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Balance between cell division and differentiation during plant development

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ABSTRACT The processes which make possible that a cell gives rise to two daughter cells define the cell division cycle. In individual cells, this is strictly controlled both in time and space. In multicellular organisms extra layers of regulation impinge on the balance between cell proliferation and cell differentiation within particular ontogenic programs. In contrast to animals, organogenesis in plants is a post-embryonic process that requires developmentally programmed reversion of sets of cells from different differentiated states to a pluripotent state followed by regulated proliferation and progression through distinct differentiation patterns. This implies a fine coupling of cell division control, cell cycle arrest and reactivation, endoreplication and differentiation. The emerging view is that cell cycle regulators, in addition to controlling cell division, also function as targets for maintaining cell homeostasis during development. The mechanisms and cross talk among different cell cycle regulatory pathways are discussed here in the context of a developing plant.

KEY WORDS: *cell cycle, development, Arabidopsis thaliana*

Introduction

Progression through the cell division cycle requires duplication of the genetic material and the delivery of the newly duplicated genomes to the two daughter cells during mitosis. This occurs in coordination with increases in other cellular components and changes in cell architecture and it represents one of the key processes in living organisms. In addition to the temporal and spatial regulation of the cell division cycle, the acquisition of a multicellular body plan imposes extra layers of complexity and regulation. Multicellularity is probably one source of evolutionary differences in the regulation of cellular processes. In fact, it is more appropriate to consider the concept of cell proliferation, instead of cell division, since it includes cell cycle control itself, cell cycle arrest and reactivation, endocycle, cell differentiation and cell death. In addition, these processes considered at the cellular level must be coupled to the particular ontogenic program. Plants and animals have evolved very different developmental strategies. While organogenesis in animals occurs during embryogenesis, organ initiation and growth in plants is a post-embryonic and continuous process that occurs over the entire lifespan of the organism. This remarkable fact relies on the existence of stem cell niches, e.g. in the shoot and root apical meristems (Nakajima and Benfey, 2002; Weigel and Jurgens, 2002) that continuously provide new cells that eventually take specific differentiation patterns. A second aspect relevant for the present discussion is the ability of plants to regenerate. Cells in certain locations can dedifferentiate and revert to a totipotent (or pluripotent) state, proliferate in a highly controlled manner and take multiple cell fates to form an entire organ or adult plant.

These processes involve specific regulatory networks that impinge on cell proliferation. Thus, an increasing interest focuses on answering the question of whether our current concepts of cell cycle regulators define all what they really do. An emerging view is that cell cycle regulatory components, in addition to controlling cell cycle progression, also have some roles in the coordination of cell division in the context of a developing organism. Altering cell cycle control has profound consequences in organogenesis, although plants seem to be very tolerant to changes in the level of cell cycle regulators. Furthermore, disturbances in cell proliferation are not associated with programmed cell death or oncogenic transformation, as it occurs in animals. The mechanisms and cross talk among different regulatory pathways that impinge on cell proliferation during plant development are discussed in the paragraphs below.

Abbreviations used in this paper: ABA, abscisic acid; CDK, cyclin-dependent kinase; CK, cytokinin; RBR, retinoblastoma-related.

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The plant cell cycle machine

Studies in single-cell model systems (yeast and mammalian cells in culture) have provided during the last two decades most of our current knowledge of molecular mechanisms regulating cell cycle transitions. Phylogenetic analysis of cell cycle regulators, together with molecular, cellular and genetic approaches, has revealed that the general strategies for the basic cell cycle machinery and control are highly conserved in all eukaryotes. Thus, experimental studies and the availability of genomic sequences of several plant species, most remarkably *Arabidopsis thaliana* (http://www.arabidopsis.org/home.html; http://mips.gsf.de/proj/thal/db/index.html), indicate that conservation of cell cycle regulators also occurs through the plant kingdom. Some exceptions and the presence of plant-specific cell cycle genes have been also found.

Cyclin-dependent kinases (CDK) are also the major drivers of plant cell cycle transitions. The *Arabidopsis* CDK family is a complex family of 12 members (Vandepoele, *et al.*, 2002). CDKA is the typical PSTAIRE-containing CDK, homologous to yeast Cdc2 and necessary for G1/S and G2/M transitions. CDKB proteins are plant-specific CDKs that are expressed from S through M phase (B1; PPTALRE) and in G2 and M phases (B2; PPTTLRE).

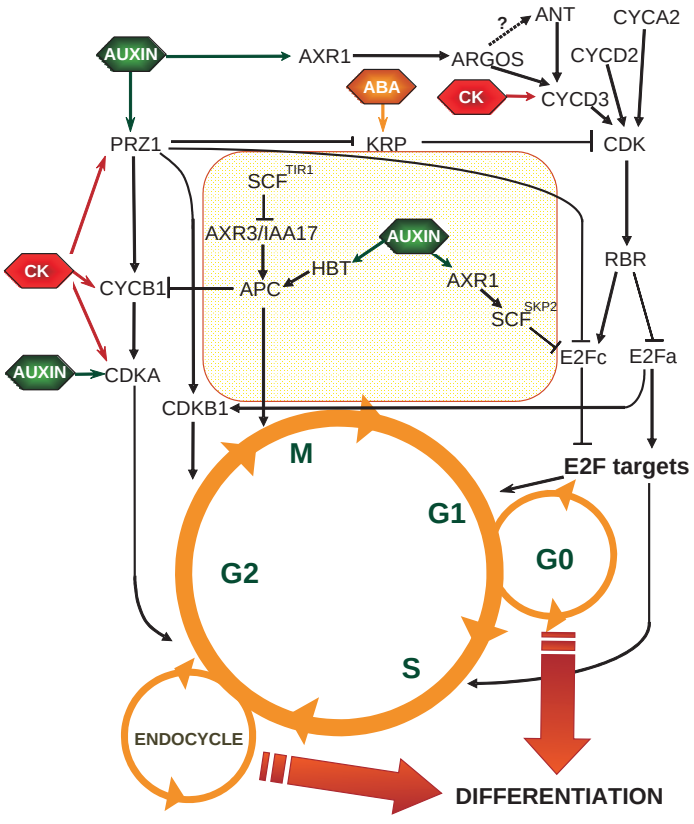

Fig. 1. Hormonal control of the level and/or activity of cell cycle regulatory components. *CDK/cyclin complexes drive the G1/S and G2/M transitions. Hormone signaling affects either transcription of stability in several cell cycle regulators. This map includes information derived from different plant species or organs. Consequently, it may not apply in a general sense. The main message is to highlight the interconnections of different hormone signaling pathways with cell cycle transitions, mainly G1/S and G2/M. Abbreviations are given throughout the text.*

It has been shown that CDKB1 is required for stomatal development (Boudolf, *et al.*, 2004a). CDKC (PITAIRE) is a CHED-related kinase with no known cell cycle function. CDKD and CDKF function as a CDK-activating kinase (CAK). Cyclins (CYC) are the CDK activator subunits. More than 40 different cyclins have been identified in the *Arabidopsis* genome (Vandepoele, *et al.*, 2002; Wang, *et al.*, 2004). The main cyclins are 10 cyclins A, 9 cyclins B and 10 cyclins D, of which some of them will most likely be involved in cell cycle transitions. For a comprehensive account of these data, including extensive expression analysis in synchronized cells, which is out of the focus of this review, the reader is referred to previous reports (Menges, *et al.*, 2002; Dewitte and Murray, 2003). CDK/cyclin activity also depends on the function CDK inhibitors (human p27Kip-related proteins; KRP), scaffold proteins (CKS) related to yeast Suc1 and regulatory kinases (WEE1; Vandepoele, *et al.*, 2002) and phosphatases (CDC25-like; Landrieu, *et al.*, 2004).

The role of individual CDK/cyclin complexes *in vivo* is far from being completely known, although increasing amount of information is becoming available from *in vitro* studies and expression studies. They seem to participate in, at least, three major cell cycle control points. One is the negative regulation of the retinoblastoma-related (RBR) protein by specific phosphorylation of S or T residues, although the consequences of this are not fully understood. RBR was originally identified in maize based on the ability of a plant DNA virus protein (RepA) to interact with RBR through a LXCXE amino acid motif (Xie, *et al.*, 1995; Grafi, *et al.*, 1996; Xie, *et al.*, 1996). Later many different plant species (Dewitte and Murray, 2003), including *Arabidopsis* that encodes a single RBR gene (Ebel, *et al.*, 2004), were shown to contain RBR-encoding genes. Plant RBR proteins share features of the three human members of the pocket protein family. RBR binds to and negatively regulates the activity of E2F/DP transcription factors. *Arabidopsis* contains six E2F (a through f) and two DP (a and b) genes (letters are proposed instead of numbers since they are not orthologues of the human E2F1-7 and DP1-2 genes). In short, E2Fa, b and c contain DNA binding, DP heterodimerization, RBR interaction and transactivation domains (de Jager, *et al.*, 2001; Mariconti, *et al.*, 2002). The other three members, E2Fd, e and f (also known as DEL2, 1 and 3, respectively) are homologues of the recently identified human E2F7 (Bracken, *et al.*, 2004). They are atypical since they have a duplicated DNA binding domain and bind DNA without dimerizing with DP (de Jager, *et al.*, 2001; Kosugi and Ohashi, 2002a; Mariconti, *et al.*, 2002) and, at least in the case of E2Ff, do not interact with RBR (Ramirez-Parra, *et al.*, 2004). E2F/DP complexes typically control the expression of genes required for G1/S transition and S-phase progression. Among these, PCNA, the DNA polymerase δ processivity factor (Kosugi and Ohashi, 2002b), the ribonucleotide reductase subunits (Chaboute, *et al.*, 2000; Chaboute, *et al.*, 2002), members of the pre-replication complexes (preRC) such as CDC6 (Castellano, *et al.*, 2001), CDT1 (Castellano, *et al.*, 2004) or MCM3 (Stevens, *et al.*, 2002), among others (de Jager, *et al.*, 2001; Kosugi and Ohashi, 2002b; Ramirez-Parra, *et al.*, 2003; Vlieghe, *et al.*, 2003). Interestingly, genes required in other cell cycle phases, e.g. CDKB1, are also E2F/DP targets (Boudolf, *et al.*, 2004b), or involved in metabolic processes not directly related to cell cycle progression, such as nitrogen assimilation (Vlieghe, *et al.*, 2003) or cell wall expansion (Ramirez-Parra, *et al.*, 2004), are also E2F targets. Future studies using

genomic approaches will certainly provide invaluable information on the involvement of E2F transcriptional network in regulating processes related to organogenesis and differentiation.

Another pathway where CDK/cyclin activity is likely crucial is the regulation of pre-RC function during initiation of DNA replication. Both CDC6 and CDT1 have been shown to be substrates for different CDK/cyclin complexes using recombinant proteins (Castellano*, et al.*, 2001; Castellano*, et al.*, 2004). In these cases, phosphorylation seems to be a necessary step to target these proteins for proteasome-mediated proteolysis, a mechanism that applies to other plant cell cycle regulators, e.g. E2Fc (del Pozo*, et al.*, 2002a).

Transition through G2 and M is also controlled by the activity of various CDK/cyclin complexes. CDKB1, an E2F target gene maximally expressed in G2, stimulates G2/M progression and is important for the balance between dividing and endoreplicating cells (Boudolf*, et al.*, 2004b). Other late G2/M functions, for example arrangement of the pre-prophase band, also require a CDKA activity (Weingartner*, et al.*, 2001). CYCB1 is the main activator driving G2/M transition and its level, as in other eukaryotes, is drastically reduced by proteolysis at the metaphase/anaphase transition. This occurs by the activity of the anaphase-promoting complex (APC; Capron*, et al.*, 2003a). One major regulator of APC function is CCS52 (Cebolla*, et al.*, 1999), a complex family of CDH1/FZR-related proteins (Tarayre*, et al.*, 2004). Components of the APC complex, such as HOBBIT (CDC27-like; Blilou*, et al.*, 2002) and NOMEGA (APC6/CDC16-like; Kwee and Sundaresan, 2003), have been identified.

Cytokinesis in plants is a rather unique process that implies the formation of a new cell wall to separate the two daughter cells. It involves a very complex interplay of membrane and cytoskeleton components where membrane trafficking and vesicle fusion are of primary importance (Carter*, et al.*, 2004; Mayer and Jurgens, 2004).

Hormonal control of cell cycle

The control of cell proliferation and differentiation during development depends, in most cases, on the concerted action of plant hormones. Among them, auxins and cytokinins are the best documented and they can impinge directly on cell cycle regulators (Fig. 1). In addition, other hormones, e.g. abscisic acid, ethylene, jasmonic acid and brassinosteroids, whose action is much less well characterized, also have an impact on cell cycle progression and/or arrest. These topics have been comprehensively reviewed recently (Stals and Inze, 2001; del Pozo*, et al.*, 2005) and here we provide a short account of data relevant for the discussion below.

Auxin

Auxins play a crucial role in many aspects of plant development, cell division and expansion, apical dominance, lateral root development and vascular tissue development, among other processes (Leyser, 2002). The recent identification of mutants defective in auxin signaling indicates that specific proteasome-mediated degradation of proteins plays a central role in the transduction of the auxin signal (Dharmasiri and Estelle, 2002).

The *AXR1* gene, whose mutations result in a reduction in auxin response, encodes a protein required for modification of CUL1 protein, a structural component of the SCF complex (del Pozo and Estelle, 1999; del Pozo*, et al.*, 2002b). AXR1 is involved in the proteolysis of the transcription factors E2Fc (del Pozo*, et al.*, 2002a) and AXR/IAA (Gray*, et al.*, 2001). Moreover, it is also implicated in the degradation of many other target proteins, thus explaining the pleiotropic phenotype of the *axr1* mutants. Mutations in the *PROPORZ1* (*PRZ1*) gene, identified in a screening for defects in cell proliferation in the presence of auxin and cytokinin, produce a high tendency to form calli only in presence of either auxin or cytokinin (Sieberer*, et al.*, 2003). The role of PRZ1, a transcriptional adapter protein that might regulate the expression of cell division genes, is to mediate the hormonal signal into the cell proliferation control. Consistent with a role of PRZ1 in cell proliferation, it is mainly expressed in shoot and root meristems and during lateral root development. In hormone free medium, expression of B- and D-types cyclins was reduced in the *prz1* mutant background while in hormone-containing medium *E2Fc* and *CDKB1;1* are up regulated leading to the formation of undifferentiated callus-like structures (Sieberer*, et al.*, 2003).

HOBBIT gene encodes a component of the APC complex. *hobbit* mutants, whose auxin response is partially impaired, have defects in cell division and cell differentiation. They are likely due to the stabilization of the AXR3/IAA17 transcription factor, one of the ubiquitin-dependent targets of the SCF^{TIR1} pathway (Blilou*, et al.*, 2002). Anomalies similar to those observed in the *hobbit* mutants are also found in other auxin signaling mutants, e.g. *axr6*, *monopteros* and *bodenlos*. *AXR6* encodes CUL1 that is part of SCF complexes involved in a variety of pathways and plays an important role in auxin response (Hellmann*, et al.*, 2003). *BODENLOS (BDL)* and *MONOPTEROS* (*MP*) encode IAA12 and ARF5 proteins, respectively (Hardtke and Berleth, 1998; Hamann*, et al.*, 2002).

Auxin is sufficient to up-regulate the CDKA;1 expression, but the kinase activity and the subsequent entry into mitosis is only induced by the addition of cytokinin (Zhang*, et al.*, 1996). However, there is direct evidence that auxin also regulates the expression of some regulatory subunits. Thus, alfalfa *CYCA2;2* expression is induced by auxin and during lateral root initiation and elongation (Roudier*, et al.*, 2003). Consistent with such expression pattern, CYCA2 has been involved in mitotic cycles but not in endocycles and cell differentiation.

Cytokinins

Cytokinins (CK) are implicated in essential plant growth-related processes, e.g. induction of cell division and shoot formation and development (Mok, 1994), activation of dormant lateral buds (Napoli*, et al.*, 1999), delayed senescence (Gan and Amasino, 1995), among others.

Cytokinins regulate cell cycle progression both at the G1/S and G2/M transitions (Fig. 1). The transcriptional activation of *CYCD3* by cytokinins is the main evidence for the involvement of cytokinin in G1/S regulation (Soni*, et al.*, 1995). Furthermore, constitutive expression of *CYCD3*;*1* produces hormone-independent growth of *Arabidopsis* calli (Riou-Khamlichi*, et al.*, 1999). However, CK are also important in the regulation of G2/M transition. In cultured tobacco cells, which do not need CK for growth, endogenous CK concentration peaks around the S and M phases (Redig*, et al.*, 1996). Lovastatin, an inhibitor of CK biosynthesis, blocks cells in mitosis and exogenous addition of CK bypasses this block, supporting the idea that CK levels are rate-limiting for the G2/M

transition in tobacco cells (Laureys*, et al.*, 1998). CK likely stimulates tyrosine dephosphorylation and subsequent activation of CDK (Zhang*, et al.*, 1996). In tobacco, auxin application increases the amount of CDK protein, but only cytokinin-mediated dephosphorylation produces the activation of CDK (Zhang*, et al.*, 1996).

Transgenic tobacco plants that overexpress constitutively cytokinin oxidases (CKXs) have low endogenous CK levels and present severe growth retardation (Werner*, et al.*, 2001; Schmulling, 2002). These plants have smaller shoot apical meristems (SAM) and leaves with reduced size. These phenotypes are mainly due to a reduction in the rate of cell division. Cytokinin-deficient plants show enhanced meristematic activity leading to increased growth of the primary root. It has been proposed that CKXs control the exit of cells from root meristems. However, they act as positive regulators of cell division in the shoot apical meristem and as negative regulators in the root apical meristem (Werner*, et al.*, 2003). The opposite phenotypes are observed in plants with increased levels of cytokinins, e.g., *Arabidopsis–amp1* mutant plants (Chaudhury*, et al.*, 1993), which show altered shoot apical meristems, increased cell proliferation, constitutive photomorphogenesis, early flowering time and transcriptional activation of cyclin *CYCD3* (Riou-Khamlichi*, et al.*, 1999; Nogué*, et al.*, 2000). Likewise, mutants in the *SUPERSHOOT* (*SPS*) gene, which also show increased levels of cytokinins, exhibit massive overproliferation of axilary meristems (Tantikanjana*, et al.*, 2001).

Other hormones

Abscisic acid (ABA) is a general plant-growth inhibitor, involved in stress-response. ABA inhibits cell division and/or DNA synthesis in different plant cell types (Newton, 1977; Robertson*, et al.*, 1990). The block occurs at the G1/S transition, likely by increasing the levels of KRP1 (Wang*, et al.*, 1998). ABA also down regulates genes required for DNA replication, e.g., CDT1a, a component of the pre-RC complexes (Castellano*, et al.*, 2004), topoisomerase I (Mudgil*, et al.*, 2002), or TERT, required for telomere replication (Yang*, et al.*, 2002). Other hormones such as brassinosteroids (BR; Clouse, 2002), gibberellins (GA; Davies, 1995), ethylene (ET; Guo and Ecker, 2004) and jasmonic acid (JA; Turner*, et al.*, 2002) play specific roles in cell expansion (BR, GA), reproductive organ development (BR, GA, JA), wound response and senescence (JA) and cell proliferation (BR, ET). Microarray analysis of brassinosteroid-regulated genes shows deregulation of genes implicated in cell elongation and cell wall organization (Goda*, et al.*, 2002). Brassinolide up-regulates expression of *CYCD3* and *CDKB1;1*. In fact, BR addition can partially rescue the short-hypocotyl phenotype of plants with reduced levels of *CDKB1;1* (Yoshizumi*, et al.*, 1999; Hu*, et al.*, 2000). JA blocks G1/S and G2/M transitions (Swiatek*, et al.*, 2002) by unknown mechanisms. GA activates cell division (Asahina*, et al.*, 2002) and in cooperation with ethylene and auxin, controls stomata development in the hypocotyl epidermis, a process that requires proliferation of precursor cells with limited stem cell potential (Saibo*, et al.*, 2003). However, the information about the molecular interactions between these hormonal pathways with the cell cycle regulatory network is scattered and still poorly understood.

Role of cell cycle regulators during development

Studies in whole animal systems, e.g. mouse, *Drosophila*, are revealing unanticipated roles of cell cycle regulators during development that are cell- and organ-specific (Humbert*, et al.*, 2004). The significant differences in organogenesis between animal (embryonic) and plants (post-embryonic) make comparable studies in genetically tractable plants systems, e.g. *Arabidopsis*, a powerful way to understand fundamental questions. This is a key question since development requires coordinated cell proliferation and, obviously, in the absence of a correct proliferation program development is impaired. Thus, what is the importance of cell division in development? Two opposing views have emerged over the years. One responds to the so-called “organismal theory” that claims that cell division simply follows a predetermined developmental program. The other is the “cellular theory” whereby cell division instructs organogenesis and development. Several examples exist that supports the view that a complex cross talk occurs between cell division control and development (Mizukami, 2001; Beemster*, et al.*, 2003; Tsukaya, 2003). Recent evidence discussed below, indicate that the function of a variety of cell cycle regulators during cell cycle progression, arrest and reactivation is controlled in a cell type-, tissue- and organ-specific manner. In this way, cell cycle regulators may play roles as targets coupling cell proliferation with development and their appropriate function is crucial for patterning. In the paragraphs below we discuss the major phenotypic consequences of altering the function of different cell cycle regulatory components in the context of a whole plant.

Cyclin-dependent kinases (CDK)

Overexpression of *Arabidopsis* CDKA;1 does not produce macroscopical changes while a dominant negative version inhibits cell division but not morphogenesis (Hemerly*, et al.*, 1995). Similarly, CDKA overexpression in maize endosperm increases kinase activity but has no effect on endoreplication. On the contrary, overexpression of dominant negative version of CDKA reduces significantly ploidy level (Leiva-Neto*, et al.*, 2004). *CDKB1;1* is expressed in cells of the stomatal lineage. A decrease in the activity of CDKB1;1, a kinase controlling the balance between mitotically dividing cells and endoreplicating cells (Boudolf*, et al.*, 2004b), impairs stomatal development by blocking meristemoid cell division (Boudolf*, et al.*, 2004a). Interestingly, these cells still acquire stomatal cell identity, indicating that cell differentiation can be uncoupled from cell division. Mutations in the *PROPORZ1* (*PRZ1*) gene, produces increased expression of *CDKB1;1* and *E2Fc*, leading to the formation of undifferentiated structures with proliferating cells (Harrar*, et al.*, 2003). *Arabidopsis hen3* (*HUA ENHANCER3*) mutants that lack CDKE, a homologue of human Cdk8, show improper specification of floral organs and termination of stem cell activity in the floral meristem (Wang and Chen, 2004).

Cyclins

Plants encode a complex set of cyclins, e.g. more than 40 in *Arabidopsis* (Wang*, et al.*, 2004), which are considered to likely play distinct roles at different developmental stages. Overexpression of *Arabidopsis CYCD2* increases growth rate by shortening the G1 phase in meristems (Cockcroft*, et al.*, 2000). Overexpression of *Arabidopsis CYCD3;1* allows cytokinin-independent growth and induces ectopic divisions producing leaves with more but smaller cells (Riou-Khamlichi*, et al.*, 1999; Dewitte*, et al.*, 2003). Interestingly, in spite of this sustained proliferative potential extra cells acquire a correct identity. In these plants, as well as in *Arabidopsis* plants expressing tobacco *CYCA3;2* (Yu*, et al.*, 2003),

hyperplasia is associated with a suppression of the endocycle program associated with leaf development. This effect is also observed in trichomes, which become multicellular when *CYCB1;2* is expressed (Schnittger, *et al.*, 2002). Consistent with this, one of the defects in the *Arabidopsis siamese* mutants, which has multicellular trichomes (Walker, *et al.*, 2000) is that *CYCD3;1* is up regulated. Furthermore, overexpression of *AINTEGUMENTA* (*ANT* ; Mizukami and Fischer, 2000) or the auxin-inducible *ARGOS* (Hu, *et al.*, 2003) genes increase organ size by inducing cell proliferation, an effect that is mediated by up-regulating *CYCD3* expression. *CYCA3;2*, an early G1/S-activated gene, seems to be a functional homologue of animal cyclin E (Yu, *et al.*, 2003). Thus, while reduction in *CYCA3;2* expression produces defective embryos and impairs callus formation, overexpression leads to a reduction in cell differentiation potential and prevents plant regeneration from leaf discs. These data reinforce the importance of a correct balance between cell division and cell differentiation for a correct morphogenesis.

CDK inhibitors

Plants encode CDK inhibitors, the Kip-related (KRP) proteins, loosely related to the human p27 protein (De Veylder, *et al.*, 2001), but plants lack homologues of the human p21 and INK4-related proteins. *Arabidopsis KRP1-7* genes exhibit a highly specific expression pattern, suggesting distinct roles in cells with a different physiological status. Thus, KRP1 and KRP2 are expressed in endocycling cells while KRP4 and KRP5 are detected in mitotically dividing cells (Ormenese, *et al.*, 2004). Overexpression of KRP1 or KRP2 inhibits cell division and changes morphogenesis of leaves that contain less but larger cells (Wang, *et al.*, 2000; De Veylder, *et al.*, 2001), an effect partially reversed by overexpression of an inducer of cell division, such as CYCD3 (Zhou, *et al.*, 2003). Likewise, overexpression of tobacco CDK inhibitor (KIS1) reverses the altered leaf phenotype of plants expressing *CYCD3* ectopically (Jasinski, *et al.*, 2002). This indicates that a proper balance of cell division activity and cell cycle arrest is required to develop a correct morphogenetic pattern. Interestingly, the coupling of KRP1/2 and CYCD3 functions seems reminiscent of the situation found for p27 and cycD1 in mice (Tong and Pollard, 2001).

Retinoblastoma-related (RBR) protein

The *in vivo* roles of RBR (reviewed in Gutierrez, *et al.*, 2002; Dewitte and Murray, 2003), one of the main targets of CDK/cyclin complexes (Nakagami, *et al.*, 1999; Boniotti and Gutierrez, 2001; Nakagami, *et al.*, 2002), have been elusive for the past years. Only recently, direct evidence of RBR as a negative regulator of cell proliferation has been obtained. Loss-of-function mutations in the *RBR* gene results in an impairment to restricts mitosis in the haploid nuclei of the female gametophyte and endosperm nuclei, leading to a lethal phenotype (Ebel, *et al.*, 2004). One of the functions of RBR is to contribute to repress the expression of genes regulated by the E2F/DP family of transcription factors. Initial studies, both in plants and animals, indicated that E2F/DP complexes regulated genes involved in cell cycle progression and DNA replication, e.g. *PCNA* (Egelkrout, *et al.*, 2002; Kosugi and Ohashi, 2002b), *MCM3* (Stevens, *et al.*, 2002), *CDC6* (Castellano, *et al.*, 2001), *CDT1* (Castellano, *et al.*, 2004). However, an *in silico* search revealed genes in *Arabidopsis* containing at least one E2F/DP binding site (TTTCCCGCC) in their promoters and belonging to a diverse collection of functional categories (Ramirez-Parra, *et al.*, 2003). Transcriptomic analysis has expanded the set of potential target genes that are up or down regulated in plants with altered E2F/DP activity (Vlieghe, *et al.*, 2003).

E2F/DP transcription factors

E2Fa, in cooperation with DPa, is a regulator of S-phase genes. When overexpressed ectopically, E2Fa/DPa induces cell division as well as endoreplication in organs such as leaves and hypocotyls (De Veylder, *et al.*, 2002). E2Fa/DPa-mediated hyperplasia is eliminated by co-expression of a dominant negative mutant of CDKB1 while the endoreplication phenotype is enhanced (Boudolf, *et al.*, 2004b).

E2Fc is a transcriptional repressor (del Pozo, *et al.*, 2002a; Kosugi and Ohashi, 2002c) that cooperates *in vivo* with DPb (del Pozo *et al.,* submitted) and is abundant in cell cycle arrested cells. Upon cell cycle stimulation, E2Fc (and possibly DPb) is phosphorylated by CDK/cyclin complexes and targeted for proteasome-mediated degradation by SCF^{SKP2} complexes (del Pozo, *et al.*, 2002a). Loss of E2Fc function produces organs with more but smaller cells, increases the expression of cell cycle genes and reduces the ploidy level strongly suggesting that E2Fc/DPb participates in the balance between cell proliferation and differentiation (del Pozo *et al.,* submitted).

As mentioned above, three E2F family members in *Arabidopsis* (E2Fd-e-f, also named DEL2-1-3, respectively) are atypical since they act in a DP-independent manner. *E2Fe* (*DEL1*), which is expressed in dividing cells, is an inhibitor of the endocycle program. Leaves of E2Fe (DEL1) overexpressors show slightly reduced ploidy levels (Vlieghe, *et al.*, 2005). Likewise, the reverse effect in the *del1-1* mutants was not very significant, reinforcing the idea that several genes regulate the balance between division and endoreplication. It is also interesting that E2Fe (DEL1) is able to reduce by half the endoreplication phenotype of E2Fa/DPa overexpressors, but not the hyperplastic phenotype (De Veylder, *et al.*, 2002; Vlieghe, *et al.*, 2005).

E2Ff has been shown to have an unanticipated role in regulating cell expansion once cells have abandoned the cell cycle (Ramirez-Parra, *et al.*, 2004). This occurs through down-regulating the expression of a set of genes, which are E2F targets, involved in cell wall biogenesis. Alterations in *E2Ff* levels produces changes in the size of organs where growth occurs essentially in one dimension, e.g. hypocotyls, roots, by changing cell size but not cell number, endoreplication level or the expression of cell cycle genes.

Therefore, it would be extremely informative to address the importance of the function of E2F complexes in different cell types for appropriate development and specific morphogenetic patterns in different organs.

DNA replication factors

Pre-replication complex (pre-RC) components are involved in initiation of DNA replication. A strict control on their availability restricts the triggering of more than one initiation event in each cell cycle, a process known as DNA replication licensing. Based on the information derived from studies with yeast and human cells, the pre-RC components are the origin recognition complex (ORC), a six-subunit complex, CDC6, CDT1, geminin and the minichromosome maintenance (MCM) complex, also a six-subunit complex (Bell and Dutta, 2002).

Ectopic expression of CDC6 (Castellano*, et al.*, 2001) or CDT1 (Castellano*, et al.*, 2004) is sufficient to induce extra endocycles or cell division in a cell type-specific manner. A subset of leaf epidermal cells (the subsidiary cells in stomatal complexes that can give raise to secondary meristemoids and new stomata) are stimulated to proliferate while, trichome initials, that undergo differentiation-associated endocycles, trigger more endocycles (Castellano*, et al.*, 2004). It is worth mentioning that when Cdt1 activity is increased in animals, similar consequences are obtained (Del Bene*, et al.*, 2004). Gametophytic development (McCormick, 2004; Yadegari and Drews, 2004), for detailed reviews) and the early embryonic stages seem to be particularly sensitive to alterations in pre-RC function. Thus, mutations in the *ORC2* gene leads to failure in nuclear division control (Collinge*, et al.*, 2004), in the *PROLIFERA (PRL)* gene, that encodes MCM7, produces abnormal patterns of division planes (Holding and Springer, 2002) and in the *CDC45* gene, which acts downstream pre-RC, to sterility (Stevens*, et al.*, 2004).

It is likely that the molecular interactions of pre-RC components have been basically conserved in plants. However, current evidence reveals that altering pre-RC function has consequences beyond the cellular level. This strongly suggests that pre-RC is an important coordinator for the balance between cell proliferation, cell differentiation and patterning in a developmental context.

Upon completion of DNA replication during S-phase, cells face the decision of continuing in the cell cycle or exiting it in two possible ways: arrest and differentiate or switching to the endocycle program. Although endoreplication occurs in all eukaryotes (Edgar and Orr-Weaver, 2001), in plants is a typical feature of a large proportion of cells in the plant body. In fact, entering specific differentiation programs frequently requires or is associated with the acquisition of a certain polyploidy level. Disappearance of CYCB1 seems to be a prerequisite (Cebolla*, et al.*, 1999). The switch to the endocycle program is regulated and/or affected by different gene products. CCS52, originally identified in alfalfa (Cebolla*, et al.*, 1999), is a Fizzy-related (Fzr) activator of the anaphase-promoting complex (APC; Capron*, et al.*, 2003b), most likely required for CYCB1 degradation. The relevance of CYCB1 in this switch derives from studies in *Arabidopsis* trichomes where ectopic expression of *CYCB1;2* (but not *CYCB1;1*) results in the appearance of multicellular structures, containing 2C nuclei, instead of the normal unicellular, polyploid branched trichomes (Schnittger, *et al.,* 2002). Defects in other APC components also lead to accumulation of CYCB1 and, consequently, impair cells to develop mitosis correctly (Blilou*, et al.*, 2002; Capron*, et al.*, 2003b; Kwee and Sundaresan, 2003).

Other genes that affect cell proliferation

Other genes which are not direct cell cycle regulators have, nevertheless, a clear impact on cell proliferation and, consequently, on organogenesis. The *root hairless2* (*rhl2*) and *hypcotyl6* (*hyp6*) mutants have a pleiotropic phenotype that include, among other features, dwarfism and a reduction in the ploidy level (Hartung*, et al.*, 2002; Sugimoto-Shirasu*, et al.*, 2002). These genes encode subunits of topoisomerase VI (TOPVI) and, surprisingly, other mutations in these genes have been identified in a screening for plants with altered sensitivity to brassinosteroids (Yin*, et al.*, 2002). This unforeseen connection points to a complex interplay of hormone action with cell cycle control and development (see above discussion). This is further illustrated by the altered growth properties observed in mutants in the *CONSTITUTIVE TRIPLE RESPONSE1 (CTR1)* gene that also have an altered pattern of ploidy level in many organs (Gendreau*, et al.*, 1999), although the mechanism is unknown. Overexpression of *STRUWWELPETER* (*SWP)* stimulates cell division in the leaf epidermis leading to altered organ structure (Autran*, et al.*, 2002). Likewise, silencing of *DEK* gene (a calpain homologue) expression in tobacco also produces extended cell division potential in the leaf epidermis (Ahn*, et al.*, 2004). These plants have an altered pattern of expression of several cell cycle genes, suggesting that their availability may depend on calpain activity. Recent evidence point to the RBR/E2F pathway as one major regulator of cell division and differentiation potential in leaves as deduced from studies where RBR function is inactivated (Desvoyes *et al.,* submitted). Several other genes (see the chapter on leaf morphogenesis) also impinge on the proliferative potential of cells although the molecular mechanisms behind are only beginning to be understood. For example, *ANGUSTIFOLIA* (*AN* ; Tsuge*, et al.*, 1996; Kim*, et al.*, 2002) and *ROTUNDIFOLIA* (*ROT3* and *ROT4* ; Kim*, et al.*, 1998; Narita*, et al.*, 2004) regulate cell division along the two leaf axes and *CINCINNATA* (*CIN*), an *Antirrhinum majus* TCP family member, is required for cell cycle arrest (Nath*, et al.*, 2003). A recent observation implicates the microRNA *JAW-D* as a direct regulator of *TCP* genes (Palatnik*, et al.*, 2003), which is a repressor of *CYCD3* (Gaudin*, et al.*, 2000). In other cases, circumstantial evidence implicates CYCD3 as a key regulatory component. Overexpression of *ARGOS* or *AINTEGUMENTA* (*ANT*; Mizukami and Fischer, 2000; Hu*, et al.*, 2003) increases organ size by stimulating cell division in all organs, an effect channeled, at least in part, by up regulation of *CYCD3* expression. Further studies are required to establish the connection of these genetic pathways and their implications in the control of cell proliferation and differentiation potential.

Developmentally regulated cell division potential

The post-embryonic nature of organogenesis in plants and its continuous occurrence throughout the life of the organism are features with an obvious impact on the control of cell proliferation. Cells that abandon the meristems, where active cell division occurs, exit the cell cycle or remain in an extended cell cycle arrest, poorly understood in molecular terms. Then, they can be recruited to form the primordia of different organs, a process that depends on developmental cues, hormonal signals and environmental challenges. Organogenesis requires both an increase in cell number and hence reactivation of cell proliferation in a highly controlled manner and cell patterning followed by progression through distinct differentiation programs. Some of these aspects are discussed in detail elsewhere in this volume.

The transition from embryonic to vegetative growth is another key step. However, a striking feature of plants is their ability to regenerate. This implies that some cells in certain organs can dedifferentiate, revert to a totipotent stem cell state and proliferate in a controlled manner to originate entire organs or even somatic embryos. Furthermore, these embryos are fully proficient to originate an adult plant. Obviously, these steps have a direct relevance for the topic discussed in this review. The molecular basis for certain cells to revert to a proliferative state is largely unknown.

However, indirect evidence suggests that resetting of their transcriptional program is likely a major event (Grafi and Avivi, 2004). *PICKLE* (*PKL*), a chromatin remodeling factor, is required to leave the embryonic fate through repression of *LEAFY COTYLEDON* (*LEC1* and *LEC2*) and *FUSCA3* (*FUS3*) that confer embryonic identity (Dean Rider, *et al.*, 2003). FUS3 is a regulator of ABA and GA biosynthesis (Gazzarrini and McCourt, 2003), stressing the key role of hormonal signaling in these early developmental steps. Conversely, ectopic expression of *LEC1* or *LEC2* induces embryo-like structures (Lotan, *et al.*, 1998; Stone, *et al.*, 2001). Furthermore, the chromatin assembly factor 1 (CAF-1) regulates the expression of *WUSCHEL* (*WUS*) and *SCARECROW* (*SCR*) in the root apical meristem (Kaya, *et al.*, 2001). Since MSI1, together with FASCIATA1 (FAS1) and FASCIATA2 (FAS2), constitutes CAF-1 and is a RBR-interacting protein (Ach, *et al.*, 1997), the possibility exists that the RBR/E2F pathway might have a role in the embryonic/vegetative transition and vice versa.

Development of lateral roots constitutes an example of *de novo* organogenesis. One of the main effects of auxin in plant development is the induction of lateral roots (LR) by initiating pericycle cell division. Nevertheless, the molecular events that take place to develop these organs are only beginning to be understood (Casimiro, *et al.*, 2003; Vanneste, *et al.*, 2005). Most pericycle cells, as they leave the meristem, contains high levels of *CDKA* and *KRP2* transcripts, but lack *CYCB1* (Himanen, *et al.*, 2002). However, it was known that ectopic expression of *CYCB1* is not sufficient to trigger LR formation (Doerner, *et al.*, 1996). Current data also argue against the idea that pericycle cells had left the cell cycle and reached a differentiated stage. An alternative is that they remain with an extended meristematic activity (Casimiro, *et al.*, 2003). Recently an inducible system has been designed in which the pericycle cells can be synchronized with the auxin transport inhibitor NPA and then these cells were able to re-enter into cell division upon auxin induction (Himanen, *et al.*, 2002; Himanen, *et al.*, 2004). Microarrays analysis has served to identify over 900 genes whose expression changes significantly upon LR induction (Himanen, *et al.*, 2004). Auxin addition triggers several cell cycle genes expression progressively. *CYCD3;1*, *E2Fa* and histone *H4* genes are quickly induced, *CDKB* was also induced early, although later that the S-phase genes. In addition, the expression of CDK inhibitors *KRP1* and *KRP2* was rapidly and strongly reduced (Himanen, *et al.*, 2002). Based solely on gene expression patterns LR development would consist of several stages: G1 block, auxin perception, transduction of auxin signal and progression through G1/S/G2 and eventually division.

A large number of mutants that show defects in LR formation have been identified (Casimiro, *et al.*, 2003), many of these are affected in auxin signal transduction and several are involved in proteasome-mediated protein degradation. This is the case of the *axr1* and *tir1-1* mutants. TIR1 is an F-box protein that targets proteins for degradation through the proteasome (Gray, *et al.*, 2001). The AUX/IAA17 protein, which is a transcriptional repressor of the auxin signal, is a well-characterized target of the SCF^{TIR1} complex. Several of the *aux*/*iaa* mutants also show severe growth defects, including those in LR formation (Dharmasiri and Estelle, 2002). Members of the NAC (NAM/ATAF/CUC2) family of transcription factors are involved in a variety of developmental processes (Olsen, *et al.*, 2005). One of its members, NAC1 acts downstream of TIR1 and is required to trigger LR formation (Xie, *et al.*, 2000). Transduction of auxin signal depends on SINAT5, a RING protein that negatively regulate NAC1 function by proteolysis (Xie, *et al.*, 2002). Identifying the molecular links between proliferation control and auxin signaling during LR formation is therefore of primary importance.

It is clear that regulated cell proliferation is a prerequisite for development. Conversely, transduction of developmental cues is necessary to initiate differentiation processes ultimately leading to differentiated cells and organogenesis. In the case of plants, the continuous organogenetic activity during the entire life, the biology of stem cells and their ability to regenerate are also processes intimately related to cell proliferation control. Therefore, the main conclusion that we can draw from the studies discussed in the previous paragraphs is that we need to increase our efforts to determine the role of cell cycle regulators in whole organisms and in the context of development. Learning about the cross talk between cell proliferation and development will be extremely valuable not only to understand specific processes but also to answer basic questions in developmental biology.

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