with root swelling, probably due to disorganization of cortical microtubules (Serralbo et al. 2006). Recently, Wu et al. (2010) hypothesize that plant separase is the link between microtubules

disorganization and the superabundance of CYCB1;1. Separase is a protease activated at the onset of anaphase cleaving the cohesin complex, which holds sister chromatids together (Oliveira and Nasmyth 2010), and its action seems to be involved in CYCB1;1 destruction, either directly or indirectly.

Modulation of CDK activity is also achieved by interaction with proteins of the interactor of CDK (ICK)/Kip-related protein (KRP) and SIAMESE (SIM) families (Dewitte and Murray 2003; Churchman et al. 2006; Inze and De Veylder 2006). The ICK/KRP family contains seven members (ICK/KRP1–7) (Vandepoele et al. 2002), whereas the SIM subfamily contains five members (Peres et al. 2007) in *Arabidopsis*. Global transcriptomic analysis in synchronized *Arabidopsis* cell cultures reveals that ICK/KRPs show different patterns of regulation during cell cycle reentry and cell cycle progression, with sequential peaking in cell cycle phases (Menges et al. 2005). Interestingly, *ICK/KRP2* is expressed at high levels in sucrose-starved cells, declines on cell cycle resumption, and does not show any later regulation during subsequent cell cycle progression, suggesting a specific role in cell cycle reentry (Menges and Murray 2002; Menges et al. 2005). Gene expression analysis of *ICK/KRPs* genes in *Arabidopsis* plants reveals that *ICK/KRPs* are generally expressed at low levels but showed preferential expression in specific tissue/developmental conditions (Torres Acosta et al. 2011). Furthermore, several *ICK/KRPs* and *SIM* members are transcriptionally regulated by hormones (Wang et al. 1998; Himanen et al. 2002) or in response to biotic and abiotic stresses (Peres et al. 2007). In addition to their transcriptional regulation, ICK/KRP proteins are post-translationally regulated by proteolysis (Verkest et al. 2005; Jakoby et al. 2006).

Overexpressing an *ICK/KRP* gene reduced plant size, suppressed lateral root formation, and conferred smaller serrated leaves with fewer yet larger cells (Wang et al. 2000; De Veylder et al. 2001; Jasinski et al. 2002, 2003; Zhou et al. 2002; Barroco et al. 2006; Bemis and Torii, 2007; Kang et al. 2007). In line with an interaction with the D-type cyclins, the effects of elevated KRP levels could be attenuated by co-expressing a D-type cyclin (Jasinski et al. 2002; Schnittger et al. 2002b; Zhou et al. 2003). Ploidy analysis reveals that high levels of ICK/KRP proteins inhibit the G_1-to-S phase transition of both mitotic and endocycles, whereas a moderate increase affects mainly mitotic cell cycles (Verkest et al. 2005). Furthermore, KRP proteins can act as scaffolds to promote the interaction between CYCDs and CDKs, as recently shown for KRP2 which catalyses an interaction between CYCD2 and CDKA (Sanz et al. 2011).

The orderly destruction of the kinase partners and regulators allows for the coordination of the cell cycle. The level of the several cell cycle factors is controlled by the action of ubiquitin ligases, as ubiquitinylation targets the factors for destruction by the proteasome. During the cell cycle, the anaphase promoting complex (APC), which plays an important role in exiting mitosis, and the SKP1/Cul1/F-Box protein complex (SCF complex) are the key E3 ubiquitin ligase complexes controlling the stability of cyclins and other regulatory factors. CDK-mediated phosphorylation can stimulate recognition by the F-box proteins of specific substrates, and target them for destruction, hence providing a mechanism

which gives direction to the cell cycle. Furthermore, the action of these cell cycle factors can link several cell cycle phases together.

G1/S regulators, such as D-type cyclins, as they prime the cells for a mitotic cell cycle (Schnittger et al. 2002b), have been proposed to mediate the expression of mitotic CDKB kinases via the E2F/DP pathway (Boudolf et al. 2004).

Regulation of the cell cycle during root development under optimal conditions involves several aspects including the spatial control of cell proliferation in the different tissues and the coordination between cell division and cellular growth. During mitotic cell cycle progression, both cell growth and division seemed to be tightly linked, as revealed by loss of function of the translationally controlled tumor protein, a regulator of the TOR kinase pathway. Abolishing its function slows down both cell cycle progression and the growth of mitotic cycling cells (Brioudes et al. 2010).

In summary, cell division, driven by the action of CDKs, is restricted to specific tissues in roots.

3 Size Control of the Proximal Root Apical Meristem and the Mitotic Cell Cycle

In the root tip, the progeny of the stem cells undergo additional divisions in the proximal meristem, the so-called transit amplifying cell proliferation, before they elongate in the differentiation/elongation zone. While the elongating cell is often described as "cells leaving the meristem," the reality is that the stem cell niche at the root's tip (as defined by the QC and the initials) grows away from an elongating cell. Earlier elongation of the cells in the proximal meristem will deplete the meristem of dividing cells and will result in a shorter root apical meristem with fewer cells. Hence, the question "What controls the size of the root apical meristem?" can be reformulated toward "How does the distance from the stem cell niche influence the division/elongation probability of a cell?" when considering this problem from a cellular angle. We have now strong evidence that the decision between dividing or elongation is achieved by balancing auxin and cytokinin signaling in the transition and elongation zone, with auxin stimulating division and preventing elongation and cytokinin having an opposing function, which in combination with an auxin gradient of which the maximum migrates away together with the quiescent center, provides an elegant solution.

A model on the basis of available information on the density and orientation of auxin transporters, cell shape, and auxin transport parameters predicts a maximum auxin concentration in the QC and a steep auxin gradient in the proximal meristem, which drops according to the cell number from the quiescent center (Grieneisen et al. 2007; Laskowski et al. 2008). This is broadly in agreement with the analytical measurements of auxin levels on cell-sorted protoplasts derived from different apical tissues (Petersson et al. 2009), albeit they have a lower spatial resolution, as well as with the available expression patterns of auxin responsive genes, such as

members of the *PLETHORA (PLT)* family, in the different root tissues. Indeed, *PLT1* and *PLT2* proved to be crucial for interpreting this "instructive" auxin gradient in root growth and development (Aida et al. 2004). *PLT1* and *PLT2* encode for AP2-domain transcription factors, and losing the function of both results in the loss of stem cells, an arrest of transit-amplifying divisions, and reduction of cell expansion (Galinha et al. 2007).

Conceptually, meristem cells are characterized by their competence to divide and their undifferentiated status, and chromatin modifiers seem to play an important role in this process. Indeed, histone acetyltransferase are required to sustain *PLT* expression and maintain both transit-amplifying divisions and the root stem cell niche at the root's apex (Kornet and Scheres 2009). Furthermore, the action of SUMO E3 ligase is vital to repress endocycles in the root and shoot meristem, and in the root this SUMO E3 ligase acts in the PLT pathway (Ishida et al. 2009). In summary, the root tip is characterized by an auxin maximum, and auxin is required to sustain transit-amplifying divisions (Ishida et al. 2010).

A dynamic system for size control of the meristem during development was recently proposed by Moubayidin et al. (2010). In the transition zone at the border of the meristem, cytokinins stimulate the expression of *SHY2*, encoding for an auxin/indole acetic acid (AUX/IAA)-type protein that interacts with and suppresses the activity of auxin response factors, thereby inhibiting the expression of auxin responsive genes. Elevating SHY2 levels or reducing TIR1-AUX/IAA-ARF-dependent auxin signaling (Ishida et al. 2010) reduces the meristem size and promotes the onset of endoreduplication. Among the auxin responsive genes are the *PIN-FORMED* auxin efflux carriers, which are of major importance for polar auxin transport (Wisniewska et al. 2006; Feraru and Friml 2008; Geldner et al. 2009). Cytokinins reduce the meristem length by stimulating the expression of *SHY2* through ARR cytokinin responsive transcription factors, which are also stimulated by the RGA DELLA protein. The levels of RGA expression are suppressed by gibberellins. Gibberellin-mediated destruction of DELLA proteins also mediates the rate of cell proliferation in the root apical meristem, and this is proposed to be a consequence of reduced cell expansion and associated division of the endodermis layer in the root apical meristem (Achard and Genschik 2009; Ubeda-Tomas et al. 2009), suggesting a key role for the endodermis in controlling the growth rate in the root apical meristem. Auxin can also stimulate the biosynthesis or the activity of gibberellins (Fu and Harberd 2003), providing a positive feedback.

Apart from this elegant mechanism, brassinosteroids also influence meristem size (Gonzalez-Garcia et al. 2011; Hacham et al. 2011) by influencing both cell elongation and the proportion of dividing cells in the proximal meristem. Recent evidence suggests that the epidermis responds to brassinosteroids and that brassinosteroids can influence the activity of quiescent center cells and differentiation of cells in the distal meristem.

The potential to divide diminishes in cells above the proximal meristem and in terms of cell cycle control, one could argue that the transition from a mitotically cycling cell toward an endocycling cell can be achieved by removing M-phase factors. Certainly, manipulating levels of mitotic cyclins and plant-specific CDKBs

modulates the onset of endoreduplication (Schnittger et al. 2002a; Boudolf et al. 2004, 2009). CCS52A1, an activator of the anaphase complex, is able to target CYCA2;3, a mitotic cyclin, for destruction in the elongation zone of the root (Boudolf et al. 2009) and elevating CYCA2;3 levels delayed the onset of cell elongation (Ishida et al. 2010). These arguments indicate that mechanisms associated with the G2–M transition are putative targets for elongation onset pathways to interfere with the cell cycle. Nevertheless, this does not exclude that factors involved in the G1–S transition that prime cells for a mitotic division by linking the different cell cycle phases are important targets. Indeed G_1 cyclins, such as D-type cyclins, are able to stimulate the G_1–S transition and to prime cells for a mitotic cell cycle (Schnittger et al. 2002b; Dewitte et al. 2003, 2007; Qi and John 2007), thereby preventing endocycles and elongation. In this respect, one link to the core cell cycle machinery could be the stimulation of CYCD-interacting KRP2 and SIAMESE inhibitors by the DELLA proteins (Churchman et al. 2006; Peres et al., 2007; Achard and Genschik 2009). With increased levels of CYCD2;1 throughout the plant, there is still a discernable transition zone above the meristem leading up to the final elongated zone (Qi and John 2007). Ectopic expression of CYCD2;1 conferred transit-amplifying cell divisions at a smaller cell size in the proximal meristem, resulting in shorter meristems with higher cell numbers. In addition, ectopic expression of CYCD2;1 reduced endoreduplication and final cell expansion in tissues above the root apex. This indicates that D-type cyclins can promote transit-amplifying divisions in the RAM and overcome a cellular size threshold mechanism that integrates cell size with the decision to divide. However, our interpretation on the effectiveness of the SHY2 control mechanism for the size of apical meristem in these experiments is limited by our understanding of how modifying the threshold size for cell division and increasing the number of cell compartments in the proximal RAM influences the steepness of the auxin gradient, and it is therefore hard to judge whether elevating CYCD levels bypasses the SHY2-based control mechanism, or if the auxin gradient is affected as well. Nevertheless, loss of function of CYCD4;1, a D-type cyclin gene induced by sucrose, conferred premature elongation in the transition zone in the pericycle, indicating that D-type cyclins prevent, to some extent, the onset of elongation in some tissues (Nieuwland et al. 2009).

4 Maintaining the Stem Cell Population in the Distal Meristem and the Procambium; CLE Loops

In roots as in shoots, cells acquire different identities depending on their relative position, and their differentiation is governed by noncell autonomous regulatory loops, based on the diffusion of signaling ligands and recognition by membrane receptors, impinging on the action of *WUSCHEL*-related HOMEOBOX genes. Current models for the maintenance of the stem cell population in the distal and

vascular meristem comprise feedback loops related to the WUS/CLAVATA regulatory loop that controls the shoot stem cell population (Sarkar et al. 2007; Hirakawa et al. 2008, 2010a, b; Stahl et al. 2009). It is proposed that the duplication and diversification of the WUS/CLV module is part of the evolutionary origin of the root system of land plants (Dolan 2009). In the vasculature, the TDIF peptide (CLE41/44) is secreted by the phloem, and upon recognition by the TDR/PXY (TDIF receptor/phloem intercalated with xylem) membrane protein kinase in the cambial cells and probably in collaboration with other members of the CLE peptide family (Whitford et al. 2008), they regulate the proliferation of procambial /cambial stem cells and prevent their differentiation into xylem. Also, this interaction is required for correct orientation of the plane of cell division (Etchells and Turner 2010). In *Arabidopsis*, the WUSCHEL-related HOMEOBOX gene, WOX4, is a key target of the TDIF signaling pathway and is required for promoting cell division of the procambial/cambial population, but not for preventing differentiation of cambial cells into xylem (Hirakawa et al. 2010a). It is therefore feasible that the cytokinin signaling pathway, which prevents differentiation of cambial cells into xylem (Mahonen et al. 2006; Helariutta 2007), acts independently of WOX4. In agreement with this, related CLE peptides have the capacity to suppress protoxylem formation in a cytokinin-dependent manner (Kondo et al. 2010). Apart from controlling the fate and number of cells within the vasculature, cytokinins promote secondary radial growth in *Arabidopsis* roots and shoots, and the cambium cells are particularly responsive to cytokinins (Matsumoto-Kitano et al. 2008).

The differentiation of columella cells below the QC in the distal meristem is governed by the CLE40, a CLAVATA-like peptide, and the ARC4 receptor kinase signaling loop (Stahl et al. 2009). Unlike in the shoot apical meristem, where stem cells express the CLV3 ligand, the differentiated daughter cells of the columella stem cells express the CLE40 ligand, which is perceived by and stimulates expression of the ARC4 receptor-like kinase. In the root stem cell niche, WOX5 is expressed in the quiescent center and it maintains cell fate in adjacent cells in the distal and proximal meristem (Sarkar et al. 2007). The action of ARC4 represses WOX5 expression, thereby suppressing stem cell fate (De Smet et al. 2008; Stahl et al. 2009). This mechanism allows the CLE40 peptide produced in the tip of the columella to control the number of stem cells under the quiescent center, and the effect on differentiation is well documented; but it is still unclear how this connects to the temporal regulation of the cell cycle in the stem cells. In this context, it is interesting to note that the expression of WOX5, as of its shoot counterpart WUS, also depends on the action of two related phosphatases, POL1 and PPL1. These phosphatases appear to be of key importance for cellular polarization before cell division, asymmetric cell divisions, and stem cell maintenance (Gagne et al. 2008; Song et al. 2008). Losing the function of these phosphatases results in abnormalities of *PIN1* expression and distribution and ectopic expression of the MP/ARF5 auxin response factor (Gagne et al. 2008). Moreover, since other members of the WOX family mediate *PIN* transcription (Breuninger et al. 2008), it is conceivable that WOX5-mediated auxin transport provides an additional regulatory mechanism.

The retinoblastoma-related (RBR) protein has emerged as a central player at the crossroads of cell differentiation and cell proliferation (Johnston and Gruissem 2009; Borghi et al. 2010; Johnston et al. 2010). RBR directly interacts with a cohort of factors including those involved in chromatin organization, regulates differentiation pathways via downstream targets of transcription factors, and regulates cell cycle progression via the E2/DP transcription factors (Shen 2002). Surprisingly, the stem cells of the distal meristem proved to be particularly sensitive to modulating RBR levels. Levels of RBR are inversely correlated with cell division frequency in those stem cells and directly with the cellular differentiation of stem cells into statocysts (Wildwater et al. 2005). Furthermore, enhancing levels of known suppressors of RBR activity, such as D-type cyclins and E2F/DP transcription factors, triggers cell division, while elevating KRP protein level stimulates differentiation and suppresses cell division, and one can speculate that auxin can mediate the CYCD/RBR/E2F module in these distal stem cells in several ways. For example, auxin can stabilize the E2F transcription factors (Magyar et al. 2005) that could stimulate CDKB levels (Boudolf et al. 2004), induce CYCD expression (Oakenfull et al. 2002), and stimulate KRP destruction (Himanen et al. 2002; Sanz et al. 2011).

4.1 Post-embryonic Formative Divisions in the RAM

The three principal root tissues are radially organized, the epidermal cell layer covers the ground tissues, cortex, and endodermis, which in turn surround the stele, and this organization is laid out during embryogenesis. During embryogenesis, the action of SCHIZORIZA, a heat shock transcription factor, is required for establishing the ground tissue stem cells (Pernas et al. 2010), and regulating the asymmetric cell divisions of the ground tissue stem cells and specification of the cortex cell fate (ten Hove et al. 2010). The formative division of the ground tissue requires the action of the SCR/SHR transcription factor complex (Helariutta et al. 2000; Nakajima et al. 2001; Heidstra et al. 2004; Cui et al. 2007), which regulates genes related to cell cycle progression and CDK activity (Dhondt et al. 2010; Sozzani et al. 2010). Within the targets of SCR/SHR, the cyclin *CYCD6;1* gene was identified. In the root of embryos and seedlings, *CYCD6;1* is expressed in the cortex–endodermis initial. Further, in older seedlings, *CYCD6;1* expression marks the formative division of the endodermis cells which results in an additional cortex layer. CYCD6;1 proved to boost the division of the cortex endodermis initial during embryogenesis and growing seedlings (Sozzani et al. 2010). As CYCD6;1 lacks the canonical LXCXE motif in *Arabidopsis* and other plant species (Menges et al. 2007), it still remains to be established how this D-type cyclin acts in this process.

4.2 Environmental Signaling in the Root Apex via Redox Homeostasis

Redox homeostasis has emerged as an important player that mediates many developmental and physiological processes in plants, which include root growth, hypocotyl elongation in etiolated conditions, and responses to biotic and abiotic stresses. The cell's redox status is mainly determined by the net contribution of different redox couples and many short-lived reactive molecules, like reactive oxygen species (ROS) and reactive nitrogen species (RNS). In plants, the major redox systems are thioredoxin (NTR/TRX), glutathione (GSH/GSSG), and ascorbic acid (AA/DHA) (Banhegyi et al. 1997; May et al. 1998; Arrigo 1999; Schafer and Buettner 2001; Arrigoni and De Tullio 2002; Filomeni et al. 2002; Noctor et al. 2002; Potters et al. 2002, 2004; De Tullio and Arrigoni 2003; Bashandy et al. 2011a). GSH and AA are biochemically interconnected via the ascorbate/glutathione cycle. ROS and RNS have many diverse biological activities. The diversity comes from the enormous variety of chemical reactions and biological properties associated with them. Their concentrations within the cells seem to be determining their biological function. Initially, they were thought to be primarily harmful, increasing tissue damage after infection processes. However, their role was reevaluated after the discovery that these species are endogenously produced. We now know that these compounds not only are purposely synthesized, but also are fast and reliable direct indicators of "something is happening" in order to induce a proper adaptive response (De Tullio et al. 2010).

Redox balance is the basis for the activation of several enzymes and transcription factors, due to the presence of redox-sensitive residues, whose oxidation/reduction is responsible for changes in protein conformation and activity as well as for downstream consequences, such as cell cycle arrest. These enzymes include superoxide dismutases, peroxidases, dehydroascorbate reductases, glutathione reductases, and peroxiredoxins, which can shift their activity in response to redox conditions (Dietz 2008). Redox reactions can occur in membranes, such as thylakoids, plastid envelope, and plasma membrane, and in aqueous cell phases (Dietz and Pfannschmidt 2011). Upon such modifications, cellular redox status plays a critical role in regulating cell proliferation (Reichheld et al. 1999; Den Boer and Murray 2000; Shackelford et al. 2000). In plants, changes in the absolute amounts and/or ratios of reductants/oxidants affect cell proliferation, as shown by the *root meristemless 1* (*rml1*) mutant, in which less glutathione is synthesized because of a mutation in gamma-glutamylcysteine synthetase, the first enzyme in glutathione biosynthesis. In this mutant, the embryonic root meristem forms normally possibly due to maternal-derived glutathione, but cells within cease to produce new derivatives and the meristem disorganizes shortly after germination (Vernoux et al. 2000). Interestingly, the *rml1* mutant of *A. thaliana* is able to develop lateral roots (Cheng et al. 1995), which suggest that GSH is specifically required for cell divisions within the root apical meristem. Similarly, glutathione biosynthesis was required to sustain cell divisions in cell suspensions (Sanchez-Fernandez et al. 1997;

Potters et al. 2004). Interestingly, recent reports (Teotia et al. 2010) concluded that alteration of redox balance by knocking out two members (RCD1 and SRO1) of the poly(ADP-ribose) polymerase (PARP) superfamily led to compromised development. The double mutant *rcd1 sro1* accumulates both ROS and RNS and displays an abnormal root apical meristem. Furthermore, the zone of cell division is smaller than in wild-type roots and the identity of the QC is compromised. Additional studies with the AA/DHA redox couple also support previous results. High levels of AA increase the rates of cell proliferation in plant cells (Kerk and Feldman 1995; Liso et al. 2004), whereas addition of the oxidized form of AA, DHA, delays cell cycle progression (Potters et al. 2002, 2004).

In conclusion, several lines of evidence suggest that the accumulation of reduced components (AA and GSH) increases the rates of cell proliferation in plant cells, whereas the accumulation of the oxidized forms (DHA and GSSG) delays cell cycle progression. Furthermore, the in vivo localization of these redox couples reinforces their connection with cell proliferation, whereas GSH is mainly associated with the actively dividing proximal meristem cells, characterized by a short cell cycle, GSH is almost not detectable in QC cells, characterized by a long cell cycle (Sanchez-Fernandez et al. 1997). Similarly, ASC is absent in QC cells and ASC oxidase, an enzyme involved in the oxidation of AA to DHA, is accumulated in QC cells (Kerk and Feldman 1995; Liso et al. 2004), suggesting a linkage between the accumulation of oxidized forms and the arrest of QC cells in cell cycle progression (Jiang et al. 2003).

A possible mechanism underlying direct redox control of the cell cycle involves A-type cyclins. Several A-type cyclins are involved in S-phase progression (Dewitte and Murray 2003). Previous reports pointed out the differential expression of two A-type cyclins in BY-2 tobacco cells under oxidative stress, which result in cell cycle arrest (Reichheld et al. 1999). Interestingly, these A-type cyclins are not detected in the QC of the *Arabidopsis* primary root (Burssens et al. 2000), characterized by a more oxidized status and the arrest of cells in G_1 phase (Kerk and Feldman 1995; Sanchez-Fernandez et al. 1997; Kerk et al. 2000; Jiang et al. 2003; Liso et al. 2004).

Many lines of evidence link auxin signaling to changes in redox status (Takahama 1996; Jiang and Feldman 2003). High levels of auxin induce in plants a more oxidizing environment (Joo et al. 2001; Pfeiffer and Hoftberger 2001; Schopfer 2001; Schopfer et al. 2002; Tyburski et al. 2008, 2009). This change in redox status is mainly due to the generation of several ROSs, such as hydrogen peroxide (Brightman et al. 1988; Joo et al. 2001) and superoxide ions (Schopfer 2001). These ROSs could be generated by oxidation of IAA (Kawano 2003) or, indirectly, as a consequence of auxin affecting the activities of redox-associated systems (Takahama 1996; Kisu et al. 1997; Jiang et al. 2003; Pignocchi et al. 2003; Pignocchi and Foyer 2003). In agreement with this concept, the redox status of the QC, where auxin is strongly accumulated, is different from that in adjacent rapidly dividing cells. The QC has a more oxidizing environment (Kerk and Feldman 1995; Sanchez-Fernandez et al. 1997; Kerk et al. 2000; Jiang et al. 2003; Liso et al. 2004) and a large group of transcripts associated with regulating redox status is found (Jiang et al. 2010). Similarly, perturbing basipetal auxin flux by transport inhibitors

induces an increase in the ASC/DHA ratio in QC cells and a decrease in the other tissues of the root apical meristem (Jiang et al. 2003). These data collectively show that auxin could affect gene expression by both stimulating the degradation of the aux/IAA proteins (Tan et al. 2007) and via redox regulation. Interestingly, recent reports also conclude that alteration in redox status influence auxin signaling. Auxin transport and levels are perturbed in mutants affected in TRX and GSH redox systems (Bashandy et al. 2011a, b; Cheng et al. 2011). Treatments with redox components (DHA and the AA precursor GalL) or the use of inhibitors of GSH synthesis (BSO) confer remarkably similar effects on the expression pattern of QC identity markers and auxin housekeeping in roots. Taken together, these results suggest a regulatory loop between redox status and auxin levels, with profound implications for QC specification and maintenance.

Changes in environmental and nutrient conditions affect root apical meristem organization (Lopez-Bucio et al. 2003). ROS and RNS have been reported to be induced rapidly by several different types of environmental stresses in a variety of plant species and to regulate the plant response to the biotic and abiotic stresses. Novel tools, such as redox-sensitive promoters driving reporter genes, have enabled us to detect changes in redox conditions in vivo in response to changing conditions (Jiang et al. 2006; Heiber et al. 2007). It is well-known that low temperatures (Lee et al. 2004; Aroca et al. 2005), metals (Sharma and Dubey 2007), pathogens (Torres 2010), and nutrient deficiency (Tyburski et al. 2009) induce production of ROS and RNS in specific tissues. Although these diverse forms of stress affect root morphology in an analogous way by reducing primary root growth and promoting branching (Potters et al. 2007), the mechanisms of redox generation and sensing in response to those specific conditions are still poorly understood. The characteristic response of the *Arabidopsis* root system to low phosphorous (P) availability is an interesting example to illustrate the complexity of these processes. In an effort to understand how P deficiency is perceived in plants and influences root development, Tyburski et al. (2010) showed that ROSs are involved in the developmental adaptation of the root system to low P availability. Interestingly, rapidly growing roots of plants grown on P-sufficient medium synthesize ROS in the elongation zone and QC of the root. When seedlings are grown in conditions of P deficiency, the primary root growth slows down and concomitantly, ROSs in the QC relocate to cortical and epidermal tissues. Previously, Sanchez-Calderon et al. (2005) indicated that when *Arabidopsis* plants are grown in conditions of P deficiency, the number of cells in the root apical meristem decreases until it is depleted. In these roots, all root apical meristem cells differentiate and the QC is almost indistinguishable. One could argue that these changes in root architecture in response to phosphate starvation could be directly due to changes in ROS location and/or abundance. However, this scenario is even more complicated since these responses are also modulated by the auxin (Lopez-Bucio et al. 2003) and gibberellin–DELLA signaling pathways (Jiang et al. 2007). Intriguingly, plant DELLAs promote survival during adversity by reducing the levels of ROS (Achard et al. 2008), suggesting a putative linkage between ROS and gibberellin signaling pathways in the developmental adaptation of the root system to low P availability. In conclusion, many lines of evidence allow us to conclude that redox status in response

to stress is a major regulatory element in order to induce a proper adaptive response of the root system, which is dependent on the establishment and maintenance of the primary root meristem. Identifying direct ROS and RNS target genes from secondary affect genes now requires further study.

5 Cell Proliferation Outside the Root Apex: Reactivation of the Pericycle

Lateral root founder cells are primed in the pericycle at the xylem poles in the basal meristem. In line with this, reducing the density of cells in the basal meristem, as a consequence of losing CYCD4;1 function, reduces the final density of lateral roots (Nieuwland et al. 2009). Transcript profiling revealed oscillating gene expression in the basal meristem correlated with the gain of competence for lateral root formation, as marked with the synthetic auxin response reporter DR5. This oscillating gene expression, which can be influenced by auxin, was proposed to be the underlying mechanism for establishing the spatiotemporal distribution of lateral root primordial (Moreno-Risueno et al. 2010). Another model for founder cell specification relies on localized auxin fluxes acting as instructive signals in the basal meristem (De Smet et al. 2007; Dubrovsky et al. 2008) and in agreement with this, the localized destruction of the AUX/IAA28 triggers expression of GATA23, a transcription factor required for founder cell specification (De Rybel et al. 2010). Future research is expected to reveal how both models can be united.

Cell division is reactivated once the distance between the root tip and founder cell reached a threshold to form a lateral root primordium by a series of divisions according to a well-defined sequence of transversal, periclinal, and anticlinal divisions (Casimiro et al. 2003; Peret et al. 2009). Auxin treatment is sufficient to induce the first asymmetric division, and lateral root initiation requires the destruction of the SLR/IAA14 AUX/IAA repressor, which is catalyzed by auxin, resulting in activation of the auxin response factors ARF7 and ARF19. The successive activation of the Bodenlos/IAA12-MONOPTEROS/ARF5 module is required for the organization and patterning of the lateral root (De Smet 2010). The number of cells at the pericycle cell pole that undergo periclinal divisions and thus participate in the formation of the lateral root primordium is restricted by the action of the ARC4 receptor kinase, which is expressed in the smallest daughters of the first two asymmetric transversal divisions, resulting in the definition of a core in the primordium, of which the two cells undergo the first periclinal divisions (De Smet et al. 2008).

Although cell proliferation is required for the formation of lateral roots, stimulation of the cell cycle by enhancing the levels of G1/S regulators, such as CYCDs or E2F/DP transcription factors, is not sufficient for lateral root induction, but these factors mediate the sensitivity of the pericycle to auxin (Vanneste et al. 2005; de Smet 2010; Sanz et al. 2011). Indeed CYCD2;1 is rate limiting, to a certain extent, for auxin-induced lateral root formation (Sanz et al. 2011). Likewise, enhancing the

level of KRP proteins, which can inhibit CYCD/CDKA activity, suppresses lateral root formation and conversely, mutations in KRP2 stimulate lateral root formation (Himanen et al. 2002; Sanz et al. 2011). While CYCD2;1, is induced by sucrose, as is the related CYCD4;1, KRP2 levels are controlled by auxin, enabling auxin to control CYCD2;1 activity post-translationally (Himanen et al. 2002; Sanz et al. 2011). It is still an open question whether these CYCD-related pathways are targets of the SLR/IAA14-ARF7-ARF19 pathway or if they control the basal sensitivity toward auxin by intervening with the initial cell cycle progression at the pericycle xylem pole (Casimiro et al. 2003).

6 Conclusion and Perspective

Analysis of the genetic model plant *Arabidopsis* has recently revealed key regulatory pathways that mediate cell proliferation in the various processes in the apex and mature tissues of the root and has highlighted the role of cell cycle regulators in specific processes. The challenge now is to unravel how developmental and environmental signaling pathways are connected to the core cell cycle machinery and to establish how these mechanisms influence the architecture of the root system under various growth conditions.

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