

First published on March 20, 2009: e0120. 10.1199/tab.0120

The Arabidopsis Cell Division Cycle

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Plant cells have evolved a complex circuitry to regulate cell division. In many aspects, the plant cell cycle follows a basic strategy similar to other eukaryotes. However, several key issues are unique to plant cells. In this chapter, both the conserved and unique cellular and molecular properties of the plant cell cycle are reviewed. In addition to division of individual cells, the specific characteristic of plant organogenesis and development make that cell proliferation control is of primary importance during development. Therefore, special attention should be given to consider plant cell division control in a developmental context. Proper organogenesis depends on the formation of different cell types. In plants, many of the processes leading to cell differentiation rely on the occurrence of a different cycle, termed the endoreplication cycle, whereby cells undergo repeated full genome duplication events in the absence of mitosis and increase their ploidy. Recent findings are focusing on the relevance of changes in chromatin organization for a correct cell cycle progression and, conversely, in the relevance of a correct functioning of chromatin remodelling complexes to prevent alterations in both the cell cycle and the endocycle.

BASIC STRATEGIES OF THE EUKARYOTIC CELL DIVISION CYCLE

The cell division cycle is a highly regulated process with the purpose of giving rise to two daughter cells. It encompasses events that take place from the birth of a cell until its next division. For this to occur, successful progression through the cell cycle requires, first, duplication of cellular components, including the genetic material, organelles and other macromolecular structures, and then, their delivery to the newly formed daughter cells. In the large majority of the cases, the two daughter cells are identical to their mother. This is mainly aimed at increasing the cell population. In some cases, however, active mechanisms lead to an asymmetrical division whereby two daughter cells with differences in size and/or composition of some key cellular components are produced. This kind of division has profound consequences on the physiology of the two daughter cells, e.g. stem cell division.

A good wealth of information has accumulated over the past years on different processes occurring during the cell cycle. Detailed biochemical, molecular, cellular, genetic, genomic and developmental approaches have been applied to the study of the cell division cycle. All of them have served to define three main defining features common to all eukaryotes: the occurrence of multiple cycles, their coordination and the unidirectional nature of cell cycle progression.

Multiple cycles

The idea that the cell division cycle is actually made up of at least two cycles, the growth and the division cycles, was put forward more than three decades ago (Mitchison, 1971; Mitchison et al., 1991). More recent studies have fully supported this concept.

Duplication of cellular components, other than the genetic material contained in the nucleus, is referred to as the "cell growth cycle". It basically consists of a rather continuous increase in cell mass from its birth to its physical separation during cytokinesis.

Once the cellular components have been duplicated they need to be delivered to the daughter cells. Thus, mitosis, i.e. a "chromosome segregation cycle", accounts for the separation of the duplicated genome, whereas the physical separation of the two daughter cells conforms the "cytokinesis cycle".

Duplication of the genetic material, that is the nuclear DNA and its associated proteins that together constitute the chromatin, occurs during a discrete period during the life of a proliferating cell, the S-phase or the "DNA synthesis cycle". This implies that in an asynchronous proliferating cell population only a certain proportion of them are actually progressing through the S-phase.

Several biochemical activities also show a cyclic behavior. One example is the "CDK cycle", defined by the high/low activity of cyclin-dependent kinases. In addition, two well defined increases in the expression of sets of genes just before the initiation of

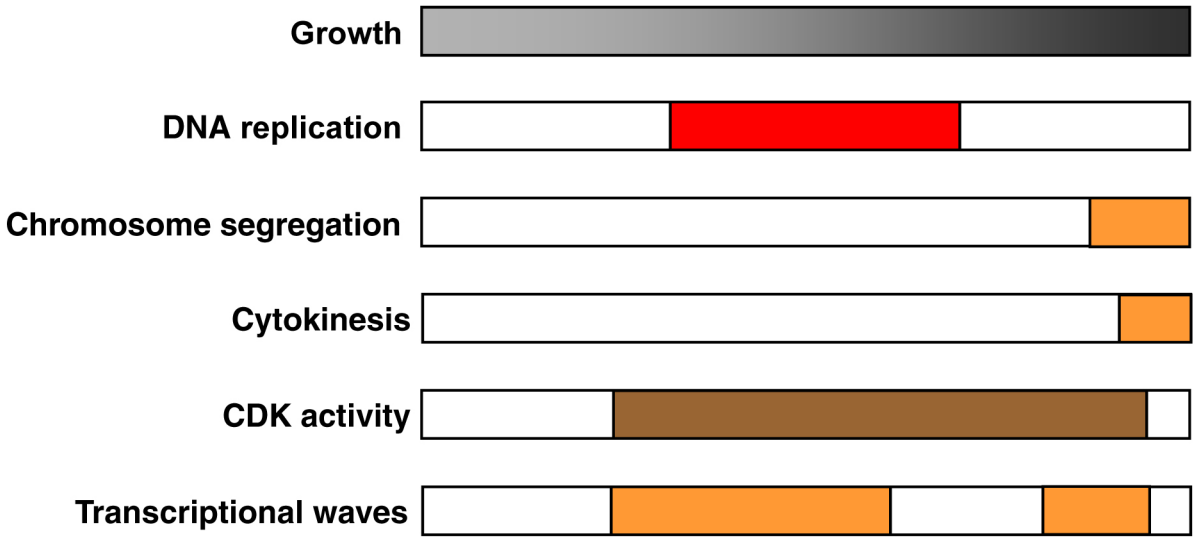

Figure 1. Multiple cycles.

Dividing cells are engaged in different processes, some which are depicted here and are relevant for cell division. They show a cyclic pattern and, frequently, they are functionally interconnected. The superimposition of these cycles gives rise to the functional stages that define the cell division cycle.

the S-phase ("the G1/S expression cycle") and before the entry in mitosis ("the G2/M expression cycle").

The superimposition of these, and other less well defined cycles in a given cell generates what we normally know as the cell division cycle with its typical succession of phases: G1 (or gap between mitosis and DNA replication), S-phase, G2 (or gap between DNA replication and mitosis) and mitosis, including cytoplasmic division or cytokinesis (Figure 1).

Coordinated cycles

The multiple cycles that constitute the cell division cycle do not progress independently of each other. Instead, a strict cross-talk between them contribute the their coordinated occurrence. For example, the increase in cell mass during the growth cycle determines the time of initiation of the S-phase. In this process, accumulation of G1 cyclins likely play a role as they stimulate CDK activity that inhibits the action of repressors of cell cycle progression leading to the up-regulation of the G1/S expression wave controlled by activator transcription factors. Likewise, a G2 checkpoint supervises the successful completion of the S-phase and allows the increase in cyclins and other components that triggers initiation of mitosis.

Unidirectional progression

The molecular mechanisms by which the series of events that occur during the cell division cycle are coordinated contribute to their unidirectionality. Thus, once a given transition has taken place there is no possible way of going back in the cell cycle. This unique property is at the basis of the molecular interactions that allow cell cycle progression. This is comparable to the blood flow through a vain system whose reversal in direction is impeded by the vein valves. Consequently, when animal cells encounter problems in progressing through a particular cell cycle stage, or receive appropriate signals, cells arrest either transiently or permanently, or die. The latter does not seem to be an outcome in plant cells. Only occasionally they may "choose" to exit the cell cycle and initiate either a cell differentiation program or entering an alternative cell cycle, the endocycle (see below).

The molecular basis for unidirectionality is that the activity of components that drive cell cycle transitions is modified in an irreversible manner. Different pathways account for regulating the availability of cell cycle components such as specific activation, or repression, of gene expression, changes in subcellular localization, posttranslational modifications and selective proteolysis through the proteasome.

UNIQUE FEATURES OF THE PLANT CELL CYCLE

The overall evolutionary conservation of the basic components of the cell cycle machinery is striking. However, the regulatory mechanisms evolved vary between plant and animal cells largely due to some unique features of the cell division cycle in plants.

- Some cell cycle genes are unique to plant cells, some of which can participate in plant specific processes (Vandepoele et al., 2002).
- Cytokinesis in plants is completely different from animal cytokinesis. Differences largely derive from the need to form a new cell wall between the two daughter cells (Jürgens, 2005).
- The haploid nuclei generated after meiosis undergo two or three divisions during male and female gametophyte de-

velopment (McCormick, 2004; Yadegari and Drews, 2004). This offers the possibility of studying the possible differences between the haploid and the diploid cell cycle within the same organism (Kim et al., 2008).

- Organogenesis is a post-embryonic process that occurs in a continuous manner throughout the entire lifespan. Thus, the continuous occurrence of cell divisions within meristems in an iterative manner produce the cells that eventually will differentiate into the cell types that form an organ, e.g. root and shoot meristems give rise to the root system and the entire aerial part of the plant (Gutierrez, 2005; Scheres, 2007).
- Many cells in the adult plant body retain a significant ability to dedifferentiate and acquire a pluripotent state, conferring an enormous plasticity to the plant. The process, which is very poorly understood at the molecular level, is aimed at the reentry of differentiated into the pool of proliferating cells (Grafi and Avivi, 2004).

THE ARABIDOPSIS CELL CYCLE MACHINERY

Our understanding of the mechanistic aspects of cell cycle progression has experimented an exponential growth over the past two decades. Shortly after the identification of the human homologue of the yeast cell cycle kinase (Lee and Nurse, 1987; Nurse, 1990), the plant homologues were also cloned (John et al., 1989; Ferreira et al., 1991). The remarkable conservation of cell cycle genes in eukaryotes has been confirmed with genome-wide studies in Arabidopsis (Vandepoele et al., 2002). Below I present a succinct description of the basic cell cycle machinery. The reader is directed to recent comprehensive reviews for details (Dewitte and Murray, 2003a; Gutierrez, 2005; Inzé and De Veylder, 2006; De Veylder et al., 2007). Table 1 contains a list of genes discussed in this chapter.

Arabidopsis contains a complex family of 12 CDKs classified into A through F groups, and a large group of CDK-like genes (Menges et al., 2005). For all members, except for the C and E, a direct participation in cell cycle activities has been found. CDKA, with its typical PSTAIRE amino acid motif, plays a pivotal role in driving cell cycle progression. Other CDKs are defined by related amino acid motifs (Vandepoele et al., 2002). The presence of a single CDK that regulates the G1/S and the G2/M transitions is a feature shared between plant and yeast cell cycle control. The rest of the cell cycle machinery has revealed a closer resemblance between plant and animals, although some components are plant-specific. Among these, CDKB members have the signature PP/STA/TLRE, their mRNA and protein levels peak at G2 and mitosis and their kinase activity is maximal in mitosis (Porceddu et al., 2001; Boudolf et al., 2004). In this way, CDKBs and CDKA cooperate to regulate the G2/M transition. CDKD and CDKF function as CDK-activating kinases (CAKs) as they phosphorylate CDKA at residue T161, a modification that produces a conformational change that allows substrate recognition. While CDKD is related to human CAK, CDKF is plant-specific. CDKC, which are linked with spliceosomal components (Kitsios et al., 2008), and CDKF have not been yet shown to have a role in cell cycle control.

Arabidopsis contains a large collection of cyclin genes (Wang et al., 2004), of which ~30 appear to have a putative cell cycle

Table 1. List of cell cycle genes mentioned in the text.

CDKA;1	AT3G48750	*KRP4*	AT2G32710
CDKB1;1	AT3G54180	*KRP5*	AT3G24810
CDKB1;2	AT2G38620	*KRP6*	AT3G19150
CDKB2;1	AT1G76540	*KRP7*	AT1G49620
CDKB2;2	AT1G20930	*SIM*	AT5G04470
CDKC;1	AT5G10270	*CKS1*	AT2G27960
CDKC;2	AT5G64960	*CKS2*	AT2G27970
CDKD;1	AT1G73690		
CDKD;2	AT1G66750	*RBR*	AT3G12280
CDKD;3	AT1G18040	*E2FA*	AT2G36010
CDKE;1	AT5G63610	*E2FB*	AT5G22220
CDKF;1	AT4G28980	*E2FC*	AT1G47870
		E2FD/DEL2	AT5G14960
CYCA1;1	AT1G44110	*E2FE/DEL1*	AT3G48160
CYCA1;2	AT1G77390	*E2FF/DEL3*	AT3G01330
CYCA2;1	AT5G25380	*DPA*	AT5G02470
CYCA2;2	AT5G11300	*DPB*	AT5G03415
CYCA2;3	AT1G15570		
CYCA2;4	AT1G80370	*ORC1A*	AT4G14700
CYCA3;1	AT5G43080	*ORC1B*	AT4G12620
CYCA3;2	AT1G47210	*ORC2*	AT2G37560
CYCA3;3	AT1G47220	*ORC3*	AT5G16690
CYCA3;4	AT1G47230	*ORC4*	AT2G01120
		ORC5	AT4G29910
CYCB1;1	AT4G37490	*ORC6*	AT1G26840
CYCB1;2	AT5G06150	*CDC6A*	AT2G29680
CYCB1;3	AT3G11520	*CDC6B*	AT1G07270
CYCB1;4	AT2G26760	*CDT1A*	AT2G31270
CYCB2;1	AT2G17620	*CDT1B*	AT3G54710
CYCB2;2	AT4G35620	*GEM*	AT2G22475
CYCB2;3	AT1G20610	*PCNA1*	AT1G07370
CYCB2;4	AT1G76310	*PCNA2*	AT2G29570
CYCB3;1	AT1G16330	*FAS1*	AT1G65470
		FAS2	AT5G64630
CYCD1;1	AT1G70210	*MSI1*	AT5G58230
CYCD2;1	AT2G22490		
CYCD3;1	AT4G34160	*WEE1*	AT1G02970
CYCD3;2	AT5G67260		
CYCD3;3	AT3G50070	*KNOLLE*	AT1G08560
CYCD4;1	AT5G65420	*HINKEL*	AT1G18370
CYCD4;2	AT5G10440		
CYCD5;1	AT4G37630	*CCS52A1*	AT4G22910
CYCD6;1	AT4G03270	*CCS52A2*	AT4G11920
CYCD7;1	AT5G02110	*CCS52B*	AT5G13840
CYCH;1	AT5G27620	*AUR1*	AT4G32830
		AUR2	AT2G25880
ICK1/KRP1	AT2G23430	*AUR3*	AT2G45490
ICK2/KRP2	AT3G50630	*TSL*	AT5G20930
KRP3	AT5G48820		

role (Vandepoele et al., 2002). These cyclins belong to the A- (10 cyclins), B- (11 cyclins), D- (10 cyclins) and H-types (1 cyclin). Generally speaking, they are involved in S-phase progression, mitosis and the G1/S transition, respectively (see details in (Inzé and De Veylder, 2006; De Veylder et al., 2007). Expression of D-type cyclins is subjected to transcriptional regulation by growth promoting-factors such as auxin, cytokinins, brassinosteroids and sucrose (see section on hormonal control). Plant cyclins are selectively degraded through the proteasome. Cyclins A and B contain a consensus D-box required for proteasome targeting (Renaudin et al., 1996; Genschik et al., 1998). Some cyclins B are degraded during mitosis by a specific ubiquitin E3 ligase known as anaphase promoting complex (APC) and its functional relevance was revealed by the retarded growth of cells expressing a non-degradable cyclin B (Weingartner et al., 2003). APC-mediated degradation of cyclin B is dependent on one (or more) of the CDH1-like subunits identified in the Arabidopsis APC (CCS52A1, AT4G22910; CCS52A2, AT4G11920; CCS52B, AT5G13840; (Tarayre et al., 2004; Fülöp et al., 2005). Cyclin CYCD3;1 (AT4G34160) and other D-type cyclins, contain a PEST amino acid motif that also mediates its degradation by the proteasome (Lechner et al., 2002; Planchais et al., 2004).

The activity of CDK/cyclin complexes is negatively regulated by CDK inhibitors. Two of them were identified in a yeast two-hybrid as interactors of Cdc2 kinase (ICK1/KRP1, AT2G23430; ICK2/KRP2, AT3G50630; (Wang et al., 1997; Lui et al., 2000; De Veylder et al., 2001; Jasinski et al., 2002; Zhou et al., 2003). These as well as the other five members of the family (De Veylder et al., 2001; Coelho et al., 2005) contain a box with high homology to the human CDK inhibitor $p27^{Kip}$ protein, and are known as KRP3-7. All of them interact with cyclins D both physically and functionally (Wang et al., 1998; Lui et al., 2000; De Veylder et al., 2001; Jasinski et al., 2002; Schnittger et al., 2003; Zhou et al., 2003). ICK2/KRP2 and perhaps other members are targeted for proteasome-mediated proteolysis (Verkest et al., 2005). A novel class of CDK inhibitors has been recently identified. The founder member is SIM (SIAMESE; AT5G04470), a nuclear localized 14 kDa protein that contains a cyclin-binding consensus sequence and the motif present in ICK/KRP (Churchman et al., 2006). Later, a family of SIM-related (SMR) proteins has been reported (Peres et al., 2007). A recent report has demonstrated the role of KRP in regulating cell cycle arrest in haploid cell cycles. Thus, KRP6/7 are specifically degraded by an ubiquitin E3 ligase known as SCF^{FBL17} (for Skp1/Cullin/F-Box FBL17; (Kim et al., 2008).

Initial studies led to the identification of the first plant cell cycle regulators, CDKA;1 (AT3G48750) and CYCB1;1(AT4G37490) highly related to the yeast proteins. However, in the mid 90's, two reports directly predicted the existence of a plant homologue of the human tumor suppressor retinoblastoma (RB) protein, which is not present in yeast. This strongly suggested that many aspects of plant cell cycle regulation might well be more related to those of other multicellular organisms. Thus, D-type cyclins were identified that contained a LxCxE amino acid motif (Dahl et al., 1995; Soni et al., 1995), also present in human cyclins D where it mediated interaction with human RB. Likewise, the early RepA protein of plant geminiviruses also contained the same LxCxE motif, which was required for efficient viral DNA replication in cultured cells (Xie et al., 1995). Subsequent studies have identified the RB-related (RBR) protein in several plant species (Grafi et al., 1996; Xie et al., 1996; Dewitte and Murray, 2003b; Shimizu-Sato et al., 2008).

Consistent with the presence of a plant RBR (Arabidopsis RBR, AT3G12280), members of the E2F family of transcription factors were also identified (Ramirez-Parra et al., 1999; Sekine et al., 1999; Magyar et al., 2000; Ramirez-Parra and Gutierrez, 2000). Arabidopsis contains six E2F (a to f) and 2 DP (DPa, AT5G02470 and DPb, AT5G03415). E2Fa (AT2G36010), E2Fb (AT5G22220) and E2Fc (AT1G47870) require heterodimerization with either DPa or DPb for function whereas E2Fd/DEL2 (AT5G14960), E2Fe/DEL1 (AT3G48160) and E2Ff/DEL3 (AT3G01330) can act independently of DP proteins (Ramirez-Parra et al., 2007). The structural basis for this difference resides in the fact that the E2F/DEL proteins contain two DNA binding domains, instead of only one present in the E2Fa-c proteins.

E2F/DP factors regulate the expression of a collection of genes required for cell cycle progression but also of genes belonging to other functional categories. In all cases, E2F-responsive promoters contain at least one consensus E2F-binding sequence (TTTSSCGS), which is identical to that of occurring in animal cells. Combination of bioinformatics and microarray experiments has yielded a collection of putative E2F responsive genes over the entire Arabidopsis genome (Ramirez-Parra et al., 2003; Vandepoele et al., 2005; Naouar et al., 2008). Some of these have been experimentally demonstrated to be actually E2F target genes (Ramirez-Parra et al., 2007). Among them, we find genes encoding proteins required for DNA replication, such as, subunits of the origin recognition complex (ORC; ORC1a, AT4G14700; ORC1b, AT4G12620; ORC2, AT2G37560; ORC3, AT5G16690; ORC4, AT2G01120; ORC6, AT1G26840; Diaz-Trivino et al., 2005), CDC6A (AT2G29680) and CDC6B (AT1G07270) (Castellano et al., 2001), CDT1A (AT2G31270) and CDT1B (AT3G54710); Castellano et al., 2004), PCNA (AT1G07370; AT2G29570) (Egelkrout et al., 2001), and ribonucleotide reductase subunits (Chabouté et al., 2000; Chabouté et al., 2002). Interestingly, some of these DNA replication factors also have a function in other linked processes. Thus, CDT1, in association with GEM (*GLABRA2* expression modulator, AT2G22475), controls cell division potential and the hair/non-hair cell fate decision in the root epidermis (Caro et al., 2007). ORC1 is also a transcriptional activator in Arabidopsis of certain genes, among them *CDT1a*, *ORC3* and *MCM3*; ORC1 binding to these promoters increases acetylation of histone H4 and trimethylation of H4K20 in association with transcriptional activation (Sanchez and Gutierrez, 2009). Factors involved in the DNA replication-associated chromatin assembly, such as the three subunits of chromatin assembly factor 1 (known as FASCIATA (FAS1; AT1G65470), FASCIATA2 (FAS2; AT5G64630) and MULTICOPY SUPPRESSOR OF IRA1 (MSI1; AT5G58230) in Arabidopsis) depend on E2F activity (Ramirez-Parra and Gutierrez, 2007b). Also genes required later in the cell cycle, e.g. in G2 such as *CDKB1;1* (AT3G54180; Boudolf et al., 2004) or for APC activity, such as *CCS52A2* (AT4G11920; Lammens et al., 2008), are also E2F targets.

Other transcription factors contribute to other cell cycle transitions. Thus, a role for some MYB factors has been shown at the end of the cell cycle to control the expression of proteins required late in G2 or during mitosis, e.g. KNOLLE (AT1G08560), among others, are targets of MYB3RA1, MYB3RA2 and MYB3R2 (Ito et al., 1998; Ito et al., 2001).

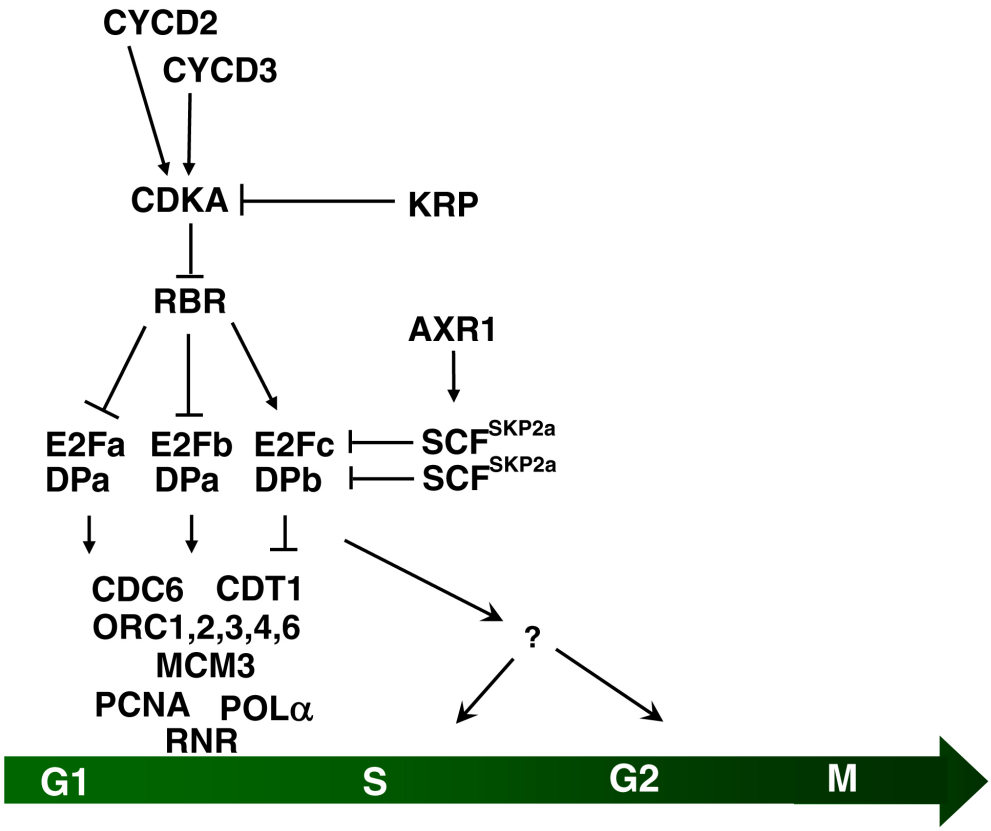

Figure 2. Basic pathway controlling the G1/S transition.

THE G1/S AND G2/M TRANSITIONS: CELLULAR AND DEVELOPMENTAL LEVELS

Various hormones (cytokinin, auxin, brassinosteroids) and growth factors (sucrose) are important regulators of G1 phase progression and G1/S transition because they positively regulate the expression and/or activity of CYCD and CDKA. CDKA is likely the only kinase required for the G1/S transition as it forms complexes with CYCD (Gutierrez, 2002; Inzé and De Veylder, 2006). A CAK-dependent step is also likely to activate CDKA/CYCD complexes. CDK activity is further subjected to negative regulation by KRPs, whose expression is positively regulated by abscisic acid (ABA).

The major target of CDKA/CYCD complexes in G1 is the RBR protein and a CDK-dependent phosphorylation of RBR has been shown in various systems (Figure 2) (Nakagami et al., 1999; Boniotti and Gutierrez, 2001; Nakagami et al., 2002). The ability of CDKA/CYCD complexes to act on RBR depends on the presence in CYCD of the LxCxE amino acid motif that mediates interaction with RBR (Ach et al., 1997). Phosphorylation of RBR leads to its dissociation of the RBR-bound E2F/DP transcription factors. E2Fa and E2Fb dimerize preferentially with DPa whereas E2Fc with DPb (Rossignol et al., 2002; del Pozo et al., 2006; Sozzani et al., 2006). E2Fa, b and c, but not other E2F factors, have been shown to interact with RBR. Another regulatory step is achieved by selective proteasome-mediated proteolysis, which has been demonstrated for both E2Fc and DPb through interaction with the F-box protein SKP2A (del Pozo et al., 2002a; del Pozo et al., 2006). Release of RBR from its complex at E2F target promoters likely allows E2F regulatory activity to be exerted. E2Fa and E2Fb are considered as activators whereas E2Fc play largely a repressive role during cell proliferation (Gutierrez, 2005; Inzé and De Veylder, 2006; De Veylder et al., 2007). However, it is not clear whether expression of E2F target genes depends on the competitive binding of various E2F. Alternatively, preferential binding of E2F to some target genes may also occur. This may be complicated by the presence of several E2F binding sites with different effects in transcription (Egelkrout et al., 2002; Stevens et al., 2002; Ramirez-Parra and Gutierrez, 2007b). As discussed above, release of E2F activity leads to transcription of target genes whose products are needed for S-phase progression. It is interesting to note that this mechanism of G1/S transitions is subverted by geminiviruses when they infect plant cells. Early geminivirus proteins typically bind and sequester RBR, releasing E2F activity without the need of CDK activity on RBR and stimulate S-phase progression needed for virus replication (Gutierrez, 2000; Desvoyes et al., 2006; Gutierrez, 2006; Ascencio-Ibanez et al., 2008).

E2F regulated pathways have a role in various aspects of plant development. In particular, the transition of proliferating cells to the endoreplication cycle as well as the recruitment towards different differentiation states is highly dependent on E2F activity (Gutierrez, 2005).

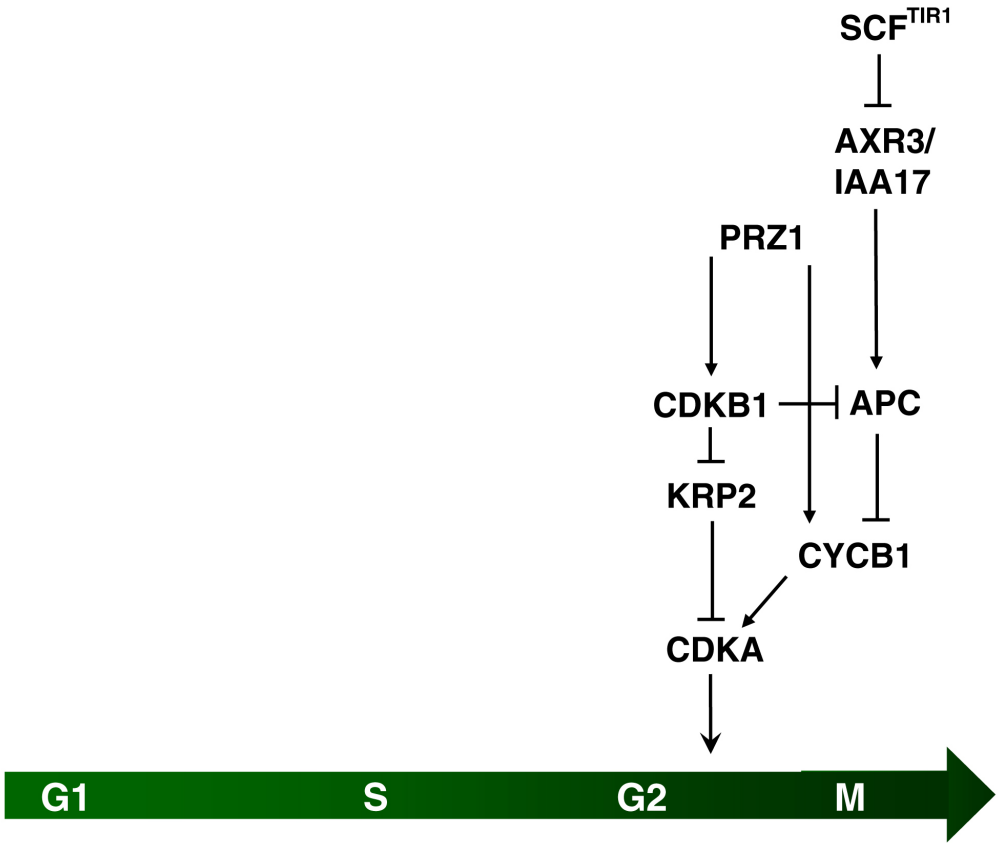

Figure 3. Basic events controlling the G2/M transition.

E2Fa, which associates preferentially with DPa (Kosugi and Ohashi, 2002; Mariconti et al., 2002), induces cell proliferation and increases ploidy level (De Veylder et al., 2002; Rossignol et al., 2002). The proliferation, but not the endoreplication effect, is eliminated by co-expression of a dominant-negative form of CDKB1;1, a typical G2 CDK (Boudolf et al., 2004). E2Fb, which also associated preferentially with DPa, regulates cell division during hormone signaling (Magyar et al., 2005; Sozzani et al., 2006). E2Fc associates preferentially with DPb and has a major repressor activity in arrested cells (del Pozo et al., 2002a; Kosugi and Ohashi, 2002). Upon stimulation of cell division, both E2Fc and DPb are targeted for degradation by the proteasome through the ubiquitin E3 ligase SCF^{SKP2} complex (del Pozo et al., 2002a; del Pozo et al., 2006). E2Fc is required for the efficient transition to the endoreplication program, as demonstrated in plants with reduced *E2Fc* mRNA levels (del Pozo et al., 2006). Interestingly, the SKP2 component of the SCF complex is also a proteasome target and is regulated in association with cell division and endoreplication potential in various organs (Jurado et al., 2008). Inactivation of RBR protein activity produces hyperplasia in young leaves and increases ploidy in older leaves (Desvoyes et al., 2006). In roots, RBR is necessary to restrict the amount of stem cells around the quiescent center, but it does not affect cell cycle duration (Wildwater et al., 2005). E2Fe/DEL1, which is expressed preferentially in proliferating cells, regulates the transition to the endocycle program during leaf development (Vlieghe et al., 2005). Interestingly, the endoreplication phenotype, but not the hyperplasia of the E2Fa-DPa overexpressing plants, is abrogated by co-expressing E2Fe/DEL1, indicating a crosstalk between different E2F family members (Vlieghe et al., 2005). The role of E2Ff/DEL3 during development was not anticipated, as it does not have a major role in cell division but, instead, it plays a role in cell elongation of differentiating cells (Ramirez-Parra et al., 2004).

A similar cascade of events occurs during the G2/M transition (Figure 3). Again CDKA is the major driver of this transition after its association with D-, A- and, particularly, B-type cyclins (Inzé and De Veylder, 2006). In addition to CDKA, the G2/M transition requires CDKB, the expression of which is dependent on E2F (Boudolf et al., 2004). Both CDKA and CDKB-cyclin complexes are activated by a CAK activity (likely CDKD and/or CDKF) before they can phosphorylate a variety of targets that contribute to enter mitosis. In case of replication stress or DNA damage, there is circumstantial evidence that CDKA is a WEE1 (AT1G02970) kinase target mediating G2 arrest (De Schutter et al., 2007). In a manner analogous to E2F in G1/S, the G2 CDKA/B-cyclin complexes phosphorylate several G2-specific transcription factors. In tobacco, these are MYB factors that have been identified to interact with MSA boxes present in the promoters of their target genes that are required for M-phase progression, e.g. KNOLLE, among others (Ito et al., 1998; Ito et al., 2001; Araki et al., 2004).

The TOR (Target of rapamycin, AT1G50030)/RAPTOR (Regulatory, associated protein of TOR; AT3G08850; AT5G01770) pathway is a key regulator of cell growth in yeast and animal cells in response to nutrient availability (Ingram and Waites, 2006). Likewise, Arabidopsis TOR and RAPTOR have a role in cell growth. Mutations in TOR have no effect when cell division is uncoupled from cell growth, e.g. during embryogenesis, but plant development arrests at later stages (Menand et al., 2002; Anderson et al., 2005; Deprost et al., 2005).

CYTOKINESIS

Plant cytokinesis is probably one of the most different aspects of the cell division cycle compared to cells from other kingdoms. Non-plant cytokinesis initiates at the outermost part of the division plane in a process whereby the plasma membrane moves towards the center of the cell by a contractile ring of actomyosin filaments. In most plant cells cytokinesis starts at the center of the division plane, a process that is helped by the phragmoplast, a cytoskeletal array that delivers and concentrates vesicles. Vesicle fusion at the center of the cell originates the cell plate, which then grows towards the periphery of the dividing cell until it finally fuses with the preexisting cell wall to separate the two daughter cells.

Membrane and vesicle fusion events are finely coordinated with two highly dynamic cytoskeletal arrays, which consist of both microtubules and actin microfilaments. One is the pre-prophase band, which appears transiently from late G2 to prometaphase and marks the position of the division plane. Another is the phragmoplast that help in the trafficking and targeted delivery of vesicles to the growing cell plate. Both, microtubules and actin filaments participate in guiding the cell plate expansion towards the periphery (Hepler et al., 2002). Cytokinesis progression, in particular the transition of microtubular arrays from anaphase to the phragmoplast is a coordination point with other aspects of the cell cycle such as cyclin B1 degradation at the metaphase to anaphase transition by the anaphase promoting complex/cyclosome (APC/C) (Weingartner et al., 2004). Microtubule dynamics at the phragmoplast require the function of kinesin-related proteins such as HINKEL (also known as NACK1 in BY-2 tobacco cells) and its target, NPK1, a MAPKKK (Nishihama et al., 2002; Strompen et al., 2002). Cytokinesis has some specific features depending on whether it occurs during meristematic cell division, endosperm cellularization or meiosis. The reader is referred to recent reviews for details on plant cytokinesis (Nacry et al., 2000; Verma, 2001; Bednarek and Falbel, 2002; Criqui and Genschik, 2002; Jürgens, 2005).

Plant cytokinesis depends on a highly coordinated dynamics of both vesicles and cytoskeletal components. The first indication that cytokinesis initiates occurs by the appearance and later accumulation of vesicles at the center of the dividing cell during telophase. These vesicles, together with microtubuli and actin filaments constitute the phragmoplast, an organelle that continues to serve as a delivery organelle for more Golgi vesicles. It is assumed that the components necessary for vesicle delivery to the cell plate are an ADP-ribosylation factor (ARF)-type small GTPase, an ARF-guanine nucleotide exchange factor (GEF), an ARF-GTPase activating protein (GAP), adaptor proteins and a dynamic GTPase. The participation of these components is supported by the sensitivity of cytokinesis to brefeldin A, an inhibitor of ARF-GEF activity (Kirchhausen, 2000; Jürgens and Geldner, 2002).

The accumulated vesicles ultimately fuse. This process requires the presence of SNARE (soluble N-ethylmaleimide-sensitive factor adaptor protein receptor) complexes, which are of two types: the v-SNARE and the t-SNARE, complexes anchored to the vesicle and target membrane, respectively. KNOLLE is a syntaxin of the SNARE complexes originally identified in a screen for cytokinesis mutants (Lukowitz et al., 1996; Lauber et al., 1997). *KNOLLE* has a characteristic and sharp peak of expression in mitosis and localizes first to the Golgi stacks and later to the cell plate. SNARE-interacting proteins have been also identified and their role in vesicle trafficking defined. Some of these interact with KNOLLE, such as SNAP25, whereas others do not, such as SYP31 (see (Jürgens, 2005) for details). SNARE function is highly specific and factors that confer such specificity, such as KEULE, have been identified (Assaad et al., 1996; Waizenegger et al., 2000; Jahn et al., 2003). Vesicle fusion contributes to form the initial cell plate that contains materials carried out by the vesicles. Continued fusion events expand symmetrically the cell plate towards the cellular periphery where eventually it will fuse with the plasma membrane.

SWITCHING TO THE ENDOREPLICATION CYCLE

In response to a variety of physiological signals or developmental cues proliferating cells can inhibit their transition to mitosis once they have completed chromosome replication. This is a requirement for the switch from the cell cycle to an alternative cycle, the endoreplication cycle, whereby successive rounds of full genome replication occur in the absence of an intervening mitosis (Figure 4). Thus, the skipping of nuclear division leads to an exponential increase in genome ploidy level (from 2C to 4C, 8C, 16C, and so forth; Figure 5). The ability to initiate endoreplication has been described for all eukaryotes (Edgar and Orr-Weaver, 2001) but it is particularly relevant during development of many plants (Kondorosi et al., 2000; Larkins et al., 2001; Inzé and De Veylder, 2006; Caro et al., 2008). The endoreplication cycle consists of two major stages, the exit from the cell division cycle and the maintenance of repeated endoreplication rounds.

While the role of endoreplication is not well understood yet, there are a number of hypothesis that explain its relevance. Endoreplication is a prerequisite to initiate certain developmental pathways, as it has been demonstrated in Arabidopsis hypocotyl cells or trichomes (Figure 6) (Hülskamp et al., 1999; Larkins et al., 2001; Boudolf et al., 2004; Castellano et al., 2004). Endoreplication also frequently correlates with increase in cell size (Melaragno et al., 1993; Traas et al., 1998). However, this is not a general situation (Beemster et al., 2002), and it has been questioned (Kondorosi et al., 2000; Sugimoto-Shirasu and Roberts, 2003). Endoreplication could be also beneficial to increase the metabolic activity of certain cells, as exemplified during maize endosperm development (Traas et al., 1998; Joubes and Chevalier, 2000; Kondorosi et al., 2000). However, this has been also somehow questioned (Leiva-Neto et al., 2004). An increased ploidy may confer a higher capacity of the plant to respond to the accumulation of mutations, to alterations in its DNA repair potential or on its response to DNA damage (Ramirez-Parra and Gutierrez, 2007a).

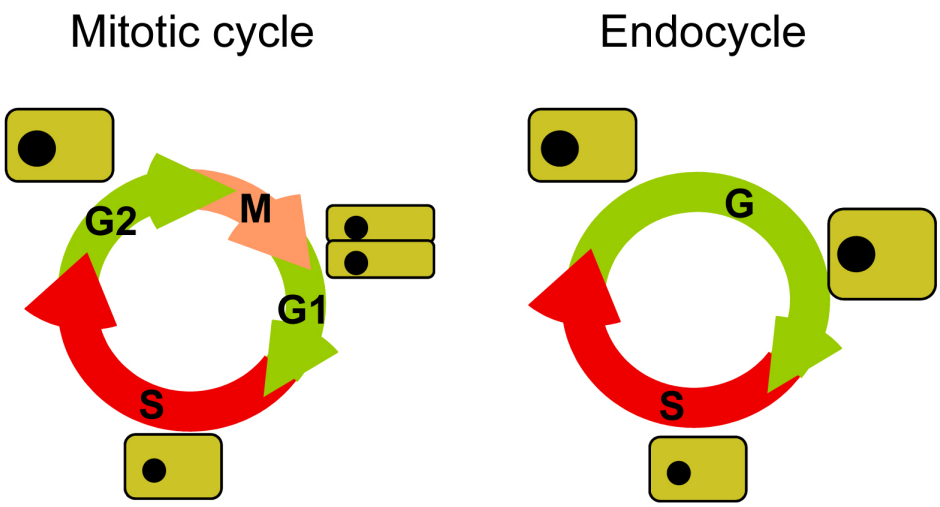

Figure 4. The mitotic cycle and the endocycle.

Schematic representation of the two basic cell cycles. In the mitotic cycle, newborn cells pass through G1, S and G2 before dividing and producing two daughter cells. In the endocycle, the M phase does not occur and cells undergo a doubling of its nuclear DNA content in each endocycle. This is frequently associated with an increase in cell mass. See text for details.

In addition to their role in the cell cycle, some regulators of cell cycle progression also play crucial roles in regulating endoreplication (de Jager et al., 2005; Gutierrez, 2005; Caro et al., 2008). This is a process that entails the switch from the cell cycle to the endoreplication cycle, the maintenance of repeated endoreplication rounds and the control of the number of rounds to be developed. Examples of cell cycle regulators with a role in endoreplication are the CDKA;1 (Hemerly et al., 1995; Leiva-Neto et al., 2004), RBR (Park et al., 2005; Desvoyes et al., 2006), some E2F/DP transcription factors (De Veylder et al., 2002; del Pozo et al., 2002a; del Pozo et al., 2006), CDC6 (Castellano et al., 2001), or CDT1 (Castellano et al., 2004).

The switch to the endoreplication cycle requires that, at least, *CYCD3;1* expression is turned off (Dewitte et al., 2003). Likewise, expression of some S-phase cyclins, such as *CYCA3;2* (AT1G47210) and *CYCA2;3* (AT1G15570), also repress endoreplication as revealed by studies of plants carrying loss of function mutations and overexpressing these cyclins (Yu et al., 2003; Imai et al., 2006). The CDK inhibitors ICK1/KRP1 and ICK2/KRP2 are preferentially expressed in endoreplicating cells. Consistent with this pattern, overexpression of *ICK2/KRP2* reduces cell division (Wang et al., 2000; De Veylder et al., 2001) and affects the switch to the endoreplication cycle (Verkest et al., 2005). KRP homologs in other plant species seem to play similar roles, e.g. in maize endosperm (Coelho et al., 2005) or tomato fruit (Bisbis et al., 2006). Together, these data point to CDK activity as a major regulator of endoreplication (Gutierrez, 2005; De Veylder et al., 2007).

The activity of various CDKA-cyclin complexes on the endocycle may be mediated, at least in part, through the phosphorylation of RBR. Virus-induced gene silencing of the tobacco *RBR* gene increases ploidy in leaves (Park et al., 2005), whereas functional inactivation of RBR in Arabidopsis leads to extra endoreplication rounds in older leaves and to hyperplasia in younger leaves (Desvoyes et al., 2006). As discussed above, E2Fa, E2Fb and E2Fc, which can interact with RBR (Ramirez-Parra et al., 2007), also play roles in the balance between cell division and endoreplication.

During the S-phase, the DNA replication machinery recruits the chromatin assembly factor (CAF-1), a complex required to facilitate the incorporation of acetylated H3-H4 dimers onto the newly synthesized DNA. CAF-1 is a heterotrimeric complex whose subunits have been conserved throughout eukaryotic evolution (Polo and Almouzni, 2006). The three Arabidopsis CAF-1 subunits (Leyser and Furner, 1992; Kaya et al., 2001; Hennig et al., 2003), FAS1, FAS2 and MSI1, are encoded by E2F target genes (Ramirez-Parra and Gutierrez, 2007a). Mutants in *FAS1* show a systemic increase in the ploidy level and an acceleration of the transition to the endoreplication cycle early after germination (Ramirez-Parra and Gutierrez, 2007b), possibly as a consequence of altered gene expression of G2-specific genes (see below).

The occurrence of endoreplication is strictly linked to organogenesis and development. The role of endoreplication during endosperm development has been demonstrated in a variety of species (Larkins et al., 2001). It correlates nicely with the accumulation of starch and storage proteins (Lemontey et al., 2000). Consequently, in species such as Arabidopsis, with a very limited or absent accumulation of storage proteins the number of endoreplication rounds is also highly reduced and they occur in only a subset of nuclei (Matzk et al., 2000). In Arabidopsis, the micropilar and peripheral endosperm contains high levels of the mitotic CYCB1;1 cyclin whereas the chalazal endosperm lacks this cyclin and contains large nuclei which have undergone several endoreplication rounds and reaching, in some cases, up to

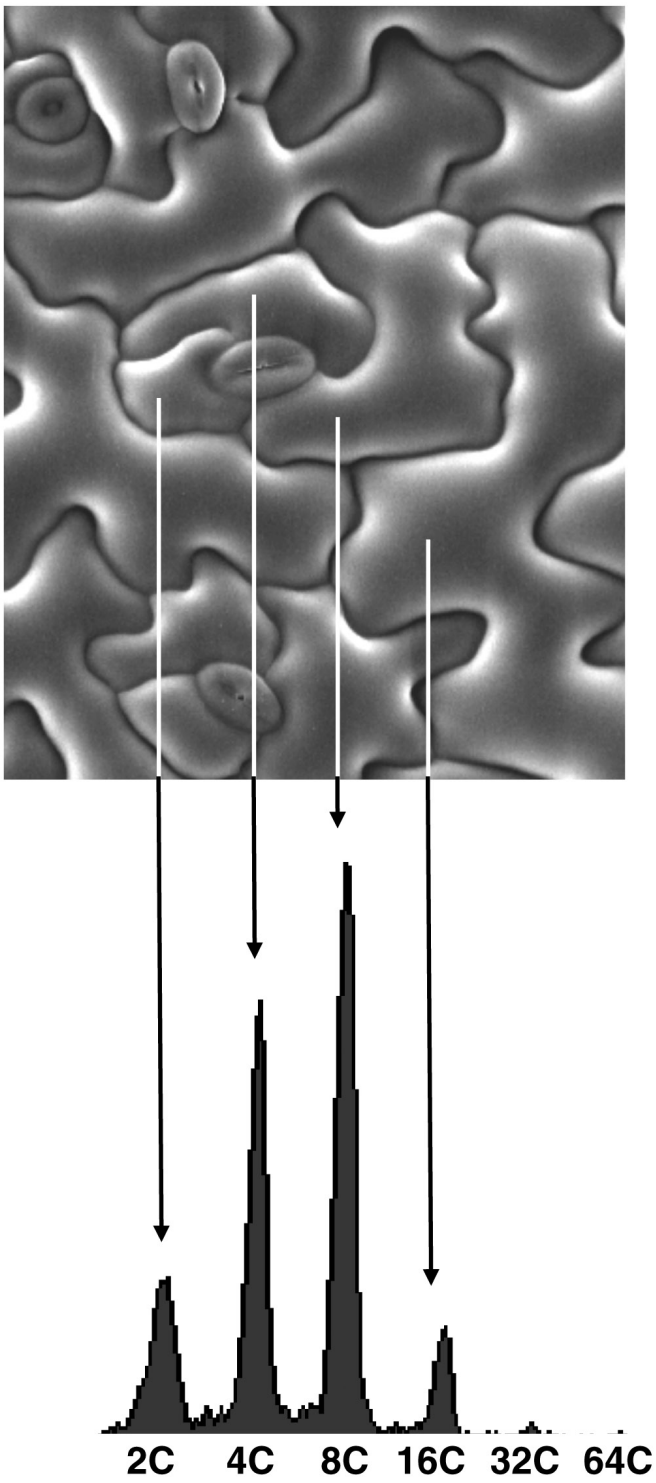

Figure 5. Nuclear ploidy pattern in the leaf.

A detail of the adaxial surface of a leaf observed with scanning electron microscopy (upper panel). Note the stomata with two guard cells and the puzzle-shaped of the epidermal pavement. In this case, increased number of endocycle, which lead to increased ploidy level, is accompanied by an increase in cell size. This is indicated in the lower panel where a ploidy pattern obtained by flow cytometry measurements is shown. Image courtesy of Bénédicte Desvoyes.

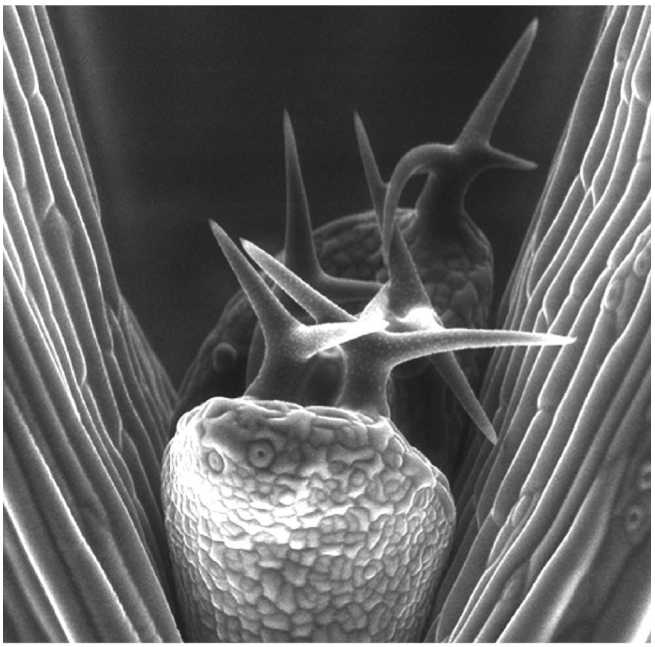

Figure 6. Trichomes.

Young trichomes emerging from the surface of the first pair of leaf primordia. Note that even at this early developmental stage, trichomes already contain a branched appearance. Part of the cotyledons appears at both sides of the leaf primordia. Image courtesy of Elena Ramirez-Parra.

24C (Boisnard-Lorig et al., 2001; Baroux et al., 2004). During maize endosperm development nuclei undergo ~5 endoreplication rounds after the exit from the mitotic cycle which takes places 8-14 days after pollination (Kowles et al., 1992; Grafi and Larkins, 1995). Initiation of endoreplication in this system is associated with a reduction in CDK activity, achieved by down regulation of *CYCB1;1* and inhibition by WEE1 and KRP, induction of a specific S-phase CDK and phosphorylation of RBR (Grafi et al., 1996; Coelho et al., 2005). Early stages of germination involve the resumption of metabolic activity from the dry seed, including cell cycle and endoreplication-associated activities, a process that depends on the regulated expression of several cyclin genes, among others (Masubelele et al., 2005).

During post-embryonic growth the hypocotyl can develop a photomorphogenic or a skotomorphogenic development depending on the presence or absence of light, respectively (Cosgrove and Durachko, 1994; Quail et al., 1995). Light-grown hypocotyls cells contain 2C, 4C and 8C nuclei whereas in etiolated hypocotyls, a third endoreplication round occurs leading to the appearance of a detectable 16C DNA peak. The choice from skoto- to morphogenesis depends on the *COP/DET/FUS* genes and *PHYA*, *PHYB* and *CRY* photoreceptors that, ultimately, control the occurrence of the third endoreplication round in dark-grown hypocotyl cells. This is suppressed by far-red light (PHYA-dependent), by red light (PHYB-dependent) and in *cop1* mutants, whereas *cry* mutants do not show ploidy changes (McNellis et al., 1994; Mayer et al., 1996; Gendreau et al., 1998).

Some plant hormones also affect hypocotyl expansion and occurrence of endoreplication rounds. Thus, mutants affected in gibberellin (GA) and ethylene (ET) synthesis or signaling show altered ploidy profiles indicative of changes in the number of endoreplication rounds underwent during hypocotyl development. Mutant *ga1* plants with reduced levels of GA have shorter hypocotyls with an altered ploidy pattern whereas other GA mutants with normal GA levels, e.g. *gai1*, do not have changes in ploidy levels (Sun et al., 1992; Dubreucq et al., 1996). ET treatment induces one extra endoreplication round in the hypocotyl cells of both light- and dark-grown seedlings (Gendreau et al., 1999). It has been suggested that the effect of ET on the endocycle can be the consequence of convergent pathways rather than a direct action of the hormone. Other mutants have been described that do not show any alteration in hormonal response but have altered ploidy pattern in the hypocotyl cells. The *root hairless2* (*rhl2*) and *hypocotyl6* (*hyp6*) mutants have defects in the occurrence of the third endoreplication round in hypocotyl cells. These genes encode the A and B subunits of topoisomerase VI that participates in decatenation of duplicated chromosomes (Hartung et al., 2002; Sugimoto-Shirasu et al., 2002). However, they show normal ploidy patterns up to the 8C DNA content. A similar phenotype has been described for the *hypocotyl7*/*root hairless1* (*hyp7*/*rhl1*) mutant (Sugimoto-Shirasu et al., 2005), which lacks topoisomerase II. These data reveal that once endoreplication is triggered, the occurrence of repeated rounds requires the participation of DNA decatenating enzymes.

Development of leaves constitutes another example where the balance between cell division and endoreplication is crucial. After recruitment of founder cells into the leaf primordia at the edges of the shoot apical meristem, cells engage in an active proliferation stage. After a few days, i.e. ~12-13 day-old for the first pair of true leaves in Arabidopsis, most cells abandon the cell cycle and switch to the endoreplication cycle, in this case associated with cell expansion (Beemster et al., 2005). It must be kept in mind that both cell proliferation and differentiation do not occur homogeneously along the leaf but show a basipetal polarity (Donnelly et al., 1999). These stages are the result of a profound change in the gene expression pattern as determined by microarray experiments (Beemster et al., 2006): CDKA and genes required for DNA replication are expressed constitutively whereas several cyclins of the A-, B- and D-types are preferentially expressed during the proliferation stage and down-regulated at later stages. At the mature stage, CDKA activity disappears most likely due to inhibition by CDK inhibitors. Consistent with this, overexpression of DNA replication initiator proteins, e.g. CDC6 or CDT1, leads to stimulation of endoreplication during leaf development (Castellano et al., 2001; Castellano et al., 2004). Other genes with a less-well defined molecular function also affect the endocycle during leaf development. These are, for example, STRUWWELPETER (SWP, AT3G04740), a factor required for RNA polymerase II recruitment, and TORNADO1 (TRN1; AT5G55540) (Autran et al., 2002; Cnops et al., 2006).

Trichomes are specialized cells present in the surface of nearly all land plants, although their morphology and distribution vary considerably depending on the species. Trichome development involves the action of several genes that determine their position, spacing and morphology (Hülskamp et al., 1999). In Arabidopsis, trichomes originate from protodermal cells of most aerial locations, e.g. in leaves they are stellate and separated by three-four pavement cells. Trichome initials exit the cell cycle early during leaf development and switch to the endoreplication program reaching a 32C DNA content (Hulskamp et al., 1994). The 2nd and 3rd endoreplication rounds occur in association with the 1st and 2nd branching events. Genetic analysis reveals that ploidy level is controlled in trichomes by several independent pathways, one of which depends on the activity of cell cycle regulatory proteins. Mutations in the *CYCA2;3* gene leads to increased ploidy level and branch index (Imai et al., 2006). Overexpression of *CYCB1;2* (AT5G06150; Schnittger et al., 2002a) or *CYCD3;1* (Schnittger et al., 2002b) leads to the formation of multicellular trichomes. Likewise, mutations in the *SIAMESE* (*SIM*) gene also produce multicellular trichomes (Walker et al., 2000). Overexpression of the ICK1/KRP1 inhibitor of CDKs leads to a reduction in the ploidy level of trichome nuclei (Schnittger et al., 2003). Therefore, it is clear that CDK activity is crucial for triggering endoreplication associated with trichome development. RBR, a target of CDK/cyclin complexes, also plays a role in this pathway. Likewise, overexpression of the heterodimeric partners E2Fa and DPa leads to trichomes with very large nuclei, suggestive of a high DNA content. Overexpression of *CDC6* or *CDT1*, E2F targets encoding subunits of the pre-replication complex are sufficient to increase ploidy level in trichomes (Castellano et al., 2001; Castellano et al., 2004), revealing a direct action of these, and possibly other, DNA replication components in regulating the transition from the cell cycle to the endoreplication cycle.

HORMONAL CONTROL OF THE CELL CYCLE

The post-embryonic development of plants requires a continuous supply of cells and consequently a very strict balance between cell proliferation and differentiation. Maintenance of cell division potential and recruitment of cells into the cell division pool is influenced by phytohormones. One characteristic of plant hormone action on cell division is that in many cases hormones directly regulate the expression of key cell cycle target genes and/or the activity of their products. Therefore, hormones play a rather direct role in controlling cell division activity (Figure 7).

Auxin

Auxin (indol acetic acid) plays key roles in a large variety of aspects of plant growth (Leyser, 2002; Friml, 2003), including cell division at both the embryonic and the vegetative stages. This has been known for decades (Hobbie and Estelle, 1994; Gray and Estelle, 2000) but the mechanistic basis for auxin activity is just starting to be delineated. The study of several mutants with an altered auxin signaling have demonstrated that auxin action on cell division and the specific degradation of proteins through the ubiquitin (Ub) pathway are intimately coupled (Dharmasiri and Estelle, 2002). The activity of auxin in many aspects of plant physiology is underscored by genome-wide studies that show that ~5% of the total Arabidopsis proteome is related to the Ub-proteasome pathway (Bachmair et al., 2001). After activation of the small peptide Ub by the E1 activating enzymes, the Ub moiety

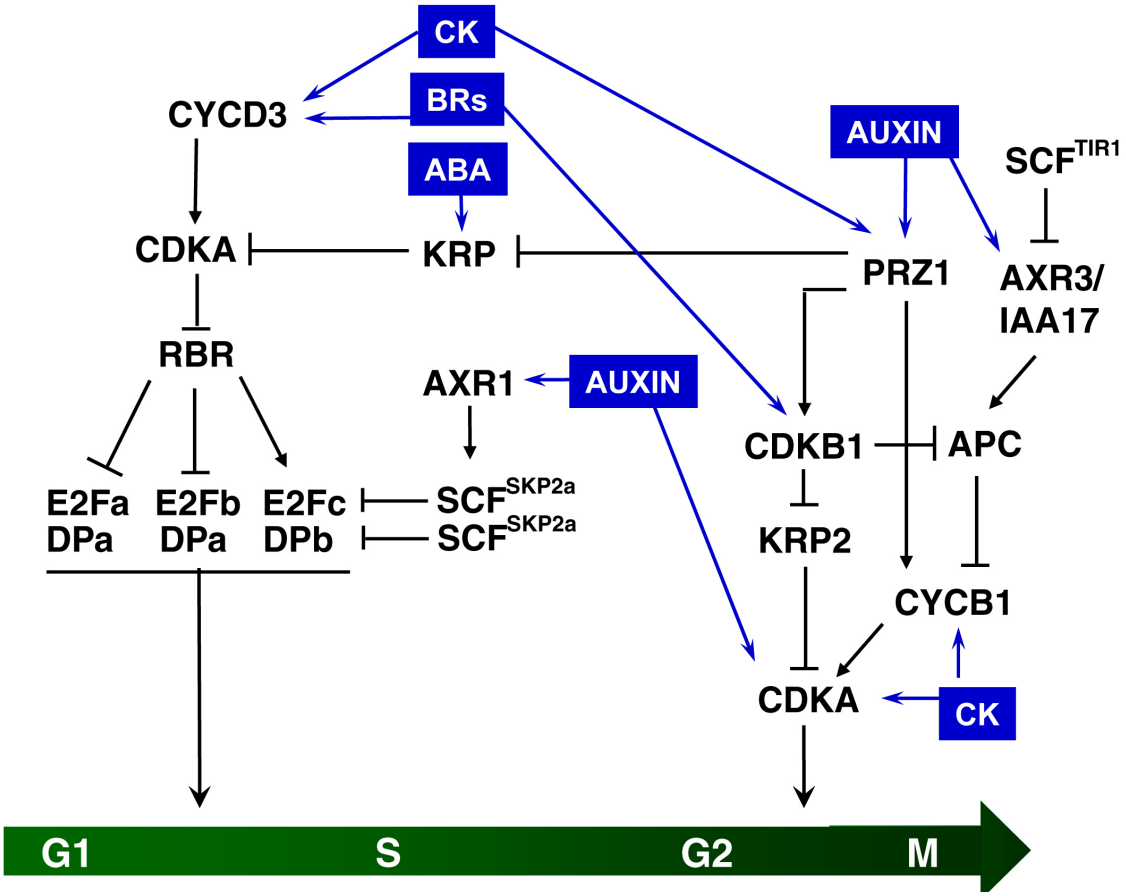

Figure 7. Hormonal control of cell cycle regulators.

The indicated phytohormones control various cell cycle regulatory components at different levels.

is transferred to an E2 conjugating enzyme and finally transferred to the target protein by the E3 ligase activity. Once the target protein is polyubiquitinated it is degraded by the 26S proteasome (Hershko and Ciechanover, 1998).

Mutations in the *AXR1* gene impair auxin response and reduce the levels of RUB1-modified CUL1, a component of active SCF complexes (del Pozo et al., 2002b). The reduced SCF activity against a variety of targets is responsible for the *axr1* pleiotropic phenotype. In the case of cell division, SCF^{SKP2} complexes degrade the E2Fc transcription factor, a potent repressor of cell division that accumulates in *axr1-12* mutants (del Pozo et al., 2002a). The transition from the skotomorphogenetic program, where proliferation is arrested, to the photomorphogenetic stage with active cell proliferation requires degradation of E2Fc. Furthermore, recent studies have shown that DPb, the heterodimeric partner of E2Fc, is also targeted for degradation by the SCF^{SKP2} complex (del Pozo et al., 2006). Mutations in *RPN10*, a regulatory subunit of the proteasome, reduce cell division and produce growth effects making plants less sensitive to auxin (as well as to cytokinins) but hypersensitive to ABA (Smalle et al., 2003). The effect on cell division is exerted through a decrease in *CDKA;1* transcription.

To identify novel cell cycle control genes a screening of a T-DNA population was carried out looking for plants with cell proliferation defects when grown in auxin- and cytokinin-containing medium (Sieberer et al., 2003). This study led to the identification of *proporz1 (prz1)*, a mutation that confers a tendency to form calli only in the presence of either auxin or cytokinin. *PRZ1* (AT4G16420) encodes a transcriptional adaptor protein that likely regulates the expression of cell division genes. Thus, in hormone-containing medium the expression of *KRP* genes is down regulated whereas that of *E2Fc* and *CDKB1;1* is upregulated. How the activity of these genes, whose expression is altered in *prz1* plants, is coordinated to produce the mutant phenotype is not known.

Lateral roots derived from pericycle founder cells, which are arrested in G1 and can respond to a local increase in auxin by re-entering the cell cycle (Beeckman et al., 2001; Casimiro et al., 2003). In fact, a local increase in auxin is necessary and sufficient to specify peicycle cells into lateral root founder cells (Dubrovsky et al., 2008). The use of an inducible system to synchronize the entire pericycle has allowed the identification of a sequential activation of cell cycle gene expression, including *CYCD3;1*, *E2Fa* and histone *H4*, then S-phase genes and later *CDKB1* (Himanen et al., 2002). Concomitantly a reduction in *KRP1* and *KRP2* gene expression occurs.

Cytokinin (CK)

Cytokinins, N6-substituted adenine derivatives, have been known for a long time to induce cell division and shoot formation (Miller et al., 1955; Skoog and Miller, 1957; Mok, 1994). CKs increase the expression of *CYCD3;1* (Soni et al., 1995) and constitutive expression of this cyclin leads to CK-independent growth of calli (Riou-Khamlichi et al., 1999).

Protein degradation is also important for CK activity during the cell cycle as revealed by the *rpn12a-1* mutants, lacking the RPN12 subunit of the 26S proteasome, which are less responsive to CKs and show increased levels of CK-induced genes (Smalle et al., 2003).

Results in other plant species have also provided relevant information on CK action on cell division. Zeatin-type CK concentrations peak at S and M phase in the tobacco cultured BY2 cell line (Redig et al., 1996). Adding lovastatin, an inhibitor of CK biosynthesis, to a BY2 culture leads to mitotic arrest, which is relieved after addition of zeatin (Laureys et al., 1998). A requirement for CK in late G2 is also revealed in other Nicotiana cultured cells that arrest in G2 in the absence of kinetin due to a reduction in CDKA activity (Zhang et al., 1996).

Abscisic acid (ABA)

A long time ago, ABA was shown to inhibit DNA synthesis in root tips and embryos (Van Overbeek et al., 1967) and cell division (Steward and Smith, 1972; Newton, 1977). Early observations of ABA on Arabidopsis cell division come from BrdU incorporation analysis (Robertson et al., 1990; Leung et al., 1994). ABA appears to have a direct role in repressing the expression of some cell cycle genes, such as *CDKA* (formerly cdc2a; Hemerly et al., 1993) or DNA replication genes, such as the DNA replication initiation *CDT1* (Castellano et al., 2004), topoisomerase I (Mudgil et al., 2002) or telomerase (Yang et al., 2002). In addition, ABA activates the expression of other genes, which are repressors of cell division, such as the CDK inhibitor *KRP1/ICK1* (Wang et al., 1998). All these activities on cell cycle gene expression are consistent with the arrest at the G1/S transition observed in tobacco BY2 cultured cells upon ABA addition (Swiatek et al., 2002).

Other phytohormones

Comparatively, much less is known about the action of other hormones on cell division. A direct link between BR signaling and cell cycle gene expression has been demonstrated for the *CYCD3* genes whose expression is upregulated upon epi-brassinolide addition, a treatment that also induces cell division (Hu et al., 2000). BR can also enhance *CDKA;1* gene expression, suggesting that BR may be a more general regulator of cell cycle gene expression than initially suspected.

Results describing effects of ethylene (ET), jasmonic acid (JA) and gibberellins (GA) on cell division are scattered and the molecular basis is only starting to be understood. ET (Dan et al., 2003; Kazama et al., 2004) and JA (Swiatek et al., 2002) inhibit cell cycle progression. Methyl jasmonate (MeJA) addition, for example, alters the transcriptome of Arabidopsis cultured cells and produces, at least, two clear response waves. In the second one, MeJA reprograms cell cycle gene expression by repressing M-phase genes and, consequently, cells become arrested in G2 (Pauwels et al., 2008). In another study, a JA increase produced by repeated wounding reduces cell number by inhibiting cell division as a consequence of a G2 arrest after *CYCB1;2* gene expression is repressed (Zhang and Turner, 2008). On the contrary, GA stimulates cell division in Arabidopsis (Asahina et al., 2002). In other plant species, e.g. deepwater rice, GA stimulates the expression of some cyclin and CDK genes that ultimately activate both the G1/S and the G2/M transitions (Sauter, 1997; Fabian et al., 2000). It would be important to deep in these studies to find out more about the molecular basis of the effects of theses hormones on cell division.

CHROMATIN STATUS AND CELL CYCLE PROGRESSION

In all eukaryotes genomic DNA is associated with proteins to form a highly compact macromolecular structure called chromatin. Most of these proteins are histones that assemble with DNA in a regularly repeated basic unit, the nucleosome: ~150 bp of DNA are wrapped around a core constituted by two copies of each H2A, H2B, H3 and H4. This apparently monotonous organization is nevertheless a highly dynamic macromolecular complex exhibiting local and global changes that are crucial for chromatin condensation, DNA replication and gene expression processes occurring during the cell cycle. The accessibility of certain sites to the transcriptional machinery is facilitated by different chromatin modification enzymes: DNA methylases (Weber and Schubeler, 2007), enzymes that introduce modifications at histone tails, such as acetylation, methylation, phosphorylation, ubiquitylation, among others (Kouzarides, 2007), the incorporation of histone variants (Ausio, 2006) and the activity of chromatin remodeling complexes (Flaus et al., 2006). The occurrence of these chromatin modifications, which can be of an extraordinary complexity and diversity, at genes with a key role in cell proliferation is revealing of primary importance for cell division control (Sanchez et al., 2008).

The repression exerted by RBR on E2F/DP transcription factors during early G1 involves the recruitment of, at least, histone deacetylases (HDAC), histone methyltransferases (HMT) and DNA methyltransferases (Dnmt1). In addition, genome-wide analysis revealed that genes encoding these and other chromatin factors are E2F targets (Menges et al., 2003; Ramirez-Parra et al., 2003; Vandepoele et al., 2005; Ramirez-Parra et al., 2007; Sanchez et al., 2008). Given the structural and functional similarities of plant RBR with its animal counterpart, it is likely that many of the chromatin factors that functionally interact with human RB will have orthologues in Arabidopsis. Thus, BRM and BRG, two members of the human SNF2 DNA-dependent ATPases of the nucleosome remodeling complexes, interact with RB (Dunaief et al., 1994). Arabidopsis *BRM* is expressed to high levels in proliferating cells and it seems to affects cell cycle gene expression (Farrona et al., 2004).

Microarray analysis has revealed that CAF-1 is necessary for the correct expression of a subset of genes involved in S-phase progression and DNA repair (Schonrock et al., 2006). Thus, *fas1* mutant plants have a constitutively active G2 checkpoint response characterized by the up-regulation of *BRCA1* (AT1G04020),

PARP1 (AT2G31320) and *RAD51* (AT5G20850), but not *Ku70/Ku80* (AT1G16970 / AT1G48050) genes whose promoters contain increased levels of acetylated H3 and H4 and a reduced level of H3K9me2 (Ramirez-Parra and Gutierrez, 2007a). Altered function of other histone chaperones, such as NAP1 and NAP1-related (NRP), involved in H2A-H2B dynamics leads to increased G2 arrest (Galichet and Gruissem, 2006; Zhu et al., 2006). In addition to the CAF-1-dependent changes in histone modifications, changes in the acetylation level of H3K18 and H4K16 have been reported (Jasencakova et al., 2003). A direct effect of ubiquitylation of H2B is to control the expression of numerous cell cycle genes, e.g. several cyclin A and B, and three CDKB genes (Fleury et al., 2007).

Chromosome condensation during mitosis starts at prophase and depends on phosphorylation of H3S10 (H3S10ph) residues from early prophase until telophase, although phosphorylation of other histone residues has been also reported (Houben et al., 2007). H3S10ph is carried out by multiple kinases in mammalian cells such as MSK1, MSK2, PKA, Aurora B, RSK2 or IKKa (reviewed in (Ito, 2007)). Arabidopsis contains three *AURORA* genes (AUR1, AT4G32830; AUR2, AT2G25880; AUR3, AT2G45490) whose expression peaks in mitosis and encode kinases that can efficiently use histone H3 as a substrate (Demidov et al., 2005; Kawabe et al., 2005; Kurihara et al., 2006). In addition, H3 can be phosphorylated by the TOUSLED (TSL; AT5G20930) kinase, whose expression is constant throughout the cell cycle but its activity increases in late G2/M, suggesting that AURORA and TSL may compete or cooperate for H3 phosphorylation (Ehsan et al., 2004). In addition to its role in chromosome condensation, H3S10ph affects transcription in other systems, likely due to its effect on other H3 modifications: it increases H3K14ac and suppresses H3K9ac and H3K9me (reviewed in (Sanchez et al., 2008)).

OUTLOOK

Cell division studies in Arabidopsis have received a significant attention during the past 15 years that have contribued to the advance in the field. In an increasing amount of cases, studies have focused not only in learning about the cell cycle machinery itself but also on the impact of cell division processes on growth and development. This is actually one of the most attractive avenues given the strict coordination of cell proliferation and organogenesis during the post-embryonic life of a plant. The possibility of combining molecular, cellular, genetic and genomic approaches should most likely produce a quali and quantitative advance in our understanding of cell proliferation during Arabidopsis develoment.

It is clear that cell division control is not an isolated process in the organism. It must be coordinated with other such as hormonal control, nutrient metabolism, light response, signaling and membrane dynamics, tanscriptional regulation and chromatin modifications, growth signals, among others. Consequently, transcriptomic analysis in the large collection of Arabidopsis mutants affected in processes apparently unrelated to cell proliferation control may lead to unexpected connections between cell division and other cellular processes. In this context, the use of approaches of systems biology should be extremely helpful in identifying unforeseen pathways coupled to cell proliferation.

In most cases to date studies on cell division have focused on how cell cycle and related genes are regulated at the level of tanscription. Of course this is valid and those studies need to be expanded. Hoever, we should not forget in the future other levels of regulation, in particular, posttanslational modifications, specific proteolytic degradation and changes in subcellular localization. The combination of different approaches and the study of cell division controlin a developmental and organismal context should lead us to move into an exciting future in the field.

ACKNOWLEDGEMENTS

Research was supported by a grant from the Spanish Ministry of Education and Science (BFU2006-5662), the European Union (MIF1-CT-2005-514524), and by an institutional grant from Fundación Ramón Areces.

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