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Preface

The plant cell cycle in context

Plants have a distinctive mode of continuous development, involving the repeated initiation and growth of new organs throughout the lifespan of the organism. Their sessile nature means that this growth must be responsive not only to developmental cues but also to changes in the prevailing conditions. Since almost all growth ultimately derives from the process of cell division, the control of the cell cycle is at the heart of understanding patterning, growth, and development in plants. The unique features of plant development are reflected in distinct modes and molecular mechanisms of cell cycle control, using underpinning conserved control modules in distinct ways. The development of our understanding of these distinct aspects of plant cell cycle control is reviewed here.

Plants have a venerable history in cell biology, and in the study of the cell cycle in particular. The first description of cells by the 17th century polymath Robert Hooke was made from a slice of bark from the cork oak (*Quercus suber*), about which he remarked somewhat disingenuously '*The first microscopical pores I ever saw, and perhaps, that were ever seen*' (Hooke, 1665). Three centuries later, Howard and Pelc (1953; see also contextual review http://www.nature.com/celldivision/milestones/full/milestone03.html) defined the stages of the mitotic cell cycle in root tip cells of the broad bean *Vicia faba*, and these were later found to be universal in all eukaryotes. Using pulse–chase experiments, they showed the separation of DNA replication and mitosis/cytokinesis into distinct synthesis (S-phase) and mitotic (M-phase) periods, separated by gap phases known as G1 and G2, and thus giving us the well-known sequence of the cell cycle G1–S–G2–M. A considerable body of work analysing different aspects of plant cell division using cytological, histochemical, and biochemical techniques over the following 35 years laid the groundwork for molecular analysis (Bryant and Francis, 1985; Lyndon, 1990; Inzé, 2007; Bryant, 2014, this volume).

Since the cloning of the first plant genes in the early 1990s (Feiler and Jacobs, 1990; Ferreira *et al.*, 1991; Hirt *et al.*, 1991), the plant cell cycle has become a subject of wide study, in particular, becoming an important system for understanding the relationship between cell cycle control and development on the one hand and with hormonal and environmental signals on the other. The papers in this volume amply illustrate the advances made in these areas and underline the increasing sophistication of research in the plant cell cycle field. The purpose of this preface is to give a outline of the development of our understanding of the plant cell cycle in the context of the papers in this issue. In addition, there have been other excellent comprehensive reviews in the recent literature of the mitotic cell cycle (de Veylder *et al.*, 2007; Gutierrez, 2009), endocycle control (de Veylder *et al.*, 2011), and the meiotic cell cycle (Wijnker and Schnittger, 2013). A brief introductory overview is provided here with a focus around the key questions of how and why the plant cell cycle is distinctive, considered in greater breadth by Harashima *et al.* (2013).

Cyclin-dependent kinases: a universal feature

There is a prevailing view that the cell cycle is conserved in all eukaryotes, particularly across the higher eukaryotes. In a broad brush view, this is true, in that there is always a separation of a distinct S-phase, and the four ordered phases of the mitotic cell cycle are almost universal—although even here there are exceptions in specialized cell types or situations such as the very rapid cycles of early animal embryos which frequently lack a G1 phase. Many of the molecular players and mechanisms are also conserved, particularly the role of cyclin-dependent kinase (CDK) activity in controlling transitions from one phase to another. The CDK catalytic subunit requires association with a cyclin and then activation by further phosphorylation for full activity. This provides for multiple levels of potential regulation of CDK activity, particularly through regulated cyclin protein synthesis and destruction, CDK–cyclin complex assembly, inhibitory and activating phosphorylation, and the binding of inhibitory proteins. All these aspects are conserved in outline, including the use of different cyclins at different times in the cell cycle. CDK activity controls progression and links together multiple cellular processes that must be co-ordinated to achieve replication, segregation, and cell division itself. As a result the cell cycle can be regarded as an oscillator of CDK activity, with low activity in the G1 phase and a peak during mitosis (Coudreuse and Nurse, 2010). This oscillator is driven by regulated

synthesis, but of particular importance is the timely proteolysis of components through the ubiquitin-mediated selective protein degradation proteasome system at specific points in the cycle (Genshick *et al.*, 2014, this volume). Indeed exit from mitosis and return to the ground state in G1 requires loss of CDK activity through the destruction of cyclins.

The cloning of the human CDK by functional complementation of the equivalent yeast mutant (Lee and Nurse, 1987) strikingly illustrated the strong conservation of at least the key regulators and this was followed by the identification of human and later *Arabidopsis* G1 (D-type) cyclins by functional complementation of an engineered yeast mutant (Xiong *et al.*, 1991; Soni *et al.*, 1995). The first few years of molecular cloning studies of the plant cell cycle thus identified many of the plant cell cycle regulators through DNA homology or conserved function, a process completed when the *Arabidopsis* genome sequence became available. The use of these approaches tended to emphasize conservation of both sequence and function. New screening approaches for interactors of these core regulators are now revealing more of the interplay with plant specific factors (Blomme *et al.*, 2014, this volume).

Cloning and sequence analysis thus showed that plants (and *Arabidopsis* is used here as the example) contain two main types of CDK involved in primary control of the mitotic cell cycle. The first of these is a CDK closely related to the 'universal' CDK of yeasts (Cdc28 in *Saccharomyces cerevisiae* and Cdc2 in *Schizosaccharomyces pombe*) and animals, where it is called CDK1. These proteins all contain the conserved amino acid sequence PSTAIRE in their cyclin-binding domain. However, other plant CDKs did not show strong homology to CDK types in other organisms and, for this reason, the plant CDKs were named using letter suffixes (Joubes *et al.*, 2000). Hence plant CDKA is equivalent and functionally interchangeable with CDK1, Cdc28, and Cdc2, whereas plant CDKBs are distinctive in their sequence having either PPTALRE or PPTTLRE.

The CDKBs are present in higher plants in two sub-types called CDKB1 and CDKB2, both represented by two genes in *Arabidopsis* (CDKB1;1, CDKB1;2, CDKB2;1, and CDKB2;2), in contrast to the single CDKA;1 gene. The remarkable feature of the CDKB genes is that they are expressed only in mitotic cells, from the S-phase until the M-phase. The CDKB1 genes are expressed from S phase and peak in G2, whereas the CDKB2 genes are expressed somewhat later from G2–M (Menges *et al.*, 2005). Such cell-cycle-regulated expression is conventionally associated with the cyclin subunit of CDK–cyclin complexes (cyclins being so called because they are unstable proteins that oscillate in abundance) rather than CDKs, and this cell cycle regulation is a unique feature of the plant-specific CDKB class of CDKs. As a result, expression in intact plant tissues is 'spotty', with signal only being present in cells at theses stages of the mitotic cell cycle. By contrast, CDKA is rather broadly expressed, both in plant tissues and during the cycle.

Why do plants possess a mitotic-specific CDK showing highly regulated expression? The most likely explanation is connected to the prevalence of an alternative cell cycle in plant development, known as the endocycle which is characterized by endoreduplication (or endoreplication) of DNA. Endoreduplication results from S-phase without a following mitosis (i.e. a Gap phase–S-phase cycle) and, therefore, gives rise to a doubling of nuclear DNA content through the complete replication of chromosomes which can be repeated several times. Endoreduplication is a widespread feature associated with tissue and organ growth in most plants (de Veylder *et al.*, 2011). Plant growth is continuous and associated with the repeated formation of new organs, such as leaves and flowers. This occurs on the flanks of the shoot meristem, where the initiation of a new organ is accompanied by rapid cell division which generates the majority of the cells that will comprise the organ (Carraro *et al.*, 2006). Mitotic cycles giving rise to cell division are therefore primarily concentrated in meristematic regions, such as at the tips of growing shoots and roots. As the organ becomes more distant from the meristem due to its further growth, division reduces and cell expansion and differentiation occurs (Andriankaja *et al.*, 2012). These processes actually account for most of the growth of the organ and are accompanied in many cell types by endoreduplication of one or more rounds (generating nuclei of >4C). This process is of particular importance in fruit growth, as reviewed by Chevalier *et al.* (2014, this volume) for the tomato model system. An additional correlation is also seen with UV tolerance, as suggested by Gegas *et al.* (2014, this volume). As a consequence of the importance of endoreduplication, the switch from the mitotic to the endocycle is an important feature of cell cycle control in plants. At the molecular level, this occurs through the inactivation of mitosis-promoting factors from the cell cycle, and CDKB1 appears to play the most important role: in its presence, the cycle leads to mitosis whereas, in its absence, an endocycle results (Boudolf *et al.*, 2004, 2009). One view is thus that the endocycle is the default cycle and that mitosis requires the addition of the mitotic factors represented by CDKB. Alternatively, the control of cell cycle phase transitions can be viewed in terms of different thresholds of CDK activity as proposed by Coudreuse and Nurse (2010) who showed that, in yeast, there was a lower threshold for DNA synthesis (G1/S) and a higher threshold for mitosis (G2/M). Hence de Veylder *et al.* (2011) proposed that, in a mitotically active cell, CDK activity must pass the required threshold level for DNA replication and the higher level need for mitosis. For endocycles, however, CDK activity must exceed the lower threshold required for DNA synthesis, but must not be so high that mitosis is triggered (de Veylder *et al.*, 2011). In this view, the main role of CDKB is to provide additional kinase activity rather than acting as a specific mitotic factor.

G1-to-S-phase control and the initiation of DNA replication

Different cyclin types are involved in controlling different stages of the cell cycle, providing both specificity of regulation and the potential to target different substrates. Specifically, different cyclins are characteristically expressed and important in G1 phase, G1-to-S-phase and G2-to-M-phase control (Figure 1). When *Arabidopsis* G1 cyclins were identified, it was a major surprise that they contained, near their N-terminus, a short sequence comprising LXCXE (X=any amino acid) that had already been identified in

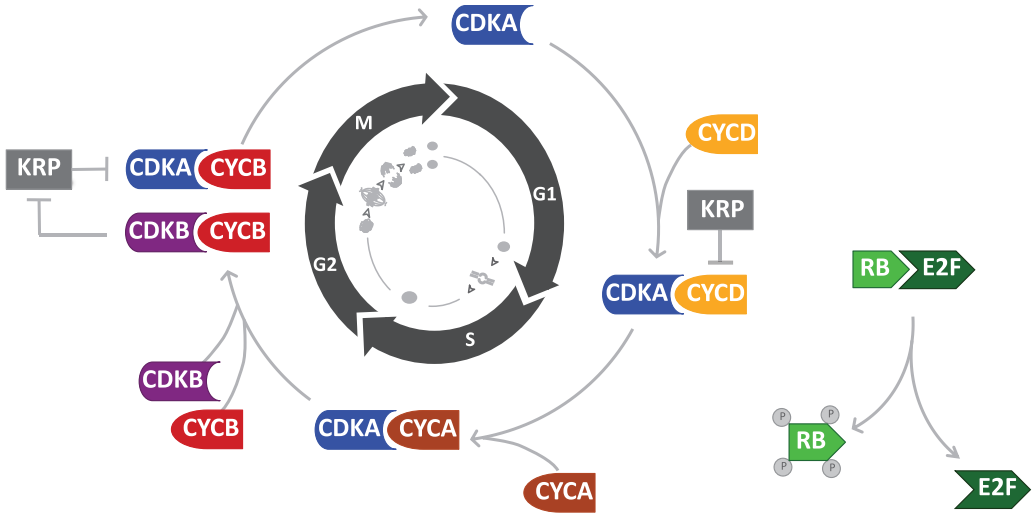

Fig. 1. Simplified view of the plant cell cycle. Progression from G1 phase is initiated through the phosphorylation of the RBR protein by CDKA, which is activated by the binding of D-type cyclins (CYCD). KRP proteins can bind to both CYCD and CDKA subunits and inhibit the kinase activity of the complex. A-type cyclins associate with CDKA (and probably CDKB1; not shown) during S-phase. Mitosis-specific CDKB (of two types CDKB1 and CDKB2) along with B-type cyclins (CYCB) are required for mitosis. KRP proteins can be phosphorylated and inactivated by CDKB kinase activity, further increasing CDK activity levels in mitosis (Boudolf *et al.*, 2004).

mammalian G1 cyclins (called D-type cyclins) and shown to be responsible for interacting with a tumour-suppressing protein called the retinoblastoma protein (RB). RB in humans is a member of a small family of three proteins that share a so-called pocket domain and that have various roles in suppressing cell division and promoting both differentiation and quiescence in different situations (Dick and Rubin, 2013). One major mechanism of pocket protein function is to bind a class of transcription factors known as E2F (actually a heterodimer of E2F and DP subunits), which promote the expression of genes required for cell cycle progression from G1 into S-phase. The binding of RB through its pocket domain to E2F blocks its transcriptional activation potential and can turn it from a transcriptional activator into a repressor. Hence progression through the G1/S boundary requires the activation of E2F which, in turn, necessitates RB removal. This occurs through RB phosphorylation by cyclin D-CDKs (in mammals CDK4 and CDK6 associated with cyclin D), targeted to the pocket domain by the LXCXE motif of cyclin D (van den Heuvel and Dyson, 2008).

The finding of RB binding proteins, followed shortly by the identification of retinoblastoma-related proteins (RBR) in plants was a major surprise, since, at that time, they had not been found outside mammals to which they were generally considered to be limited, neither were they found in yeasts or other fungi. Rather this pathway involving cyclin D–RB–E2F is a characteristic of the higher eukaryotic lineages, including algae and microalgae (diatoms) (Bišová and Zachleder, 2014, this volume; Huysman *et al.*, 2014, this volume).

This pathway is utilized by DNA viruses that require host DNA polymerases to replicate their genome. In mammals, these include the DNA tumour viruses such as human papillomavirus (causing cervical cancer), adenovirus, and simian virus 40 (SV40; Giacinti and Giordano, 2006). All these tumour viruses encode proteins essential for tumourgenicity that carry an LXCXE motif and inactivate RB to drive cells into S-phase and proliferation. Plant gemini viruses, many of which have important agricultural impacts, particularly in tropical regions, also encode proteins with LXCXE motifs that are essential for replication and inactivate RBR and push cells into S-phase (Hanley-Bowdoin *et al.*, 2013).

In mammals, the phosphorylation of RB is started by cyclin D–CDK4/6 but completed by another cyclin–CDK combination of cyclin E–CDK2. Cyclin D and cyclin E of mammals are fundamentally different in their regulation and role. Cyclin D genes are expressed in response to external signals, such as growth factors, and are very unstable proteins. However, they do not alter much in abundance during the cell cycle. As such, they act as sensors of conditions promoting cell division. Their activity leads to the phosphorylation of RB and the cell passes through a point known as the restriction (R) point (equivalent to a more obviously named point START in yeast), beyond which the cell becomes committed to the cell cycle because the activation of E2F is sufficient to switch on one of its key targets: cyclin E. The rising levels of cyclin E lead to more RB phosphorylation and hence E2F activity in a positive feedback loop. Cyclin E, therefore, is activated as an E2F target, accumulates at the G1-to-S phase transition and is then destroyed later in S-phase, therefore showing a characteristic cyclic behaviour (Woo and Poon, 2003).

Hence, in plants, RBR plays key roles in cell proliferation control and, it has more recently emerged, in controlling symmetry of division (Desvoyes *et al.*, 2014, this volume). It should also be appreciated that RB and RBR play wider roles than simply regulation of E2F factors, in particular, in association with chromatin assembly and modification factors (Kuwabara and Gruissem, 2014, this volume).

In plants, the G1 cyclins are represented by a much larger group of genes than the three present in mammals. All higher plants have six conserved sub-groups of cyclin D genes, named CYCD1–CYCD7 (the CYCD2 and CYCD4 subgroups cannot

be distinguished on the basis of sequence homology) (Menges *et al.*, 2007). There are ten genes in *Arabidopsis*, with three members in the CYCD3 subgroup and two in CYCD4. Other plants have different numbers of genes in each subgroup. As in animals, some of these genes have been shown to respond to external signals, both hormonal and developmental. For example, CYCD2 and the related CYCD4;1 respond to sucrose availability and levels (Riou-Khamlichi *et al.*, 2000; Nieuwland *et al.*, 2009) and CYCD3 genes mediate responses to the key phytohormone cytokinin in the cell cycle (Riou-Khamlichi *et al.*, 1999; Dewitte *et al.*, 2007). Other CYCD genes have been shown to be directly regulated by transcription factors known to have key developmental roles; for example, CYCD6;1 is regulated by *SHORTROOT* (Sozzani *et al.*, 2010), which acts with a second factor *SCARECROW* that itself binds and regulates RBR through an LXCXE motif to provide feedback regulation (Cruz-Ramirez *et al.*, 2012). These data, combined with the specific expression patterns of different CYCD during development (Collins *et al.*, 2012), are consistent with the larger number of CYCD genes compared with animals being linked to the greater significance for environmental and developmental regulation of the plant cell cycle. Plants, however, lack cyclin E, and its place may be taken by CYCD3 which is rate-limiting for the G1/S transition in mitotic cycles (Menges *et al.*, 2007). It is, however, important to note that CYCD genes are not expressed in endocycling cells, in which S-phase entry still requires RB/RBR inactivation and E2F activity. In *Drosophila*, this is controlled by cyclin E; in plants, probably by a type of cyclin A which in both animals and plants is expressed and active in the S-phase.

The onset of the S-phase is marked by the firing of DNA replication origins which, in yeast and mammals, absolutely requires both the G1/S CDK activity and a second dimeric kinase called CDC7/DBF4. Plants have not been found to have CDC7/DBF4 and what may play its role is unknown [see Bryant, 2014, this volume, for a discussion of DNA polymerases, and Bass *et al.* (2014, this volume) for new methods for analysing the structural and temporal programme of DNA replication in maize]. It is also now increasingly appreciated that S-phase involves not only DNA replication, but also the reassembly of chromatin and its associated modifications and marks onto replicated DNA (Raynaud *et al.*, 2014, this volume).

G2-to-M-phase control

The G2 and M-phases of the cell cycle mark the distinction between the mitotic and endocycles, and the regulation of progression into mitosis is dependent on the accumulation of CDK activity with cyclin B. In animals, this is CDK1 but, in plants, it is primarily CDKB as discussed above due to its sharp accumulation at this point, although CDKA presuambly contributes to the overall level. CDK activity is also regulated by negative phosphorylation near its N-terminus by the WEE1 kinase which is present in plants and is important in stopping the cell cycle in response to DNA damage. In animals and yeast, removal of this inhibitory phosphate requires a specialized phosphatase known as CDC25, which is absent from plants. What fulfils this role in plants is unknown.

Inhibitors of CDK activity: Kips and Sims

CDK interacting proteins play important roles both in scaffolding CDK–cyclin interactions, and inhibiting CDK activity. In mammals, two main classes exist, the first being inhibitors of CDK4 (INK4) that function by inhibiting the association of CDK4 and cyclin D. The second are the Kip/Cip family, that inhibit kinase activity of other CDK complexes. In plants, a family of proteins (represented by seven genes in *Arabidopsis*) known as Kip-related proteins (KRPs; also as Inhibitors of CDK; ICK) share a small conserved domain with the Cip/Kip family. The KRP family appear to inhibit both CDKA and CDKB activity, and KRP2 plays a role in modulating CDKB during the transition to endocycles (Boudolf *et al.*, 2004).

A second family of plant CDK regulatory proteins is known as the SIAMESE (SIM) family (Peres *et al.*, 2007), because of the discovery of their founder member as a mutant affecting the development of leaf hairs (trichomes) in *Arabidopsis*. Trichomes are normally three-branched structures consisting of a single cell. A single endoreduplicated nucleus is found at the convergence of the branches. *Sim* mutants develop multicellular trichomes, because they fail to initiate the endoreduplication cycle (Churchman *et al.*, 2006). SIM and related SMR proteins specifically bind CDKA and CYCD and are proposed to regulate the cell cycle in response to biotic and abiotic stresses (Peres *et al.*, 2007).

The co-ordinating role of phytohormones

Most of the plant hormones described are known to interact directly or indirectly with the cell cycle and/or cell elongation/expansion, itself normally closely linked with endoreduplication as discussed above. This is reviewed in the context of root growth by Takatsuka and Umeda (2014, this volume). In particular, auxin and cytokinin have long been defined as essential for the proliferation of plant tissue in culture. Cytokinin has been shown to act in the cell cycle primarily through transcriptional regulation of the *CYCD3* genes (Riou-Khamlichi *et al.*, 1999; Dewitte *et al.*, 2007). Auxin is known to act, in part, through stabilization of the E2FB protein which promotes mitotic cycles (Magyar *et al.*, 2005), and ectopic expression of stablized E2FB is sufficient to allow cell division in culture in the absence of exogenous auxin. A second role has recently been

described for auxin in the ubquitin pathway targeting cell cycle repressors for proteolysis and thereby promoting division (del Pozo *et al.*, 2014, this volume). Further roles exist for gibberellins in both promoting division and cell expansion (Ubeda-Tomás *et al.*, 2009).

Cell growth and the cycle

Several reviews here touch on aspects relating to the link between growth of cells and the cell cycle. This linkage is particular relevant to green algae as shown by Bišová and Zachleder (2014, this volume), who explore how the complex multiple fission cycles shown by some organisms in this group may represent an adaptation to alternating light/dark periods. In higher plants, recent work has shown that the TOR kinase signalling pathway integrates with auxin signalling to connect hormonal and nutrient pathways, resulting in environmental responses in growth and division. As discussed by Henriques *et al.* (2014, this volume), downstream of TOR, S6K and the ribosomal S6 protein mediate cell growth responses, and the interplay with the cell cycle is further considered by Sablowski and Dornelas (2014, this volume).

Afterword

This short overview presents a simplified view of the plant cell cycle, focusing primarily on its comparison with mammalian cell cycles to highlight the differences, aiming to set the scene for the detailed reviews in this issue. Plants are a fascinating and versatile system to understand the adaptation of the control machinery of the cell cycle to a continuous and environmentally responsive mode of growth and to the need to co-ordinate division of neighbouring cells because of their attachment by semi-rigid cell walls. Indeed, cell division plays important roles in developmental processes and patterning (Munoz-Nortes *et al.*, 2014, this volume) and many CDK interacting proteins appear to have roles in organ growth and development (Blomme *et al.*, 2014, this volume). Engineering of plant growth and development will require a fuller understanding of these controls and their integration.

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