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Cell cycle control and plant development

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Abstract

The cell cycle is driven by the activity of cyclin-dependent kinase (CDK)-cyclin complexes. Therefore, internal and external signals converge on the regulation of CDK-cyclin activity to modulate cell proliferation in specific developmental processes and under various environmental conditions. CDK-cyclin activity is fine-tuned by multiple mechanisms, e.g., transcriptional control, protein degradation, phosphorylation, and binding to CDK inhibitor. These molecular mechanisms underlie the regulation of the entry into or the exit from the cell cycle, the rate of cell cycle, or the transition from the mitotic cell cycle to the endocycle. The multiple mechanisms regulating CDK-cyclin activity coordinately enable the elaborate control of cell cycle by various upstream signals. Here we review the molecular mechanisms that regulate the cell cycle and the endocycle in plants. We also introduce the recent progress in elucidating the regulatory mechanisms underlying plant development and the stress response in terms of cell cycle control.

Key words: cell cycle, endocycle, phytohormone, DNA damage checkpoint, CDK.

1. Introduction

Higher plants continuously develop organs throughout their life cycle, and this process is dependent on the flexible control of cell division and cell expansion. As plant cells do not move within their organs and plants form their body by laying cells like building blocks, the spatiotemporally optimized control of cell division and expansion plays a central role in the highly elaborate morphogenesis and differentiation of each organ. Studies on cell division control in plants have benefited from genetic analyses using the model plant *Arabidopsis thaliana*. The genome sequence of *A. thaliana* has revealed that there are many cell cycle-related genes with counterparts in yeast and animals, and most of the cell cycle regulators are encoded by multiple loci. They have specific or redundant functions in cell cycle regulation; however, it has been difficult to identify the particular function(s) of each gene. Functional analysis of these regulators has suffered from the fact that cell cycle progression is a fundamental process in plant development; thus, a deficiency in the regulatory mechanisms is predicted to cause a lethal phenotype. However, recent advances in high-throughput analyses and the accumulation of useful genetic material has enabled us to tackle the challenging questions: How do cells "know" when and where to divide, terminate, or expand in a specific developmental context? How do plants adjust cell division and expansion in response to growth conditions and environmental stress? How is the transition from the mitotic cycle to the endocycle controlled?

To solve these questions, it is essential to understand the fundamental mechanisms that control cell cycle progression. Here we introduce the underlying genetic mechanisms of cell cycle control in plants, which have been revealed by biochemical and

genetic analyses within the last 20 years. We also discuss our understanding of the regulatory mechanisms governing the endocycle, an alternate version of the cell cycle. Finally we illustrate the elaborate regulation of cell cycle progression by external stimuli and developmental signals. The integration of a wide range of knowledge will be useful to understand plant-specific strategies for their continuous development and adaptation to the environment.

2. Basic Regulatory Mechanisms of the Cell Cycle

2.1 Cyclin-dependent kinases

As in yeast and animals, cyclin-dependent kinases (CDKs) are the central regulators of the cell cycle in plants. The one-way progression of the cell cycle is established by regularly alternating the activity of CDKs. CDK activity becomes higher at the G1/S and G2/M boundaries, and is associated with the phosphorylation of a large number of proteins, leading to the onset of DNA replication and mitosis, respectively. The modification of CDK activity by transcriptional control, protein-protein interactions, posttranslational modifications, or protein degradation is the eventual convergence point that governs cell cycle progression (Fig. 1). Whereas 8 classes of CDKs (CDKA to CDKG, and CDK-like kinases [CKLs]) have been identified in *A. thaliana*, CDKA and CDKB are the only CDKs that directly regulate cell cycle progression (Vandepoele et al., 2002; Menges et al., 2005). CDKC and CDKE are presumed to regulate transcription, as deduced from the function of their mammalian homologs CDK9 and CDK8, respectively. CDKD and CDKF are CDK-activating kinases (CAKs; see below). CDKGs and CKLs are

recently identified classes that consist of 2 and 15 genes, respectively, and the latter constitute a distant and distinct phylogenetic clade from the other CDKs (Menges et al., 2005). Although CKLs show high sequence similarities among members, suggesting their recent divergence, their functions have not yet been identified.

CDKA is encoded by a single copy gene (*CDKA;1*) in *A. thaliana* and contains a conserved PSTAIRE motif in its cyclin-binding domain. CDKA;1 is the only CDK identified so far in *A. thaliana* that can complement the temperature-sensitive *cdc2* mutant of *Schizosaccharomyces pombe* (Ferreira et al., 1991). Overexpression of dominant-negative *CDKA;1* abolishes cell division (Hemerly et al., 1995), suggesting that CDKA;1 is essential for cell cycle progression in plants. Null mutations in *CDKA;1* impair the division of male gametophytes into 2 sperm cells, whereas *cdka;1* female gametophytes develop normally; thus, pollen carrying the *cdka;1* mutation cannot undergo double fertilization (Nowack et al., 2006; Iwakawa et al., 2006).

CDKB can be grouped into the CDKB1 and CDKB2 subfamilies, which are both encoded by 2 genes in *A. thaliana* (*CDKB1;1* and *CDKB1;2* for CDKB1; *CDKB2;1* and *CDKB2;2* for CDKB2). CDKBs are specific to plants (Boudolf et al., 2001; Hirayama et al., 1991; Joubes et al., 2000). The PSTAIRE motif in CDKA is replaced with PPTALRE and P(P/S)TTLRE in CDKB1 and CDKB2, respectively (Vandepoele et al., 2002). CDKBs have the unique feature that their expression is differentially regulated during the cell cycle; the *CDKB1* transcript accumulates from the late S phase to the M phase, whereas *CDKB2* is expressed in a more restricted period from the G2 to M phase (Segers et al., 1996; Umeda et al., 1999; Menges et al., 2002, 2003, 2005; Breyne et al., 2002; Porceddu et al., 2001). In addition to transcriptional control, CDKB2 expression was shown to be regulated by protein degradation because a translational fusion of

CDKB2;1 with β-glucuronidase (GUS), but not a *CDKB2;1* promoter-GUS fusion, showed a patchy expression pattern in the *A. thaliana* root meristem. Indeed, CDKB2;1 and CDKB2;2 have possible PEST motifs, which are signals for proteolytic degradation (Adachi et al., 2006). Treatment of CDKB2:GUS roots with the proteasome inhibitor MG132 increases the expression of GUS, suggesting that proteasome-mediated proteolysis regulates CDKB2 expression. However, the molecular mechanism underlying the degradation of CDKB2 protein has not been identified.

As predicted from its expression pattern, CDKB1 controls G2/M progression (Porceddu et al., 2001; Boudolf et al., 2004a). Although the detailed function of CDKB2 in cell cycle progression has not been elucidated, the 2 *A. thaliana CDKB2* genes are expressed in meristematic cells and are required for cell proliferation and the execution of genetic programs in the meristem (Andersen et al., 2008).

2.2 Cyclin

The cell cycle phase-specific expression of cyclins activates CDKs in a time-controlled manner by directly interacting with CDKs. Different CDK-cyclin pairs form complexes and regulate different stages of the cell cycle. In *A. thaliana*, ~50 genes encode cyclin-related proteins, in which 32 cyclins have putative functions in cell cycle regulation: 10 A-type, 11 B-type, 10 D-type, and 1 H-type cyclins (Menges et al., 2005).

Each cyclin gene shows a specific expression pattern during the cell cycle. The function of individual cyclins has been suggested from their expression patterns, interacting partners, and the effect caused by altering their expression. Generally, A-type cyclins (CYCAs) control S-to-M phase progression and CYCBs control the G2/M

transition and M phase progression (Inze and De Veylder, 2006). CYCDs control the G1/S transition and cell proliferation in response to external signals, e.g., phytohormones and nutrient availability. However, the expression of CYCD genes is not specific to the G1/S phase, and some are expressed at the G2/M phase (Sorrel et al., 1999; Menges et al., 2005).

The 10 genes that encode CYCAs are divided into the *CYCA1*, *CYCA2*, and *CYCA3* subfamilies, which include 2, 4, and 4 genes, respectively, in *A. thaliana* (Vandepoele et al., 2002; Wang et al., 2004a). *CYCA1* and *CYCA2* show a peak of expression at the G2/M phase, whereas *CYCA3* is expressed during the G1/S transition phase and S phase in synchronized *A. thaliana* suspension cells (Menges et al., 2005). A number of CYCA proteins can bind to CDKB and CDKA proteins (Boruc et al., 2010; Van Leene et al., 2010). Functional genetic analyses have revealed some putative functions of the CYCA proteins. CYCA2;3 was shown to form a complex with CDKB1;1 and promote the mitotic cell cycle (Boudolf et al., 2009). CYCA2;3 was shown to interact with CDKA;1 and repress endocycle progression (Imai et al., 2006). CYCA1;2 (also known as TAM) is required for meiosis in male gametophytes (Wang et al., 2004b; d'Erfurth et al., 2010). Recently, we revealed that the CYCA3;1-CDKA;1 complex phosphorylates histone H1 and retinoblastoma-related (RBR) protein *in vitro* (Takahashi et al., 2010a), suggesting that CYCA3 can act as a G1/S cyclin to promote entry into the S phase.

Eleven genes encode CYCBs in *A. thaliana*: 5 for *CYCB1*, 5 for *CYCB2*, and 1 for *CYCB3* (Vandepoele et al., 2002; Wang et al., 2004a). All of them have expression peaks at the G2/M transition phase (Menges et al., 2002; 2005). They can interact with CDKA, CDKB1, and CDKB2 (Boruc et al., 2010; Van Leene et al., 2010), although the function of these complexes in cell cycle progression is largely unexplored. The ectopic expression

of *CYCB1;1* under the control of the *CDKA;1* promoter promotes root growth without altering organ morphology, suggesting that the increased expression of *CYCB1;1* accelerates cell cycle progression and, thus, meristem activity (Doerner et al., 1996). The induction of cell division was demonstrated by the ectopic expression of *CYCB1;2* in differentiating trichomes (unicellular hairs on leaves), resulting in the formation of multicellular trichomes (Schnittger et al., 2001). CYCB2s from rice (*Oryza sativa*) form complexes with CDKB2 and activate histone H1 kinase activity *in vitro* (Lee et al., 2003). *CYCB2;2* overexpression in rice enhances root growth by increasing the cell number, indicating that CYCB2 can stimulate cell division.

Ten genes encoding CYCDs have been identified in *A. thaliana*, and they are classified into 7 subfamilies (CYCD1 to CYCD7): CYCD3 is encoded by 3 genes, CYCD4 by 2 genes, and the other 5 CYCDs are each encoded by a single gene (Vandepoele et al., 2002). *CYCD1;1*, *CYCD2;1*, and *CYCD3;1* were originally identified by screening for *A. thaliana* genes that can complement a yeast G1 cyclin mutant (Soni et al., 1995). The majority of CYCD proteins can interact with CDKA;1 (Boruc et al., 2010; Van Leene et al., 2010), and the overexpression of some CYCD genes accelerates the entry of the cell into the S phase (Cockcroft et al., 2000; Dewitte et al., 2003; Koroleva et al., 2004; Masubelele et al., 2005; Menges et al., 2006, Kono et al., 2007), suggesting that CDKA-CYCD complexes regulate the G1/S transition. In fact, the overexpression of *A. thaliana* CYCD2;1 in *Nicotiana tabacum* increased the overall growth rate of shoots, but the final size of each organ was the same as in wild-type plants (Cockcroft et al., 2000).

2.3 CDK inhibitors

In contrast to cyclins, CDK inhibitors negatively regulate the activity of CDKs by directly binding to CDKs (Morgan, 1997, Nakayama and Nakayama, 1998). A plant CDK inhibitor was first identified by screening for proteins that can interact with CDKA (Wang et al., 1997; Lui et al., 2000). Seven genes encode the CDK inhibitor Kip-related protein (KRP) family in *A. thaliana*: ICK1/KRP1, ICK2/KRP2, and KRP3 to KRP7 (De Veylder et al., 2001). ICK1/KRP1, ICK2/KRP2, or KRP6 overexpression strongly inhibits growth and affects organ morphology (Wang et al., 2000; De Veylder et al., 2001; Zhou et al., 2002). All KRPs, except KRP5, bind to CDKA;1, but not to CDKB1;1 in the yeast 2-hybrid system (De Veylder et al., 2001). Interestingly, all KRPs can interact with D-type cyclins, e.g., CYCD1;1, CYCD2;1, and CYCD3;1 (Wang et al., 1998; Zhou et al., 2002), suggesting that KRPs inhibit the activity of CYCD-CDKA complexes. KRPs are small proteins with a C-terminal domain that is required for CDK- or cyclin-binding and their inhibitory function (De Veylder et al., 2001; De Clercq and Inze, 2006). Although KRPs and animal CDK inhibitors, e.g., $p21^{Cip1}$, $p27^{Kip1}$, and $p57^{Kip2}$, show limited sequence similarities in their CDK/cyclin-binding domains, their overall structures are sufficiently different that the functions and regulatory mechanisms of KRPs are suggested to differ from those of animal CDK inhibitors (De Clearcq and Inze, 2006).

A second class of CDK inhibitors was identified in *A. thaliana*, named SIAMESE (SIM) and SIM-related (SMR) proteins (Churchman et al., 2006). SIM and SMR proteins are only found in plants, including rice, maize, tomato, and poplar, and show localized sequence similarity to KRPs within the C-terminal cyclin-binding domain (Churchman et al., 2006; Peres et al., 2007). The founder member, SIM, represses the mitotic cell cycle in endoreduplicating trichomes (Walker et al., 2000). SIM

overexpression significantly reduces growth and generates enlarged cells with increased nuclear content, suggesting that SIM inhibits the activity of CDK at G2/M and promotes endoreduplication (Churchman et al., 2006). Fluorescence resonance energy transfer (FRET)analysis demonstrated that SIM and the rice SMR protein EL2 specifically interact with CDKA;1 and CYCD proteins, but not with CDKB proteins in the nucleus (Churchman et al., 2006; Peres et al., 2007). Furthermore, EL2 was shown to inhibit the activity of CDKA;1 *in vitro* (Peres et al., 2007). However, recent interactomic analyses using tandem affinity purification(TAP) and mass spectrometry in *A. thaliana* cell suspension culture showed that SIM, SMR1, and SMR2 were co-purified with CDKB1;1, but not with CDKA;1, whereas SMR3–6 and SMR8 were associated with CDKA;1 (Van Leene et al., 2010). Interestingly, the expression of many *SMR* genes differentially responds to several stress conditions (Peres et al., 2007; see below), suggesting that *SMRs* are involved in altering cell cycle progression in response to external stress.

2.4 CDK phosphorylation

CDK activity is also regulated by phosphorylation. Phosphorylation of a conserved threonine residue (Thr-161 in *A. thaliana* CDKA;1) in the T-loop region is required for the recognition of substrates and the full activity of CDK (Nigg, 1996; Draetta, 1997). CAKs catalyze this activating phosphorylation of CDKs. In plants, 2 classes of CAKs have been identified: CDKD and CDKF (Umeda et al., 2005). The CDKD class is structurally related to the vertebrate CAK, CDK7, which phosphorylates the C-terminal domain (CTD) of the largest subunit of RNA polymerase II in addition to CDK

(Serizawa et al., 1995; Shiekhattar et al., 1995). In *A. thaliana*, 3 *CDKD* genes have been identified: *CDKD;1*, *CDKD;2*, and *CDKD;3* (originally named *CAK3At*, *CAK4At*, and *CAK2At*, respectively) (Shimotohno et al., 2003; Umeda et al., 2005). CDKD;2 and CDKD;3 phosphorylate human CDK2 and *A. thaliana* CTD *in vitro* (Shimotohno et al., 2003). The kinase activity of CDKD;3 on CDK2 was higher than that of CDKD;2, but the kinase activity on CTD is much higher with CDKD;2 than CDKD;3, suggesting that multiple CAKs differently regulate the cell cycle and transcription (Shimotohno et al., 2003). The kinase activity of CDKD;1 on CDK and CTD was not detected *in vitro* (Shimotohno et al., 2004).

CDKF (originally named CAK1At) is another CAK and plant-specific protein that is encoded by a single gene, *CDKF;1*, in *A. thaliana* (Umeda et al., 1998; Shimotohno et al., 2004; 2006). CDKF;1 can phosphorylate human CDK2 *in vitro* and CDKA;1 in *A. thaliana* root protoplasts (Umeda et al., 1998; Shimotohno et al., 2006). CDKF;1 also phosphorylates CDKD;2 and CDKD;3, thereby activating the CTD kinase activity of CDKD;2 (Shimotohno et al., 2004). These results suggest that the kinase cascade is mediated by multiple CAKs that coordinately regulate basal transcription and cell cycle progression during plant development (Umeda et al., 2005).

A null mutation of *CDKF;1* does not affect the activity of CDKA, CDKB1, or CDKB2; however, it strongly impaired cell proliferation and cell expansion during post-embryonic development (Takatsuka et al., 2009). Protein stability and the CTD kinase activity of CDKD;2 are decreased in this *cdkf;1* mutant, suggesting that defective basal transcription might cause these defects (Takatsuka et al., 2009). Therefore, it is inferred that CDKDs are mainly involved in CDK activation during post-embryonic development. Although loss-of-function mutants for *CDKD;1* or *CDKD;3*

do not show any growth defects (Shimotohno et al., 2006), further studies with multiple combinations of *cdkd* mutants will reveal the *in vivo* functions of each CDKD in plant tissues.

As expected from the importance of T-loop phosphorylation, a mutant CDKA;1 with a non-phosphorylatable Val at Thr-161 does not rescue the *cdka;1* mutant from the male gametophytic defect (Dissmeyer et al., 2007). A phospho-mimicry version of CDKA;1 with Asp at Thr-161 can rescue *cdka;1* mutants, but it shows significantly reduced kinase activity; thus, the rescued plant exhibits strongly reduced vegetative growth and sterility due to the meiotic defect (Dissmeyer et al., 2007). These results indicate that the proper regulation of T-loop phosphorylation is a prerequisite for the full activity of CDKA;1 and normal plant development.

CDK activity is modulated by the inhibitory phosphorylation of Tyr and Thr in its N-terminal ATP-binding domain. In yeast and animals, WEE1 kinase and CDC25 phosphatase regulate the phosphorylation status of these residues, thereby controlling cell cycle progression. *A. thaliana* WEE1 can phosphorylate CDKA;1 at Tyr-15 *in vitro* (Shimotohno et al., 2006). The expression of CDKA;1 in which Thr-14 and Tyr-15 are substituted with phospho-mimic Asp and Glu, respectively, results in strongly reduced cell proliferation and does not fully complement the generative cell division defect in the *cdka;1* mutant, demonstrating that inhibitory phosphorylation also controls the activity of plant CDKA (Dissmeyer et al., 2009). However, a *wee1* mutant and *cdka;1* expressing non-phosphorylatable CDKA;1 (with Val and Phe, instead of Thr-14 and Tyr-15, respectively) behave differently in terms of the DNA damage response (see below), and the functional homolog of CDC25 has not been identified in higher plants (Boudolf et al., 2006; Dissmeyer et al., 2009). Therefore, the functional significance of inhibitory

phosphorylation in plant development and the genotoxic stress response is currently unknown.

2.5 Protein degradation

Controlled protein degradation of cell cycle regulators is one of the key mechanisms that ensures the one-way progression of the eukaryotic cell cycle (Frescas and Pagano, 2008; Pesin and Orr-Weaver, 2008; Marrocco et al., 2010). The levels of many cell cycle regulators with either positive or negative functions in cell cycle progression are regulated by protein degradation in a cell cycle phase-dependent manner or in response to internal or external stimuli (Marrocco et al., 2010). Proteins for degradation are selectively labeled with poly-ubiquitin by specific E3 ubiquitin ligases (Pickart, 2001). Anaphase-promoting complex/cyclosome (APC/C) and Skp1/Cullin/F-box (SCF) are the major E3 ubiquitin ligase classes involved in cell cycle control (Vodermaier, 2004).

As the levels of cyclin proteins are the major determinant of CDK activity, cyclin degradation is an important mechanism in cell cycle control. Plant A- and B-type cyclins contain the destruction box motif that is required for proteasome-mediated degradation (Genschik et al., 1998; Colon-Carmona et al., 1999; Criqui et al., 2000; Weingartner et al., 2004). The significance of the protein degradation of cyclins was demonstrated by the overexpression of CYCB1 with a mutation in its destruction box in *N. tabacum* plantsand suspension-cultured BY-2 cells (Weingartner et al., 2004). The expression of mutated CYCB1 impairs M phase progression after anaphase, resulting in a large proportion of polyploid nuclei and abnormal organ development. Ubiquitination of CYCA and CYCB is probably mediated by APC/C, since knockout or knockdown of

APC/C subunit genes causes the accumulation of CYCA or CYCB fused with a GUS reporter (Capron et al., 2003; Kwee and Sundaresan, 2003; Perez-Perez et al., 2008; Marrocco et al., 2009).

CYCD3 expression is also regulated by proteolysis (Planchais et al., 2004). *A. thaliana* CYCD3;1 is a highly unstable protein, and its levels rapidly decrease upon sucrose depletion, which is associated with cell cycle arrest at the G1 phase. In fact, CYCD3;1 levels are significantly decreased by treatment with a protein synthesis inhibitor, cycloheximide, while they are increased by treatment with MG132 in proliferating and sucrose-starved cells (Planchais et al., 2004). These results indicate the dynamic regulation of CYCD3 levels by controlled proteolysis in response to nutrient conditions.

In addition to positive regulators of the cell cycle, the levels of negative regulators are also controlled via protein degradation. In yeast and metazoans, CDK inhibitors are degraded at the G1/S transition through SCF-type E3 ligase-mediated ubiquitination; thus, CDK is activated, resulting in S phase entry (Schwob et al., 1994; Frescas and Pagano, 2008). In plants, several KRPs, such as ICK1/KRP1 and ICK2/KRP2, were suggested to be degraded by the proteasome (Verkest et al., 2005; Jakoby et al., 2006; Ren et al., 2008). Recently, the importance of KRP protein degradation in gametophytic cell division was demonstrated. The RHF1a and RHF2a RING-finger proteins, which are components of the RING-type E3 ligase complex, were shown to be involved in KRP6 turnover during gametogenesis (Liu et al., 2008). A double mutant for *RHF1a* and *RHF2a* showed defective gametophytic cell division, and this phenotype was rescued by reducing KRP6 expression, indicating the functional relevance of KRP6 degradation. It was also shown that the FBL17 F-box protein is involved in male gametogenesis

through its targeting of KRP6 and KRP7 (Kim et al., 2008; Gusti et al., 2009). FBL17 is a component of an SCF complex and is specifically expressed in developing pollen before generative cell division. An *fbl17* mutant is defective for generative cell division in developing pollen, which is very similar to the phenotype observed in the *cdka;1* mutant, suggesting that FBL17 enables generative cell division by activating CDKA;1 via the degradation of KRP6 and KRP7 (Kim et al., 2008; Gusti et al., 2009).

Two types of E3 ubiquitin ligases are implicated in the control of KRP1 degradation: the SCF-type complex containing F-box proteins SKP2A and SKP2B, which are homologs of mammalian SKP2, and RING E3 with RING-finger protein RKP, the homolog of mammalian KPC1. In mammals, SKP2 and KPC1 are independently involved in the degradation of the $p27^{KIP1}$ CDK inhibitor (Kamura et al., 2004; Frescas and Pagano, 2008). Whereas the overall sequences of SKP2s and RKP are very different from their mammalian counterparts, some functional conservation has been demonstrated. The overexpression of *SKP2B* or *RKP* inhibits the accumulation of KRP1 and suppresses the phenotypes of *KRP1*-overexpressing plants, e.g., leaf serration (Ren et al., 2008). However, triple loss-of-function *SKP2A*, *SKP2B*, and *RKP* plants show normal morphology, regardless of the high accumulation of KRP1. Therefore, unlike gametophytic cell division, the importance of CDK inhibitor degradation during vegetative development has not been clearly demonstrated.

2.6 Transcriptional control

The transcriptional control of cell cycle regulators is largely unknown in plants, although the expression of many cell cycle-related genes is differently regulated during

the cell cycle (Menges et al., 2003). Many genes with a peak of expression at the G2/M phase, including the genes for A- and B-type cyclins, kinesin-like proteins (NACKs), and the cytokinesis-specific syntaxin KNOLLE (KN), have mitosis-specific activator (MSA) elements in their promoter regions (Ito et al., 1998; Ito, 2000; Menges et al., 2005). MSA elements are necessary and sufficient for G2/M-specific expression (Ito et al., 1998). Three Myb repeat (MYB3R) transcription factors that recognize MSA elements were first identified in tobacco (NtMYBA1, NtMYBA2, and NtMYBB) (Ito et al., 2001). NtMYBA1 and NtMYBA2 are specifically expressed from G2 to the early M phase and can transactivate MSA-containing promoters. On the other hand, NtMYBB is expressed throughout the cell cycle, and has a repressive function toward MSA elements (Ito et al., 2001). NtMYBA2 was shown to be phosphorylated and activated by CDK-CYCA or CDK-CYCB complexes, suggesting a positive feedback loop in G2/M-specific transcriptional control where MYB promotes the transcription of CYCA and CYCB, and then CDK-CYCA/B activates MYB (Araki et al., 2004). In addition, the promoters of *NtMYBA1* and *NtMYBA2* contain MSA elements and are possibly activated by their own products (Kato et al., 2009). These mechanisms are suggested to cause a burst of CDK activity and consequent entry into the M phase.

A. thaliana has 5 MYB3R proteins, MYB3R1 to MYB3R5, in which MYB3R1 and MYB3R4 are highly similar to NtMYBA1 and NtMYBA2 (Haga et al., 2007). A double mutant for *MYB3R1* and *MYB3R4* shows a defect in cytokinesis and decreased expression of some G2/M-specific genes, e.g., *CYCB2* and *KN*. Interestingly, the transcript level of *MYB3R1* does not change throughout the cell cycle, whereas *MYB3R4* has a peak of expression at G2/M (Haga et al., 2007), suggesting that the posttranslational regulation of MYB3R1 may be associated with the G2/M-specific

transcription of target genes, e.g., MYB3R1 may be phosphorylated and activated by CDK, as in the case of NtMYBA2. However, even in an *myb3r1 myb3r4* double mutant, many mitotic genes carrying MSA-elements within their promoters still display a G2/M-biased expression pattern, suggesting that other MYB3R factors and/or unidentified transcription factors are also involved in the control of their G2/M phase-specific expression. A possible candidate is another MYB protein, CDC5, which is implicated in cell cycle control in yeast and animals (Ohi et al., 1998; Bernstein et al., 1998). A homozygous *cdc5* mutant of *A. thaliana* is embryonic lethal, and *CDC5* knock-down led to defects in meristem activity and the decreased expression of *CDKB1;1* (Lin et al., 2007).

In addition to G2/M-specific regulation via the MSA-elements, *CYCB1;1* expression is quantitatively controlled through GCCCR (R is A or G) motifs in its promoter (Li et al., 2005). Class I teosinte-branched, cycloidea, PCNA factor (TCP) transcription factors bind to GGNCCCAC consensus sequences; indeed, TCP20 binds to the *CYCB1;1* promoter in a chromatin immunoprecipitation (ChIP) assay. Interestingly, GCCCR motifs are also required for the high-level expression of ribosomal protein genes in rapidly growing cells, and TCP20 also binds to their promoters, suggesting that TCP proteins may coordinate growth and division in proliferating cells (Li et al., 2005).

A. thaliana CDKA;1 is expressed not only in the dividing cells of the embryo and meristem but also in the differentiated tissues of the root, leaf, and flower (Adachi et al., 2009). Detailed promoter analyses revealed that distinct *cis*-elements independently regulate the quantitative and cell type-specific expression of *CDKA;1*. Expression in the epidermis on the abaxial side (underside) of leaves is regulated by a promoter region that is distinct from the other regulatory elements controlling its expression in the

inner layers of leaves and shoot apical meristem, including the outermost L1 layer (Adachi et al., 2009). Such cell type-specific transcriptional control of cell cycle regulators may underpin the highly organized morphogenesis of organs.

2.7 E2F-RBR pathway

E2F transcription factors are involved in control of the G1/S transition in animals and plants by mediating the transcriptional activation of many genes required for cell cycle progression and DNA replication (Inze and De Veylder, 2006; van den Heuvel and Dyson, 2008). E2F and dimerization partner (DP) proteins form a heterodimer and bind to the E2F-binding sites in target promoters. The *A. thaliana* genome encodes 3 canonical E2F proteins (E2Fa, E2Fb, and E2Fc) and 2 DP proteins (DPa and DPb). E2Fa and E2Fb function as transcriptional activators, and the overexpression of E2Fa or E2Fb with DPa induced cell proliferation in differentiated tissues and tobacco BY-2 cells (De Veylder et al., 2002; Rossignol et al., 2002; Magyar et al., 2005; Sozzani et al., 2006). On the other hand, the E2Fc-DPb complex acts as a repressor, and has a negative effect on cell proliferation and the expression of a DNA replication-related gene (del Pozo et al., 2002; 2006). The E2F-targets include many genes involved in the initiation and progression of DNA replication, DNA repair, and chromatin regulation (Ramirez-Parra et al., 2003; Vandepoele et al., 2005; Takahashi et al., 2008; Takahashi et al., 2010b).

The temporal regulation of E2F-DP activity is controlled by its interactions with a negative regulator, the retinoblastoma (Rb) protein (RBR [retinoblastoma-related] in plants). CDK-mediated hyper-phosphorylation of Rb during the G1 phase releases a

functional E2F-DP heterodimer that activates target genes and promotes S phase entry (Dyson, 1998; Shen, 2002; Attwooll et al., 2004). Plant RBR proteins interact with CYCDs and are phosphorylated by CYCD-CDKA complexes (Nakagami et al., 1999; 2002; Boniotti and Gutierrez, 2001). The functional significance of plant RBR proteins was demonstrated by genetic analysis in *A. thaliana*, which encodes only 1 RBR protein. Knockout or knockdown of the *RBR* gene causes excessive cell proliferation and defects in cell differentiation during megagametogenesis and in the root and shoot (Ebel et al., 2004; Wildwater et al., 2005; Chen et al., 2009; Borghi et al., 2010). Interestingly, loss of *RBR* or the simultaneous overexpression of E2Fa and DPa in root stem cells leads to an increase of the stem cell pool, implying that the stem cell state is maintained by the E2F-RBR pathway (Wildwater et al., 2005).

In addition to the canonical E2F proteins, plants and mammals have atypical E2F factors (Lammens et al., 2009). In *A. thaliana*, 3 atypical E2F factors have been identified, E2Fd/DEL2, E2Fe/DEL1, and E2Ff/DEL3 (DEL stands for DP-E2F-like), which have characteristics of E2F and DP (Vandepoele et al., 2002). Unlike canonical E2Fs, atypical E2Fs can bind to target DNA without forming heterodimers with DP proteins, probably because atypical E2Fs have a duplicated DNA-binding domain; one is similar to that in canonical E2Fs and the other is similar to that in DPs (Kosugi and Ohashi, 2002; Mariconti et al., 2002; Lammens et al., 2009). It is unlikely that the atypical E2Fs are regulated by the RBR protein because they do not have an Rb-binding domain (Lammens et al., 2009). Although atypical E2Fs competitively inhibit the transcription of genes controlled by canonical E2Fs (Kosugi and Ohashi, 2002; Mariconti et al., 2002), the biological functions of atypical E2Fs do not seem to be directly related to the G1/S transition (Ramirez-Parra et al., 2004; Vlieghe et al., 2005;

Lammens et al., 2008). By using a ChIP assay, E2Ff/DEL3 was shown to bind to the promoters of genes for cell wall biogenesis and expansion, which contain putative E2F-binding sites, but not to those of DNA replication genes. As a consequence, the loss-of-function or overexpression of *E2Ff/DEL3* affects cell elongation without influencing the cell cycle (Ramirez-Parra et al., 2004). E2Fe/DEL1 represses endoreduplication in proliferating cells, likely through the repression of the CCS52A2 APC activator gene (Vlieghe et al., 2005; Lammens et al., 2008; see below). Recently, the altered expression of E2Fd/DEL2 was shown to cause changes in cell division and elongation in the root meristem and the expression of several cell cycle regulators, including *E2Fa*, *E2Fb*, and *E2Fe*/*DEL1* (Sozzani et al., 2010b). Although the direct targets of E2Fd/DEL2 have not been identified, this result implies that genetic interactions among E2Fs may be involved in the proper control of cell proliferation during organ formation and tissue development.

3. Endocycle

The endocycle is an alternate version of the cell cycle that leads to endoreduplication, in which cells multiply their nuclear DNA content (ploidy) by repeating DNA replication without an intervening mitosis. Endoreduplication is often associated with cell expansion and cell differentiation; thus, the switch from the mitotic cell cycle to the endocycle is correlated with a phase change from cell proliferation to cell differentiation. The extent and relevance of endoreduplication differ among species and cell types. In *A. thaliana*, endoreduplication occurs in most organs and tissues, e.g., root, hypocotyl, leaf, and sepal; however, endoreduplication is rarely observed in tobacco and

rice. Although increased ploidy probably contributes to cell growth and expansion, cell size is not strictly correlated with the ploidy level in different tissues, species, or intraspecific variants (Sugimoto-Shirsu and Roberts, 2003). Therefore, the functional significance of endoreduplication during organ development is currently enigmatic, but many efforts toward understanding the molecular mechanisms controlling the switch from the mitotic cycle to the endocycle and endocycle progression have been made in the past decade (Breuer et al., 2010).

3.1 Endocycle machinery

To operate the endocycle, cells need to skip the entire mitotic stage, including chromosome compaction, separation, and cytokinesis. To achieve this, the activity of mitotic cyclin-CDK complexes needs to be repressed to inhibit G2-to-M progression. Furthermore, re-replication without passing through the mitotic events requires specialized mechanisms because normal mitotic cells have a regulatory system that prevents re-replication until mitosis is completed. During the mitotic cell cycle, components of the pre-replication complex (pre-RC) dissociate from chromatin after the initiation of DNA replication, thereby preventing re-replication until the end of the M phase. Lowering CDK activity at the end of the M phase through the action of APC enables the pre-RC components to associate with chromatin (Wuarin et al., 2002). Therefore, one can speculate that the specific reduction of mitotic CDK activity inhibits entry to mitosis and facilitates re-replication. In addition, studies of the endocycle in *Drosophila melanogaster* suggested that the APC is also involved in DNA replication in endocycling cells through the degradation of geminin, an inhibitor of pre-RC formation

(Zielke et al., 2008). Therefore, endocycling cells share most of the same regulatory components as mitotic cells to achieve cyclical and repetitive DNA replication, but some triggers that cause quantitative changes of these components are required for endocycle induction (Fig. 2).

CDKB1 and CDKB2 are possible CDK candidates whose activity is repressed at the onset of the endocycle, since they show a biased expression at G2/M in dividing cells (Boudolf et al., 2004b; Anderson et al., 2008). The overexpression of dominant-negative (kinase-dead) CDKB1;1 in *A. thaliana* causes the accelerated onset of the endocycle (Boudolf et al., 2004b). Conversely, the simultaneous overexpression of CDKB1;1 and its interacting partner CYCA2;3 induces ectopic cell division and strongly reduces the ploidy level (Boudolf et al., 2009). These results indicate that the downregulation of CDKB1;1-CYCA2;3 activity is one of the mechanisms that controls the transition from mitosis to the endocycle.

The level of CYCA2;3 was shown to be regulated by the APC/C activator CCS52A1. CCS52A1 is a member of the CDH1/FZR/CCS52-like APC/C activator family, which bringsthe substrate to the APC/C. *A. thaliana* expresses 3 *CCS52* genes: *CCS52A1*, *CCS52A2*, and *CCS52B*. In a *ccs52a1* mutant, CYCA2;3-GFP is stabilized in a zone where cells exit from the mitotic cycle and enter the endocycle, indicating that CCS52A1 downregulates CYCA2;3 directly or indirectly (Boudolf et al., 2009). Loss-of-function and overexpression studies showed that CCS52A1 positively regulates entry into the endocycle in roots, trichomes, and leaves (Larson-Rabin et al., 2009; Vanstraelen et al., 2009; Kasili et al., 2010). The expression of *CCS52A1* in roots starts in cells that shift from the mitotic cycle to the endocycle; thus, it may determine the timing of this switch.

CDKB1;1 has been proposed to control the transition to the endocycle by

modulating CDKA;1 activity through the regulation of the levels of the KRP2 CDK inhibitor (Verkest et al., 2005). Moderate overexpression of KRP2 decreases CDKA;1 activity in mitotically active tissue, but not in endoreduplicating tissue, and promotes endoreduplication. The weak inhibition of CDKA;1 is supposed to cause a specific inhibition of the mitotic activity of CDK; thus, leading to endoreduplication. CDKB1;1 phosphorylates KRP2, leading to its proteasome-mediated degradation (Verkest et al., 2005). CDKB1;1 mRNA and protein levels are higher in mitotically active tissue than in endoreduplicating tissue, suggesting that CDKB1;1 promotes KRP2 degradation and inhibits entry into the endocycle by maintaining CDKA;1 activity. This hypothesis offers a new mechanism by which the fine-tuning of phase-specific CDK activity is controlled through the interaction of different CDK proteins.

CDKB2 was also shown to repress entry into the endocycle (Andersen et al., 2008). *CDKB2;1* and *CDKB2;2* are specifically expressed in meristems. The expression of artificial microRNA for *CDKB2;1* and *CDKB2;2* leads to early entry into the endocycle; however, a similar result was also obtained by overexpressing *CDKB2;1*, suggesting that strict control of CDKB2 levels is crucial to maintain meristem activity and the pool of dividing cells.

The SIM and SMR family of CDK inhibitors provide another parallel mechanism that regulates CDK activity at the onset of the endocycle. A *sim* mutant develops multicellular trichomes with decreased ploidy levels (Walker et al., 2000). Conversely, the overexpression of *SIM* generates greatly enlarged cells and increased ploidy levels (Churchman et al., 2006). The *sim* mutant ectopically expresses *CYCB1;2* in trichomes, and the expression of *CYCB1;2* under the control of a trichome-specific promoter induces multicellular trichomes, as observed in the *sim* mutant (Schnittger et al., 2002).

These results suggest that SIM promotes the onset of the endocycle by reducing mitotic CDK activity during trichome development.

SMR1/LOSS OF GIANT CELLS FROM ORGANS (LGO) regulates the endocycle in sepal epidermal cells. The *A. thaliana* sepal epidermis is composed of cells of strikingly varied sizes with ploidy levels from 2C to 16C, where cell size is highly correlated with the ploidy level (Roeder et al., 2010). This endocycle-associated cell expansion is dependent on the function of SMR1/LGO, since an SMR1/LGO loss-of-function mutation resulted in the loss of giant cells in the sepal epidermis, which was accompanied by a decreased level of DNA ploidy. The endoreduplication level and the morphology of trichomes are normal in the *smr1*/*lgo* mutant, indicating that each SIM-related CDK inhibitor may control endoreduplication in a particular developmental context.

Maize (*Zea mays*) endosperm and tomato (*Solanum lycopersicon*) fruit have been used as model tissues to investigate endocycle control. Individual nuclei in maize endosperm increase their DNA ploidy from 3C to more than 96C (Kowles and Phillips, 1985), and the progression of endoreduplication is associated with a decrease of M phase-promoting CDK activity (Grafi and Larkins, 1995). Although the mechanism that specifically downregulates M phase-promoting CDK activity in developing endosperm is currently unknown, it might involve phosphorylation by WEE1 (Sun et al., 1999) or binding to KRPs (Coelho et al., 2005). In the pericarp of tomato fruit, the ploidy reaches up to 256C (Joubès et al., 1999), and the level of ploidy is well correlated with cell size and fruit weight in various tomato strains (Cheniclet et al., 2005). Knockdown of either *WEE1* or *CCS52A* decreased the ploidy level, cell size, and fruit weight, suggesting that WEE1 and CCS52A are involved in the mitosis-to-endocycle transition and/or endocycle progression (Gonzalez et al., 2007; Mathieu-Rivet et al., 2010). The molecular

mechanisms that control the expression and activity of these endocycle-promoting factors will be important in the tissue-specific regulation of cell division and cell expansion.

3.2 Developmental regulation of the endocycle

The spatio-temporally regulated transition from the mitotic cycle to the endocycle is critical for proper organ development. To control the machinery that drives the mitotic cycle and the endocycle, developmental signals, e.g., plant hormones and growth factors, are inferred to play key roles. It is easy to follow the transition from the mitotic cycle to the endocycle in *A. thaliana* roots because the root cells significantly increase their volume at the onset of the endocycle. The distribution of auxin has been shown to be critical for the regulation of cell proliferation and cell expansion in a concentration-dependent manner in the root meristem, i.e., a high concentration of auxin promotes cell proliferation in the apical region and a lower concentration allows cells to expand and differentiate in the basal region (Blilou et al., 2005; Galinha et al., 2007). Recently, it was reported that auxin guides the transition from the mitotic cycle to the endocycle by modulating the expression of cell cycle regulators (Ishida et al., 2010). Mutations in genes for auxin biosynthesis, transport, and signaling or treatment with auxin antagonists led to an increase in DNA ploidy. In auxin signaling-deficient roots, cells enter the endocycle in a more apical part compared to wild-type or non-treated plants, suggesting that auxin represses entry into the endocycle. Since this early onset of the endocycle was partially suppressed by the overexpression of CYCA2;3, auxin appears to maintain the mitotic state of cells by upregulating CDK activity.

A SUMO E3 ligase, HIGH PLOIDY2 (HPY2), is expressed in the root meristem, and its expression gradually decreases as cells leave the mitotic cycle and enter the endocycle (Ishida et al., 2009). An *hpy2* mutant shows the early onset of the endocycle and expresses very low levels of CDKB1 and CDKB2. These results demonstrate that HPY2-mediated protein SUMOylation is important in maintaining the mitotic state of cells and in repressing the endocycle. A graded distribution of auxin and the auxin-inducible AP2 transcription factor PLETHORA (PLT) may define the expression domain of HPY2 and repress premature entry into the endocycle (Galinha et al., 2007; Ishida et al., 2009).

In addition to auxin, other plant hormones, e.g., cytokinin and gibberellin (GA), also coordinate cell division and cell differentiation in the root meristem (Dello Inio et al., 2007; Achard et al., 2009; Ubeda-Tomás et al., 2009). Since the actions of these plant hormones crosstalk with the signaling mechanisms underlying the auxin response (Fu and Harberd, 2003; Dello Inio et al., 2008; Ruzicka et al., 2009; Moubayidin et al., 2010), they also affect the transition into the endocycle (Ishida et al., 2010). Furthermore, recently identified secreted small peptides, root meristem growth factors (RGFs), could be additional important regulators because they show a graded expression pattern in the root meristem with maxima in the stem cell region; in addition, they positively regulate the meristematic cell population by promoting the expression of PLT (Matsuzaki et al., 2010).

4. Regulation of the Cell Cycle by Internal and External Stimuli

4.1 DNA damage checkpoint

Because of their sessile lifestyle and their dependence on sunlight for photosynthesis, plants cannot evade genotoxic ultraviolet (UV) radiation or other threats to the integrity of their genomes. DNA damage can be induced not only by exposure to environmental stress, e.g., UV radiation and genotoxic compounds, but also by endogenous factors, e.g., replication errors and reactive oxygen intermediates (Ciccia and Elledge, 2010). Therefore, all organisms deploy defense mechanisms to operate signal transduction pathways that enable damaged cells to repair their DNA and to recover from the emergent state. To faithfully repair damaged DNA, cells must coordinate DNA repair with cell cycle progression by delaying or even arresting the cell cycle until the damage is completely repaired. This is called the DNA damage checkpoint (Fig. 3).

4.1.1 ATM, ATR, and SOG1

The DNA damage checkpoint in plants is largely unexplored. Although some factors that sense DNA damage are conserved among fungi, animals, and plants, most of the signal transducers identified in fungi and animals are not conserved in plants (Cools and De Veylder, 2009). This leads to the hypothesis that plants have specific DNA damage checkpoint mechanisms that support their different lifestyle and cellular events.

The conserved protein kinases ataxia telangiectasia mutated (ATM) and ATM and Rad3-related (ATR) transmit DNA damage signals to cellular events by phosphorylating several key proteins. Generally, DNA double-strand breaks (DSBs)

activate ATM, whereas ATR is activated in response to single stranded DNA, which is generated as a repair intermediate or by replication arrest. An *A. thaliana atm* mutant shows hypersensitivity to gamma irradiation and the DNA-alkylating agent methyl methanesulfonate and defects in meiosis (Garcia et al., 2003). On the other hand, an *atr* mutant is hypersensitive to hydroxyurea (HU), aphidicolin, and UV-B, which block DNA replication, whereas it shows only mild sensitivity to gamma irradiation (Culligan et al., 2004). These results indicate that the functional differentiation of ATM and ATR are essentially conserved between animals and plants.

In animals, the p53 transcription factor governs most of the molecular events in the DNA damage response. After DNA damage, activated ATM and ATR phosphorylate and activate Chk2 and Chk1 kinases, respectively, and these active kinases then phosphorylate p53, leading to its stabilization and nuclear accumulation (Rozan and El-Diery, 2007). As a consequence, p53 actively transcribes many genes that regulate DNA repair, cell cycle delay, and apoptosis.

Although phosphorylation targets of ATM and ATR, e.g., Chk1, Chk2, and p53 homologs, have not been identified in plants, the participation of a central regulator in the DNA damage checkpoint was uncovered by the identification of the NAC-domain-containing transcription factor SOG1 (Yoshiyama et al., 2009). After gamma irradiation, the transcript levels of hundreds of genes (for DNA repair- and cell cycle-related proteins) are rapidly elevated, and this upregulation is mostly dependent on *ATM* and *SOG1*, but not on *ATR* (Culligan et al., 2006). A *sog1* mutant fails to arrest leaf development after gamma-irradiation, which emerges in DNA repair-deficient *xpf* mutant backgrounds, and this phenotype is shared with an *atr* mutant, but not with an *atm* mutant. These results suggest that SOG1 has a role in ATM- and ATR-dependent

pathways; therefore, it may be a functional homolog of p53 and controls a broad transcriptional response to DNA damage.

4.1.2 Cell cycle regulators

To delay or arrest the cell cycle upon DNA damage, CDK activity needs to be downregulated. In animals, the ATM-Chk2 and ATR-Chk1 pathways phosphorylate Cdc25 phosphatase, leading to its degradation or sequestration from the nucleus. In addition, ATM and ATR prevent the degradation of Wee1 kinase until DNA repair is completed; thus, CDKs are inactivated by inhibitory phosphorylation (Harper and Elledge, 2007). However, this mechanism is unlikely to function in plants because Chk1, Chk2, and Cdc25 homologs have not been identified.

WEE1 is rapidly transcriptionally upregulated after DNA damage treatment in *A. thaliana* (De Schutter et al., 2007). The upregulation of *WEE1* mRNA levels in response to gamma irradiation is dependent on *ATM*, whereas it is *ATR*-dependent during DNA replication stress. A loss-of-function *wee1* mutant is hypersensitive to HU and aphidicolin, which impair DNA replication. In addition, a double mutant for *wee1* and DNA replication-deficient *e2f target gene 1* (*etg1*) exhibits severely retarded growth, which is nearly identical to the phenotype of an *atr etg1* double mutant (Takahashi et al., 2008). These results suggest that WEE1 functions in the response to DNA replication stress downstream of ATR. However, a *wee1* mutant and a non-phosphorylatable *cdka;1* (T14V, Y15F) mutant show different responses to HU; namely, the sensitivity of *cdka;1* (T14V, Y15F) to HU is the same as that of the wild-type (Dissmeyer et al., 2009). Therefore, WEE1 seems to confer tolerance to DNA

replication stress independently of the inhibitory phosphorylation of CDKA;1. It is possible that WEE1 phosphorylates proteins other than CDKA;1 to preserve cellular and meristem integrity after DNA replication stress.

Some genes encoding the SIM and SMR CDK-inhibitor families are strongly upregulated by gamma irradiation (Culligan et al., 2006). This rapid and strong upregulation is dependent on ATM. Although a role for this group of CDK inhibitors in the cell cycle checkpoint has not been demonstrated, it might have an inhibitory function on CDKs in response to DNA damage.

Although the expression levels of several mitotic cyclin or CDK genes is decreased after DNA damage treatment, *CYCB1;1* expression is rapidly and strongly upregulated after gamma irradiation (Culligan et al., 2006; Ricaud et al., 2007). This upregulation is due to transcriptional activation and posttranslational stabilization, which are mainly dependent on ATM and ATR, respectively (Culligan et al., 2006). The increased expression of *CYCB1;1* was also observed in several *A. thaliana* mutants that constitutively accumulate DNA damage, even in non-dividing cells (Suzuki et al., 2005; Inagaki et al., 2006; Breuer et al., 2007; Kirik et al., 2007; Takahashi et al., 2008). However, these mutants vary in their cell cycle-related phenotypes, e.g., some promoted entry into the endocycle, and others had reduced DNA ploidy levels. Therefore, the role of *CYCB1;1* in the DNA damage response is currently enigmatic. It might act as a counterpoise against the downregulation of other mitotic genes and participate in the control of cell cycle restart after the completion of DNA repair.

4.2 Phytohormones and the cell cycle

Plant development is highly adaptive to environmental conditions, e.g., light, nutrient or water availability, temperature, and other stresses. Several phytohormones control plant growth and development in response to external signals by regulating cell proliferation and expansion. Some of them control meristem function and organogenesis, which involve the regulation of cell division. Considerable progress has been made on characterizing the molecular mechanisms that underlie the modulation of hormone levels or distribution in response to developmental or environmental cues and the crosstalk between different hormonal signals (Wolters and Jürgens, 2009). However, it is largely unknown how these hormones regulate cell cycle progression at the molecular level.

Auxin, cytokinin, GA, and brassinosteroid are the phytohormones that regulate plant growth and development. Among them, auxin and cytokinin were classically identified as hormones that stimulate cell proliferation; the exogenous application of auxin and cytokinin is essential for callus formation in explants (Skoog and Miller, 1957). Recently, it was shown that the localized accumulation of endogenous auxin and cytokinin is crucial for controlled cell proliferation in root and shoot apical meristems, respectively (Blilou et al., 2005; Miyawaki et al., 2006).

Auxin is required for the culture of tobacco BY-2 cells. It was shown that the addition of auxin stabilizes the E2Fb protein (Magyar et al., 2005), while coexpression of E2Fb with DPa can stimulate cell proliferation and inhibit cell expansion in the absence of auxin by promoting entry into the S and M phases. These results suggest that auxin regulates cell division by controlling the protein level of E2Fb.

During lateral root development, mitotically silent pericycle cells initiate cell division after receiving auxin signals. Successive treatments with an auxin transport

inhibitor and auxin synchronously induce lateral root formation (Himanen et al., 2002). In this system, the expression of many cell cycle regulators is differently regulated after auxin treatment. A number of G2/M genes are upregulated at 6 h after auxin treatment, indicating that auxin stimulates cell cycle re-entry in pericycle cells. Interestingly, within 1.5 h of auxin treatment, the expression of KRP2 is strongly reduced. The overexpression of *KRP2* reduces the number of lateral roots (Himanen et al., 2002), and a loss-of-function *krp2* mutant has increased lateral root density (Sanz et al., 2011). Therefore, the downregulation of KRP2 and possibly other KRPs may promote lateral root initiation, suggesting a role for KRPs in connecting the auxin signal with cell cycle control.

Although the application of exogenous auxin and cytokinin at appropriate concentrations induces callus formation in plant tissues, a *proporz1* (*prz1*) mutant for the transcriptional adaptor protein PRZ1/AtADA2b forms callus-like tissue in the presence of either auxin or cytokinin (Sieberer et al., 2003). Upon callus formation, this *prz1* mutant shows altered expression of a number of cell cycle-related genes, e.g., *KRP2*, *KRP3*, and *KRP7* expression is decreased as compared to wild-type (Sieberer et al., 2003). Interestingly, the overexpression of *KRP7* partially rescues the developmental phenotype of *prz1* (Moulinier et al., 2010). Conversely, antisense suppression of multiple *KRP* genes, including *KRP2*, *KRP3*, and *KRP7*, in wild-type plants leads to abnormal plant development and the generation of callus-like tissue in the absence of exogenous phytohormones. As the yeast homolog of PRZ1/AtADA2b is a subunit of Spt-Ada-Gcn5-Acetyltransferase (SAGA), which controls histone acetylation, PRZ1/AtADA2b may control the expression of cell cycle regulators, e.g., *KRPs*, by regulating the histone acetylation of target loci, thereby regulating cell proliferation.

Cytokinin elevates the expression of *CYCD3;1* in cultured cells and *A. thaliana* plants, and its overexpression induces callus formation in explants in the absence of cytokinin (Riou-Khamlichi et al., 1999). Therefore, cytokinin is suggested to stimulate dedifferentiation and cell cycle entry through the transcriptional induction of *CYCD3*. A triple mutant for *CYCD3;1–CYCD3;3* had reduced cell numbers and increased cell size in the lateral organs of the shoot (Dewitte et al., 2007). This *CYCD3* triple mutant generates shoot apical meristem with a reduced cell number as compared with wild-type, and shows a reduced number of branching and axillary shoots, which are remarkably similar phenotypes to those observed in plants with reduced cytokinin levels (Werner et al., 2003; Dewitte et al., 2007). The endogenous cytokinin level is normal, but the cytokinin response in callus formation is impaired in *cycd3;1-3*, suggesting that the *CYCD3* genes are the key targets of cytokinin that promote cell division. *CYCD3* expression was also upregulated by brassinosteroid (Hu et al., 2000), but its physiological relevance has not yet been uncovered.

The AP2 family transcription factor AINTEGUMENTA (ANT) also coordinates cell proliferation and phytohormone signals. The overexpression of *ANT* produces larger organs in shoots by extending the period of cell proliferation and organ growth (Mizukami and Fischer, 2000). The expression of *ANT* is higher in proliferating organs, and *ANT*-overexpressing plants continue to express *CYCD3;1*, even in mature leaves, suggesting that ANT maintains cell division in growing organs (Elliott et al., 1996; Mizukami and Fischer, 2000). The auxin-inducible gene *AUXIN-REGULATED GENE INVOLVED IN ORGAN SIZE* (*ARGOS*) acts upstream of *ANT* and positively controls cell number and organ size (Hu et al., 2003), indicating a role for CYCD3 as a molecular

link between auxin and cytokinin signaling in the regulation of cell proliferation and organ development.

GA regulates cell proliferation and cell expansion in response to environmental changes (Achard et al., 2006). GA acts by promoting the destruction of DELLA proteins, which restrain cell proliferation and expansion (Itoh et al., 2008). In a GA-deficient *ga1* mutant, the rate of cell production is decreased in the leaves and roots, and this phenotype is suppressed by the quadruple loss-of-function mutations in the DELLA proteins (*gai*, *rga*, *rgl1*, and *rgl2*) (Achard et al., 2009; Ubeda-Tomas et al., 2009). The expression of *KRP2*, *SIM*, *SMR1*, and *SMR2* is elevated in *ga1* plants, and this is suppressed by the quadruple-DELLA mutant (Achard et al., 2009), suggesting that these CDK inhibitors might regulate the cell division rate under the control of the GA-DELLA module. Interestingly, auxin was shown to be necessary for the GA-mediated degradation of the DELLA proteins (Fu and Harberd, 2003), suggesting another pathway by which auxin promotes cell proliferation.

4.3 Developmental control of the cell cycle

Cell division and differentiation need to be fine-tuned in the developmental context to accomplish highly ordered morphogenesis. The understanding of the molecular mechanisms that control plant cell cycle progression in a particular developmental process has been advanced in the last few years. The existence of exceptionally large numbers of cell cycle-related genes implies that many of them act as “specialists” in each process.

Germination is the process in which the dormant embryo starts to grow by cell expansion and cell division. During germination, cells shift from the quiescent state (at G1 in *A. thaliana*) to the proliferative state by the concomitant upregulation of many cell cycle regulators in a highly ordered manner (Masubelele et al., 2005). Among them, 9 of the 10 *CYCD* genes are differentially upregulated. Loss-of-function mutants for *CYCD1;1* and *CYCD4;1* exhibit a delay in starting cell proliferation in the germinating root meristem, but the extent of the delay is different between these 2 mutants, suggesting non-redundant functions of these CYCDs in cell cycle entry during germination.

In the root apical meristem, the well-characterized transcription factors SHOOTROOT (SHR) and SCARECROW (SCR) regulate the formative asymmetric division of ground tissue stem cells, which generates cortex and endodermis cells (Helariutta et al., 2000; Heidstra et al., 2004). Using cell type-specific transcriptomic analysis and ChIP-chip analysis, *CYCD6;1* was identified as a direct target of SHR and SCR (Sozzani et al., 2010a). The expression of *CYCD6;1* is specific to ground tissue stem cells, and its loss-of-function mutant exhibits defects in their formative division. Since the SHR/SCR-independent expression of *CYCD6;1* in ground tissue cells can induce their formative division in an *shr* mutant, SHR and SCR are suggested to regulate the specific asymmetric cell division, at least in part, by upregulating *CYCD6;1* (Sozzani et al., 2010a).

During post-embryonic root development, the expression of *CYCD4;1* is specific to the pericycle cells adjacent to the xylem poles in the meristematic region, which later initiate lateral root formation (Nieuwland et al., 2009). A *cycd4;1* mutant has low cell division activity in the pericycle, leading to a decrease in lateral root density, but this

does not affect cell division in the other cell files. It was also revealed that sucrose enhances lateral root formation, in part, by upregulating *CYCD4;1* expression. Although it is currently unknown how cell division in meristematic pericycle cells controls the frequency of lateral root formation, it is intriguing that nutrient-controlled lateral root density is mediated by the control of a specific cell cycle regulator.

During leaf formation, a pair of guard cells is generated through a well-coordinated pattern of cell division in the stomatal lineage. The expression of *CDKB1;1* in cotyledons is specific to the stomatal lineage. The overexpression of dominant-negative CDKB1;1 (N161) resulted in a decrease of the total cell number and proportion of guard cells in cotyledons and leaves (Boudolf et al., 2004a). Although guard cells usually have a DNA ploidy of 2C, ~50% of the stomata in cotyledons of CDKB1;1 (N161) plants have an aberrant morphology with 4C nuclei as a result of the failure in the symmetric division of the guard mother cell. A recent report demonstrated that stomatal cell division is terminated via the negative regulation of CDKB1;1 by the 2 MYB transcription factors FOUR LIPS (FLP) and MYB88 (Xie et al., 2010). Therefore *CDKB1;1* may have a specific role in controlling the symmetric division of guard mother cell at the final step of the stomatal developmental pathway.

Both *cycd4;1* and *cycd4;2* mutants show reduced number of non-protruding cells in hypocotyls (Kono et al., 2007). Stomata are formed in the non-protruding cell file; thus, the number of stomata was decreased in the mutant hypocotyls. Conversely, their overexpression increased the number of non-protruding cells and stomata. However, in leaves, single and double mutants for *CYCD4;1* and *CYCD4;2* or their overexpression do not significantly affect cell division in the stomatal lineage, suggesting that different mechanisms control stomatal cell division between the leaves and hypocotyls.

5. Concluding Remarks

Considerable efforts have been made to understand the control of cell division in plant development; however, we are still far from a comprehensive understanding of the highly plastic regulation of plant development. Recent highlights are the demonstration of the direct control of cell cycle-related genes by transcription factors, e.g., SHR-SCR and FLP-MYB88, which play a major role in cell fate determination and cell differentiation. Although the spatiotemporal regulation of the cell cycle is not solely dependent on transcriptional control, the future identification of upstream transcriptional factors acting on the promoters of cell cycle-related genes would provide further insights into the developmental control of the cell cycle. An understanding of the mechanisms underlying the transition from the mitotic cell cycle to the endocycle is also important to reveal the processes for cell differentiation and the control of organ size. Future studies will reveal how internal and external signals control cell cycle progression and how plants maintain proper organ development under various environmental stresses.

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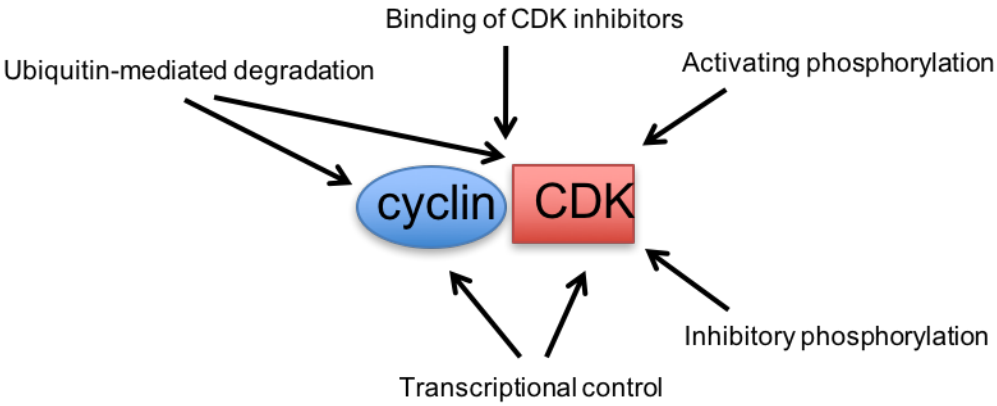
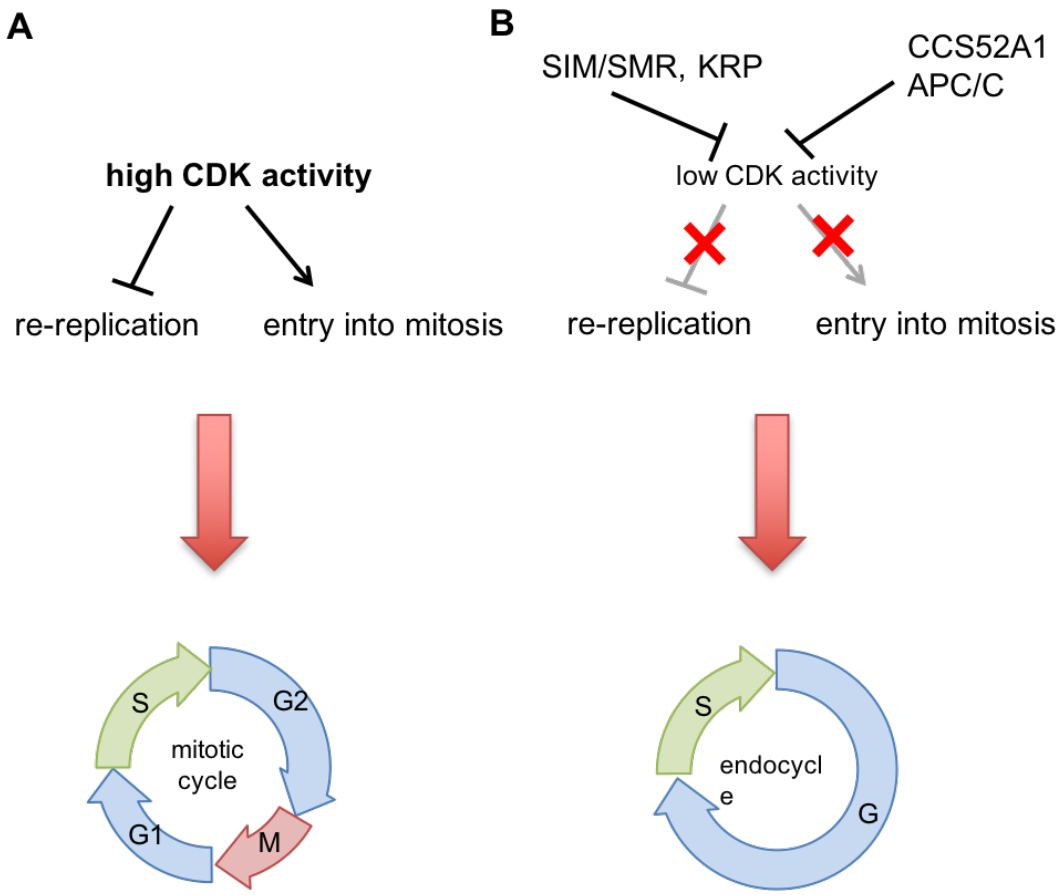
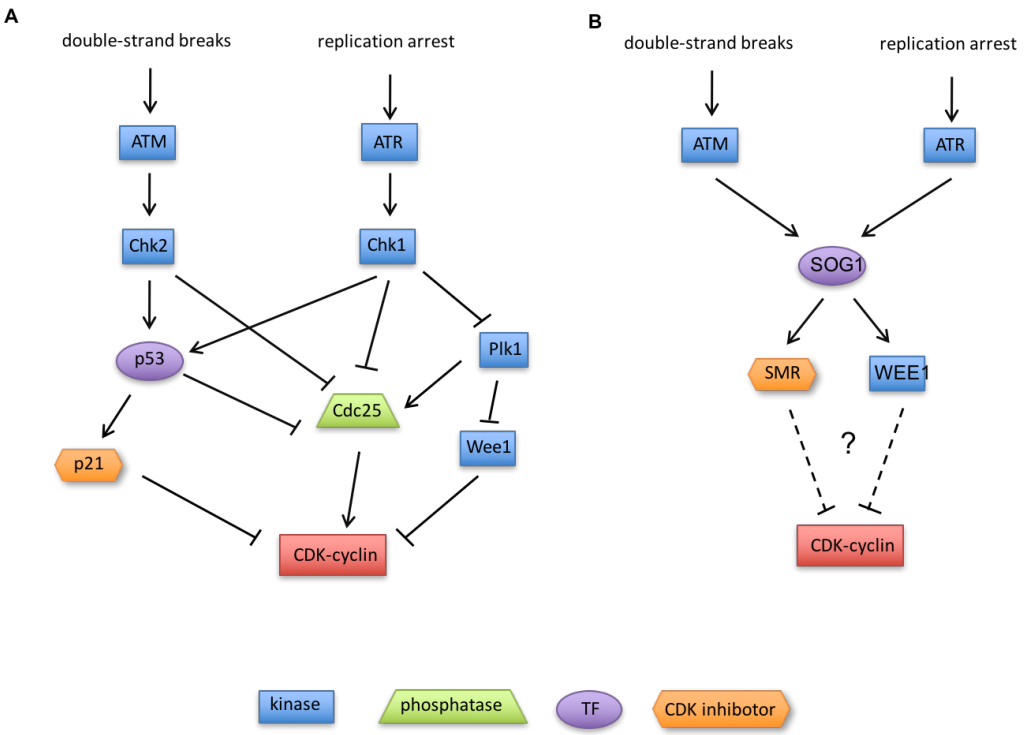


Inagaki and Umeda, Fig. 1



Inagaki and Umeda, Fig. 2



Inagaki and Umeda, Fig. 3