Regulating DNA Replication in Plants

Maria de la Paz Sanchez^{1,2,3}, Celina Costas^{1,2}, Joana Sequeira-Mendes^{1,2},
and Crisanto Gutierrez¹

¹Centro de Biología Molecular “Severo Ochoa,” CSIC-UAM, Nicolas Cabrera 1, Cantoblanco,
28049 Madrid, Spain

Correspondence: cgutierrez@cbm.uam.es

Chromosomal DNA replication in plants has requirements and constraints similar to those in other eukaryotes. However, some aspects are plant-specific. Studies of DNA replication control in plants, which have unique developmental strategies, can offer unparalleled opportunities of comparing regulatory processes with yeast and, particularly, metazoa to identify common trends and basic rules. In addition to the comparative molecular and biochemical studies, genomic studies in plants that started with *Arabidopsis thaliana* in the year 2000 have now expanded to several dozens of species. This, together with the applicability of genomic approaches and the availability of a large collection of mutants, underscores the enormous potential to study DNA replication control in a whole developing organism. Recent advances in this field with particular focus on the DNA replication proteins, the nature of replication origins and their epigenetic landscape, and the control of endoreplication will be reviewed.

Faithful genome duplication during the S phase of the cell cycle uses strategies largely conserved in all eukaryotes (DePamphilis and Bell 2011) and is pivotal to preserve genome integrity. Genome duplication in dividing plant cells has the same requirements and constraints than in animal cells, including the strict rule of occurring once and only once every cell cycle. The initial discoveries of several basic biological processes were performed in studies with plant cells, e.g., transposons, telomeres, RNA interference, to cite a few. DNA replication in eukaryotes is not an exception. Pioneering work in the mid-1950s showed the semiconservative na-

ture of chromosomal DNA replication in the common bean *Vicia faba* (Taylor et al. 1957). Since then, plant DNA replication studies have focused primarily on defining temporal patterns of DNA replication at the chromosomal level along the S phase. DNA fiber autoradiography was first used in plants to determine replicon size at the single molecule level (Nitta and Nagata 1976; Van't Hof 1976) and genome organization in early and late replicon families (Van't Hof et al. 1978; Van't Hof and Bjerknes 1981; reviewed in Bryant 2010; Costas et al. 2011a).

In this work, we will focus on: (1) plant DNA replication proteins (see also Supplemental

²These authors share the first authorship.

³Present address: Instituto de Ecología, Universidad Nacional Autónoma de México, 3er Circuito Exterior, Cd. Universitaria, México DF 04510, Mexico.

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Table 3 online); (2) plant DNA replication origins and their epigenetic landscape; (3) novel licensing mechanisms; (4) the relevance of DNA replication proteins in the control of the endoreplication cycle during plant development, and, finally; (5) a brief overview of duplication of plant DNA viruses.

DNA REPLICATION PROTEINS

The Prereplication Complex

Homologs of the major pre-RC components (ORC, CDC6, CDT1, and MCM2-7) (see Bell and Kaguni 2013) have been identified in several plant species (Gutierrez 2006; Shultz et al. 2007). Some of them, notably ORC1, CDC6, and CDT1, are encoded by duplicated genes in *Arabidopsis*. Although the coding regions of duplicated pre-RC proteins are largely conserved, their promoter regions differ considerably, suggesting that they are subjected to distinct transcriptional regulation.

ORC transcripts are abundant in cultured cells and in proliferating cells within the adult plant body. In addition, *Arabidopsis* ORC5 and ORC6 (Diaz-Trivino et al. 2005) and maize ORC3 (Witmer et al. 2003) are also expressed in nondividing cells in which they may play specific roles, still unknown, as it has been described for some metazoan ORC genes (Sasaki and Gilbert 2007). The interaction map of plant ORC subunits is also quite conserved (Witmer et al. 2003; Diaz-Trivino et al. 2005). A distinctive feature of plant ORC1 is its function as a transcriptional coactivator (Sanchez and Gutierrez 2009), contrary to the silencing role of ORC1 in yeast (Hickman and Rusche 2010). Plant ORC1 contains in its amino-terminal half a plant homeodomain (PHD) that seems to mediate interaction with trimethylated histone H3 at lysine 4 (H3K4me3) at the promoter of target genes (Sanchez and Gutierrez 2009). Interestingly, some of these ORC1-binding sites coincide with replication origins (Costas et al. 2011b), pointing to coordination between replication and transcription. It is worth noting that the Orc1 interaction with methylated histones also has been described in animals. Among the

ORC subunits in eukarya, only Orc1 has a BAH domain that mediates protein–protein interactions. The BAH domain in human Orc1 facilitates the ability of Orc1 to activate replication origins in vivo (Noguchi et al. 2006), and links H4K20me2 to DNA replication licensing and the Meier-Gorlin syndrome, primordial dwarfism that is related directly to mutations in pre-replication proteins (Bicknell et al. 2011; Kuo et al. 2012).

Plant CDC6 and CDT1 conserve the major domains of these proteins, although each of the two homologs of CDC6 and CDT1 proteins show significant divergence, in particular CDT1 (Castellano et al. 2001, 2004). Another major difference with the metazoan proteins is the absence in plants of a homolog of metazoan geminin (Gmnn), the CDT1-interacting protein that inhibits its activity (Caro and Gutierrez 2007; Miotto and Struhl 2010). Remarkably, plants contain a completely unrelated CDT1-interacting protein called GEM (GL2-EXPRESSION MODULATOR [Caro et al. 2007]). It is not known yet whether GEM has a role in DNA replication. Expression of both *CDT1a* and *CDT1b* depends on a complex regulation. Whereas both *CDT1a* and *CDT1b* are E2F targets (Castellano et al. 2004), only *CDT1a* is activated by ORC1 (Sanchez and Gutierrez 2009). Both *CDT1a* and *CDT1b* genes are also repressed by ABAP1 (ARMADILLO BTB ARABIDOPSIS PROTEIN1), a novel factor that works in association with the TCP24 transcription factor (Masuda et al. 2008).

Plant MCM2-7 proteins contain the typical conserved motifs (Sabelli et al. 1996, 1999; Stevens et al. 2002; Masuda et al. 2004; Dresselhaus et al. 2006; Shultz et al. 2009). An evolutionary conserved protein called ETG1 (for E2F TARGET1) that interacts with the MCM2-7 complex has been identified in *Arabidopsis* (Takahashi et al. 2008). ETG1 is necessary for efficient DNA replication and its absence leads to G₂ checkpoint activation and loss of chromatid cohesion, a phenotype that is enhanced in the absence of CTF18, another factor necessary for chromatid cohesion that has been confirmed in mammalian cells (Takahashi et al. 2010).

Replication Fork Assembly

MCM8, MCM9, and MCM10

MCM8 is highly conserved among eukaryotes, including *Arabidopsis*, rice, and other plants (Dresselhaus et al. 2006; Shultz et al. 2007). The major protein motifs are conserved, suggesting similar biochemical functions such as stabilization of RPA and DNA polymerase α . However, a ~ 60 amino acid stretch at the amino terminus and a ~ 20 amino acid motif, present in animal MCM8, are missing in *Arabidopsis* MCM8 (Shultz et al. 2007). Their physiological relevance, if any, remains to be determined.

Genes encoding MCM9 have been identified in several plant species (Dresselhaus et al. 2006; Shultz et al. 2007) and, frequently, they are transcribed at very low levels and in different spliced forms (Schmid et al. 2005; Shultz et al. 2007). Interestingly, plant MCM9 lacks the carboxy-terminal domain present in animal MCM9, although the functional relevance of this protein organization is not known. It must be pointed out that MCM9 is not essential for DNA replication in mammals, but the MCM8–MCM9 protein complex is involved in DNA recombination (Hartford et al. 2011; Lutzmann et al. 2012; Nishimura et al. 2012), an aspect that has not been addressed in plants.

A homolog of MCM10, a protein essential in yeast for unwinding of origin DNA and loading of DNA polymerase α (Kanke et al. 2012; van Deursen et al. 2012; Watase et al. 2012), has been identified in various plant species (Shultz et al. 2007). The degree of similarity is small compared with other replication proteins, although, remarkably, plant MCM10 conserves the CCCH-type Zn^{2+} finger that mediates its homomultimerization.

CDC45

The function of plant CDC45 is probably to serve as a switch from the pre-RC complex to the initiation complex, because *Arabidopsis* CDC45 shows a $>80\%$ similarity with *S. pombe* and human CDC45. Like in yeast and mammalian cells, *Arabidopsis* CDC45 gene expression is cell cycle regulated, showing high levels at the

G₁/S transition (Stevens et al. 2004). In spite of these similarities, its role in plant DNA replication has not been shown. *Arabidopsis* CDC45 is unable to complement a yeast *cdc45* temperature-sensitive mutant and *Arabidopsis* RNAi plant lines with reduced CDC45 transcripts did not show defects in DNA synthesis (Stevens et al. 2004).

GIN5 Complex

The genes encoding GINS subunits have been identified in the genomic sequence of *Arabidopsis*, rice, maize, and soybean, including a duplicated PSF3 gene (Gutierrez 2006; Shultz et al. 2007). Interestingly, PSF2 contains a motif conserved in vertebrate but not in yeast, reinforcing the idea of a closer evolutionary relationship between *Arabidopsis* and human proteins. The plant GINS complex has been poorly characterized biochemically, but probably in association with MCM2-7, CDC45, and DNA polymerase ϵ , participates in initiation and fork progression, like in other eukaryotes (Gambus et al. 2006; Moyer et al. 2006).

Replication Fork Progression

DNA Polymerases

Eukaryotic DNA polymerases have been grouped in five different families, of which family B contains the replicative polymerases (Johansson and Dixon 2013). Like in animals, plant replicative DNA polymerases have been classified in three-major types: DNA polymerase α (POLA), DNA polymerase δ (POLD), and DNA polymerase ϵ (POLE).

POLA

The presence of DNA polymerase α (POLA) activity in plants has been shown biochemically in maize, wheat, pea, and cauliflower (Bryant 1980; Castroviejo et al. 1990; Laquel et al. 1990; Balmukhanov et al. 1992; Bryant et al. 1992; Coello et al. 1992; Coello and Vazquez-Ramos 1995b; Garcia et al. 1997; Luque et al. 1998). More recently, the genome sequence analysis of *Arabidopsis* and

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rice allowed the identification of the four putative subunits of POLA complex (POLA1 to 4). The largest subunit (POLA1) contains the DNA polymerase activity whereas the two smallest subunits have the DNA primase activity (POLA3 and POLA4, also known as PRI1 and PRI2, respectively).

Interestingly, the *POLA1* gene, also known as *INCURVATA2* (*ICU2*), was originally identified in a genetic screen for abnormal leaf morphology and has a role in transcriptional silencing (Barrero et al. 2007; Liu et al. 2010a). The sequence features of POLA1 are conserved with the exception of a YYRRLFP motif of unknown function present in yeast and animal POLA4 subunit but not in plants (Shultz et al. 2007). Conservation of the remaining essential motifs suggests a similar function of POLA subunits in plants. In agreement with this, the plant DNA POLA complex contains a DNA polymerase activity with low processivity and a primase activity. POLA activity is regulated by phosphorylation because it increases when all subunits are phosphorylated (Coello and Vazquez-Ramos 1995a,b; Garcia et al. 1997).

POLD and POLE

Plant POLD has been described in rice, wheat, maize, and *Arabidopsis* (Richard et al. 1991; Garcia et al. 1997). The *Arabidopsis* POLD complex contains four subunits (POLD1 to D4) whereas in rice it contains five subunits (Shultz et al. 2007). Sequence analysis of *Arabidopsis*, soybean, rice, and maize indicated that the plant's largest subunits are highly conserved. The essential motif that mediates the interaction of POLD2 and POLD3 subunits with PCNA is conserved as well. The expression pattern of *POLD1* correlates with proliferative tissues and with PCNA expression (Uchiyama et al. 2002; Garcia et al. 2006). The biochemical activity of plant DNA POLD has been assessed in wheat, and also contains an associated 3'–5' exonuclease activity, which confers a proofreading ability, and is highly stimulated by PCNA (Richard et al. 1991; Laquel et al. 1993; Luque et al. 2000). Rice POLD1 and POLD2 genes are regulated by sucrose and UV treatment

(Uchiyama et al. 2002), indicating that during evolution some replication genes have become direct targets of the environmental response.

Plant POLE has been studied in *Arabidopsis* and rice, including genetic analyses that have not been performed in other multicellular organisms (Jenik et al. 2005; Ronceret et al. 2005; Yin et al. 2009; del Olmo et al. 2010). *Arabidopsis* POLE holoenzyme possesses two catalytic subunits (POLE1A and POLE1B, also called AtPOL2a and AtPOL2b), and the regulatory subunits POLE2 (or DPB2), DPB4, and DBP3a. Genetic analysis suggests that POLE1A and/or POLE2 play a crucial role in DNA replication, whereas POLE1B is not required when POLE1A is present. In fact, the catalytic activity of POLE1A is necessary during embryogenesis, floral transition, and in meristems, whereas POLE1B is expressed at detectable levels preferentially under certain stress conditions (Jenik et al. 2005; Ronceret et al. 2005). Genes encoding the POLE3 and POLE4 subunits belong to a multigenic family and are difficult to identify unambiguously in the *Arabidopsis* genome. Hypomorphic mutants of POLE1 (*esd7/abo4/till1*) show an early flowering phenotype because of changes in the expression of key flowering genes, a process that occurs through a genetic interaction of *POLE1* with *LHP1* (*LIKE-HETEROCHROMATIN PROTEIN1*) (Yin et al. 2009; del Olmo et al. 2010).

PCNA

PCNA is an essential protein, highly conserved in all eukaryotes, including plants (Suzuka et al. 1989; Kodama et al. 1991; Hata et al. 1992; Matsumoto et al. 1994; Lopez et al. 1995; Shimizu and Mori 1998; Strzalka et al. 2010). It is frequent that plant genomes contain two PCNA genes, in contrast to PCNA pseudogenes normally found in mammalian cells. Plant PCNA forms a homotrimeric complex (Sanchez et al. 2002; Strzalka et al. 2009) that binds to various cyclin–CDK complexes (Herrera et al. 2000; Sanchez et al. 2005). In agreement with the hypothesis of serving as a sliding platform to other proteins, in vitro assays showed that PCNA-associated cyclin/CDK activity phosphorylates

DNA polymerase α . Because this phosphorylation does not affect DNA polymerase activity, PCNA could recruit regulatory proteins (Gomez Roig and Vazquez-Ramos 2003). Unfortunately, a direct function on the processivity and activity of the plant DNA polymerases δ or ϵ is so far unknown. However, recombinant rice and bean PCNA stimulate human DNA polymerase δ (Matsumoto et al. 1994; Strzalka et al. 2009). In addition, two wheat DNA polymerases δ have been identified and both increase their in vitro activity and processivity when stimulated with calf thymus PCNA (Laquel et al. 1993).

The participation of plant PCNA in DNA damage processing has been shown in *Arabidopsis*. Thus, POLH (AtPol η) and POLL (AtPol λ), members of the Y and X families, respectively, interact with PCNA2 (Anderson et al. 2008; Amoroso et al. 2011) to catalyze translesion synthesis and restore replication fork progression when DNA is damaged.

RFC

All five replication factor C (RFC1–5) subunits have been identified in plants and their sequence analysis suggests that they play roles similar to other eukaryotes (Luque et al. 2002; Furukawa et al. 2003; Shultz et al. 2007; Hedglin et al. 2013). Like other DNA replication proteins, plant RFC expression occurs preferentially in proliferative tissues and is cell cycle regulated (Luque et al. 2002; Furukawa et al. 2003). RFC1 is required for replication of the ssDNA-containing wheat dwarf virus (WDV) genome to stimulate binding of the initiator Rep protein to 3'-OH containing DNA substrates (Luque et al. 2002). Besides to its role as a clamp loader, RFC1 also contributes to transcriptional gene silencing of certain genes and transposons (Liu et al. 2010b).

RPA

The eukaryotic single-stranded DNA binding (SSB) protein (RPA) is required for pre-RC activation and for ordered loading of essential initiator factors at origins (Sakaguchi et al. 2009).

Each of the three RPA subunits is encoded by several genes in plant genomes. This allows the possibility to form different species of RPA complexes (Ishibashi et al. 2006; Shultz et al. 2007). The function of these complexes remains to be determined, but, based on their localization, one complex may act in the chloroplast, whereas other complexes could participate in nuclear processes (Ishibashi et al. 2006). Moreover, studies with mutant plants revealed that *Arabidopsis* RPA1A and RPA1C (nuclear proteins) are essential for DNA replication, whereas RPA1B (chloroplast and nuclear) is not essential and is required only during DNA repair (Sakaguchi et al. 2009). Apart from its function in DNA replication, RPA2 is also required to maintain transcriptional silencing of a subset of transposon elements (Elmayan et al. 2005; Kapoor et al. 2005; Xia et al. 2006).

FEN1

The specific flap endonuclease 1 (FEN1) is conserved in plants and has been characterized so far in cauliflower, wheat, rice, and *Arabidopsis* (Kimura et al. 1997, 2000, 2003; Przykorska et al. 2004; Shultz et al. 2007). Interestingly, *Arabidopsis* has only one *FEN1* gene whereas rice possesses two. These are expressed in proliferating cells as well as in shoot and root apical meristems, but *FEN1B* is also expressed in mature organs (Kimura et al. 2000, 2003). FEN1A complements the yeast mutant strain $\Delta rad27$ (Kimura et al. 2003) and associates with PCNA, whereas FEN1B lacks a PCNA binding motif (Kimura et al. 2001), a difference that might be important for its function. The biochemical characterization of plant FEN1 indicates that this enzyme has 5' $\rightarrow$ 3'-double-strand-specific exonuclease activity and cleaves endonucleolytically at the 3' end of the unpaired region in stem-loop structures (Kimura et al. 1997, 2001).

LIG1

Plant DNA ligase 1 (LIG1) catalyzes the formation of a phosphodiester bond at single and double strand at various stages of DNA metabolism (Howell and Stern 1971; Kessler 1971).

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The *Arabidopsis* LIG1 protein can complement the *cdc9* temperature sensitive mutation in yeast and is expressed constitutively in all tissues analyzed (Taylor et al. 1998).

DNA REPLICATION ORIGINS AND THEIR EPIGENETIC LANDSCAPE

In eukaryotic organisms, there are thousands of sites scattered across the genome in which DNA replication begins (Méchali 2010; Leonard and Méchali 2013). However, the usage of all replication origins must be controlled by a strict regulatory mechanism to avoid genome instability. Origin specification, marked by the assembly of pre-RC in G₁, is the first level of regulation. All the potential origins that could be used during a particular S phase are licensed at this point. The second key step is origin firing, which occurs at the G₁/S transition and during S phase, and whereby only a small percentage of all the licensed origins become active. The strict regulation of the firing mechanism ensures that the replication of the DNA takes place once and only once per cell cycle (DePamphilis and Bell 2011).

The molecular mechanisms responsible for origin specification are only starting to be elucidated. In plants this issue is even more elusive and only during the last years significant advances have been made (Lee et al. 2010; Costas et al. 2011a; Liu and Gong 2011). An earlier approach consisted of scanning the ribosomal DNA (rDNA) region of cultured root meristem pea (*Pisum sativum*) cells to identify a replication origin within 1.5 kb at the nontranscribed spacer (NTS) of the rDNA (Van't Hof et al. 1987; Hernandez et al. 1993), a feature shared with other eukaryotes (DePamphilis and Bell 2011). These data were further confirmed by 2D-gel electrophoresis (Van't Hof and Lamm 1992). Recently, the development of genomic tools, including massive sequencing of newly synthesized DNA, yielded a genome-wide map of replication origins in *Arabidopsis* cultured cells (Costas et al. 2011b).

In multicellular organisms the DNA sequence is not sufficient for regulating the usage and function of the replication origins and other factors such as DNA methylation and epigenetic

modifications of histones may play important roles (Fig. 1). The regulation and availability of the effectors of these chromatin changes (the epigenetic modifiers such as chromatin remodeling complexes, histone chaperones and histone modification enzymes) are crucial for proper DNA replication and maintenance of genome integrity. The analysis of *Arabidopsis* origins reveals that most of them are preferentially located at the 5' ends of gene bodies and associated with highly expressed genes, as it has been described for human origins (Valenzuela et al. 2011). Additionally, they show a relatively low CG methylation whereas they are enriched in the histone variant H2A.Z (Costas et al. 2011b) and histone H3.3 (Stroud et al. 2012b). This is consistent with the depletion in CG methylation found in early and mid-S-phase replicons of *Arabidopsis* chromosome 4 (Lee et al. 2010). Moreover, the higher than average C + G content found in *Arabidopsis* origin regions (midpoint $\pm$ 100bp), associated with a low CG methylation might favor a more open chromatin that facilitates pre-RC assembly and origin activation, in agreement with results obtained in *Drosophila* (Macalpine et al. 2010) and mammalian cells (Karnani et al. 2010; Cayrou et al. 2011; Valenzuela et al. 2011).

The genome-wide maps of several histone modifications analyzed show that *Arabidopsis* origins are associated with H3K4me2, H3K4me3, and H4K5ac, and depleted of H3K4me1 and H3K9me2 (Costas et al. 2011b), a typical mark of heterochromatin in plants (Fuchs et al. 2006). Histone acetylation can affect origin specification and replication timing in other eukaryotes (Schwaiger et al. 2009; Karnani et al. 2010; Casas-Delucchi et al. 2011). In *Arabidopsis*, it is possible that acetylation in other histone residues, besides H4K5ac, is relevant for origin activation as suggested by the increase in histone H3K18ac and H4K16ac observed as S phase progresses (Jasencakova et al. 2003) and by the presence of H3K56ac in early replicons (Lee et al. 2010; Roudier et al. 2011).

The observation that the *Arabidopsis* genome was organized in two large replicon families (Van't Hof et al. 1978), strongly suggested a temporal control of DNA replication (Jackson

Figure 1. The transition from the cell cycle to the endoreplication cycle in plants. Replication origins during the S phase of the cell cycle tend to be enriched in histone H2A.Z and some epigenetic marks, such as H3K4me2, H3K4me3, and H4K5ac. Nucleosome occupancy across the replication origin is not considered here. Different pathways, including the direct action of replication proteins, affect the transition from the cell cycle to the endoreplication cycle. See the text for further explanation. Topo, topoisomerase.

et al. 2013). More recently, the combination of cell sorting of early, mid-, and late S-phase nuclei of culture cells with tiling microarray hybridization, revealed a biphasic mode of replication, with the majority of the euchromatin replicating in early/mid-S phase and the heterochromatin and remaining euchromatin replicating late (Lee et al. 2010). The early/mid-replicating domains colocalize with regions of open chromatin enriched in actively transcribed genes and H3K56ac. Conversely, late replicating domains are enriched in transposon elements and display repressive epigenetic marks (H3K9me2 and 5mC). These observations are in strong agreement with the existing reports for metazoan systems (MacAlpine et al. 2004; Hiratani et al. 2009). Interestingly, H3K56ac has a fundamental role in nucleosome reassembly following DNA replication and repair (Chen and Tyler 2008) as well as in replication-independent histone turnover at promoters (Rufiange et al. 2007). However, no direct link of H3K56ac with origin activation has been provided to date.

DNA REPLICATION LICENSING

Misregulation of origin licensing has consequences on genome stability as a result of uncontrolled rereplication. Interfering with the activity of pre-RC bound to origins that have fired in a given S phase is one strategy to prevent rereplication (Arias and Walter 2007). Several mechanisms, discussed elsewhere in this volume, have evolved to prevent rereplication, such as: (1) selective proteolysis of pre-RC components; (2) changes in their subcellular localization; and (3) binding of pre-RC inhibitors, such as geminin (Gmnn). Plants contain homologs of all pre-RC proteins and other factors that participate in licensing, except Gmnn (Caro and Gutierrez 2007; Shultz et al. 2007). Interestingly, they contain GEM, a CDT1-interacting protein that is structurally unrelated to metazoan Gmnn (Caro et al. 2007), but its role in licensing remains to be experimentally addressed.

Mechanistic studies of plant pre-RC dynamics are scarce. However, it is known that the

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MCM complex remains bound to chromatin throughout the cell cycle, except during mitosis (Shultz et al. 2009). Also, increased levels of CDC6 and/or CDT1 trigger extra endoreplication cycles, which implies full-genome duplication, instead of limited rereplication (Castellano et al. 2001, 2004). These differences with other model organisms support the idea that plant-specific mechanisms of rereplication control may have evolved (Costas et al. 2011a).

In addition to pre-RC availability, particular chromatin states are also involved in replication licensing control. The level of H3K27me1 is crucial to prevent rereplication in *Arabidopsis* heterochromatin. Thus, ATXR5 and ATXR6, encoded by E2F target genes, are monomethyl H3K27 transferases that interact with PCNA (Raynaud et al. 2006; Jacob et al. 2009). Massive sequencing of sorted 2–16C nuclei of an *atxr5 atxr6* double mutant revealed, surprisingly, a significant increase (>30%) in the amount of pericentromeric heterochromatic sequences (Jacob et al. 2010). In fact, the PCNA-interacting protein (PIP) motif of ATXR5 and ATXR6 is required to prevent the rereplication phenotype (Jacob et al. 2010). Moreover, the rereplicated sequences are preferentially located at specific loci, suggesting a heterochromatin-specific loss of licensing control, although dispersed heterochromatic regions across chromosome arms also show rereplicated material. Furthermore, the rereplication phenotype of *atxr5 atxr6* mutants requires factors involved in DNA methylation, as revealed by the reduced rereplication observed in *ddm1*, *met1* and, to a lesser extent, *cmt3* DNA methylation mutant backgrounds (Stroud et al. 2012a), although H3K27me1 is not affected by the DNA methylation level (Mathieu et al. 2005). It is worth noting that a heterochromatin-specific rereplication control depends on geminin in *Drosophila* (Ding and MacAlpine 2010). In animal cells, the level of H4K20me1 is crucial to restrain rereplication (Tardat et al. 2010). The existence of H4K20 methylation in plants has not been shown yet by mass spectrometry (Zhang et al. 2007). However, immunofluorescence and ChIP experiments show important differences with animal cells, because H4K20me1 is typical of pericen-

tromeric heterochromatin whereas H4K20me3 associates with active euchromatic promoters (Fischer et al. 2006; Fuchs et al. 2006). In fact, H4K20me3 colocalizes with a subset of ORC1-binding sites, some of which act as replication origins (Sanchez and Gutierrez 2009).

DNA REPLICATION AND ENDOREPLICATION DURING DEVELOPMENT

One characteristic feature of plant development is that organogenesis is an indeterminate and postembryonic process that occurs continuously during the life of the adult plant (Gutierrez 2005; Inze and De Veylder 2006). This growth pattern implies a high coordination to maintain the balance between pools of proliferating and arrested cells that eventually initiate differentiation and organ formation. In response to certain developmental cues, as well as to environmental factors, proliferating cells exit the cell cycle to enter the endocycle, whereby full genome duplication occurs several times in the absence of an intervening mitosis (Caro et al. 2008; Breuer et al. 2010; De Veylder et al. 2011). Endoreplication is a prerequisite for certain differentiation pathways and is regulated at the level of initiation, maintenance and number of replication rounds to be developed. It must be emphasized that endoreplication is not equivalent to a loss of the licensing control (Zielke et al. 2013), because it involves duplication of the entire genome during each endoreplication cycle instead of uncontrolled reinitiation events within a genomic locus.

As in the case of metazoa, endocycling in plant cells faces the challenge of maintaining CDK activity sufficiently below a threshold to prevent triggering of mitosis. This is achieved by controlling the levels of CDK activity through regulating the amount of CDK (protein and activity), the availability of cyclins, and the levels of CDK inhibitors (De Veylder et al. 2011). Thus, several mechanisms have evolved, in some cases independently of those acting in metazoa. It must be kept in mind that plants contain several non-PSTAIRE CDK involved in cell cycle progression and a large set of cyclins of the A-,

B-, and D types, but they lack a typical E-type cyclin (Gutierrez 2009).

The APC/C degrades several cyclins including CYCB1;1, CYCB1;2, CYCA2;3, and CYCA3;1 (De Veylder et al. 2011). In *Arabidopsis*, homologs of both Cdc20/Fzy and Cdh1/Fzr APC/C activators exist and participate in controlling the onset of endocycles by targeting various cyclins (Gutierrez 2009). The *Arabidopsis* homolog of Cdh1/Fzr is known as CCS52A (CELL CYCLE SWITCH 52A), and its loss of function produces a reduction in ploidy (Cebolla et al. 1999; Larson-Rabin et al. 2009). Interestingly, CCS52A is a target of E2FE/DEL1, one of the three atypical E2F encoded in the *Arabidopsis* genome (Ramirez-Parra et al. 2007; Lammens et al. 2008) and homolog of the human E2F7-9. Thus, the availability of APC/C activators is crucial for the endocycle switch. This is controlled in *Arabidopsis* by the UVI4 and GIG1/OSD1 (GIGAS CELLS 1/OMISSION OF SECOND DIVISION 1) proteins that interfere with the activity of the CDC20/FZY and CCS52A activators, respectively (Iwata et al. 2011). Remarkably, altering GIG1/OSD1 function increases ploidy through endomitosis whereas in the case of UVI4 is typically though endoreplication. CYCA2;3 levels are independently regulated by various proteins, such as ILP1 (Yoshizumi et al. 2006), a homolog of the mammalian GC-binding protein, and TCP15, a transcription factor that induces extra endocycles when it is overexpressed in cells genetically programmed to endoreplicate (Li et al. 2012).

Reduced activity of CDKB1;1, a non-PST-AIRE plant-specific CDK partner of CYCA2;3, increases endoreplication (Boudolf et al. 2009). CDKB1;1/CYCA2;3 activity is also required to phosphorylate several MYB transcription factors that activate the expression of G₂/M-specific genes (Araki et al. 2004; Kato et al. 2009). Plants contain two major classes of CDK inhibitors. One includes proteins with a domain conserved in animal p27 and is known as the KRP family, which in *Arabidopsis* contains seven members (Gutierrez 2009). The other is a plant-specific class constituted by SIAMESE (SIM) and SIM-RELATED (SMR) inhibitors (Walker et al. 2000; Churchman et al. 2006). Overexpres-

sion of KRP1/ICK1 and KRP2/ICK2, which are preferentially expressed in endoreplicating cells, affects the switch to endocycles in *Arabidopsis* (Wang et al. 2000; De Veylder et al. 2001; Verkest et al. 2005; Weinl et al. 2005), maize (Coelho et al. 2005), and tomato (Bisbis et al. 2006), whereas endoreplication is repressed in the *sim* mutants (Churchman et al. 2006). Interestingly, SIM interacts with the CDKA;1, the canonical PSTAIRE-type CDK, and with cyclin D, implicating this cyclin not only in the G₁/S transition but also in control of endocycles. Consistent with this, CYCD3 overexpression induces hyperplasia and reduction of the number of endoreplicated cells in various *Arabidopsis* organs (Dewitte et al. 2003) whereas a triple *cyd3;1-2-3* mutant contains reduced cell number and increased endoreplication levels (Dewitte et al. 2007). CDKA/CYCD3 are responsible for the phosphorylation of RBR (RETINOBLASTOMA-RELATED), the homolog of the mammalian RB protein. In fact, the RBR pathway regulates the number of endocycles once cells have exited the cell cycle (Park et al. 2005; Desvoyes et al. 2006; Borghi et al. 2010). Whether it is a direct effect or mediated by downstream RBR/E2F targets is not clear. For example, maintaining high levels of CDC6 and/or CDT1, which are regulated by RBR/E2F, during leaf development increases cellular ploidy (Castellano et al. 2001, 2004). Together, these data show a direct role of RBR/E2F, some of their targets, and CDK/cyclin in controlling endoreplication during development.

Several topoisomerases are also crucial for the endoreplication cycles (Fig. 1). Thus, mutations in the A and B subunits of topoisomerase VI, encoded by the *ROOT HAIRLESS2* (*RHL2*) and *HYPOCOTYL6* (*HYP6*) genes, prevent endocycle progression beyond the 8C DNA level (Hartung et al. 2002; Sugimoto-Shirasu et al. 2002). Likewise, cells of the *root hairless1/hypocotyl7* mutant that lack topoisomerase II show abnormal endocycle progression (Sugimoto-Shirasu et al. 2005). Therefore, functional topoisomerases are not needed for initiation of the endoreplication program, but they are at later stages, likely to handle topological constraints produced when the ploidy level increases. A

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systematic evaluation of the possible role of other DNA replication factors in endoreplication control would be enlightening.

A correct DNA replication-dependent deposition of histones H3 and H4 is required in *Arabidopsis* to prevent activation of the G₂ checkpoint (Fig. 1). Mutants in the *FASCIATA1* (*FAS1*) gene, encoding the large subunit of the H3-H4 chaperone chromatin assembly factor 1 (CAF-1), show a constitutive activation of the G₂ checkpoint, including transcriptional activation of *RAD51* and *BRCA1* genes, among others (Ramirez-Parra and Gutierrez 2007a). Mutant cells, instead of becoming permanently arrested or forced to enter a death pathway, trigger the endoreplication program ectopically and at developmental times in which it should not occur. It has been speculated that plants have evolved the ability to switch to the endocycle as a way to escape permanent cell cycle arrest during development (Ramirez-Parra and Gutierrez 2007b).

Although the endoreplication field is advancing quickly several key questions still remain unanswered. These include: (1) how licensing occurs in the absence of mitosis; (2) what is the replication timing and origin usage in relation to the S phase of the cell cycle; (3) what are the origins active in each endoreplication round and whether they are the same as those used during the cell cycle. Because the experimental approaches are now available, it is likely that studies in whole plants will contribute to significant advances in the coming years.

GEMINIVIRUS DNA REPLICATION

Geminiviruses are a family of plant viruses that have a significant impact in agricultural production worldwide. Their genome consists of 1 or 2 molecules of single-stranded DNA (ssDNA), ~2.4–3.1 kb in length, depending on the virus genera (Mastre-, Curto-, Topocu-, and Begomovirus). A comprehensive review of geminivirus biology has appeared recently (Jeske 2009). Others have covered aspects more related to DNA replication (Hanley-Bowdoin et al. 2004; Gutierrez 2006; Ascencio-Ibanez et al. 2008).

The replication cycle includes a first stage in which ssDNA is converted into dsDNA, a pro-

cess performed entirely by host proteins. The dsDNA is used as a substrate in which 13–16 superhelical turns are introduced by association with histone octamers (Pilartz and Jeske 1992), much in the same way as it occurs with SV40 DNA. In the second stage, new viral ssDNA molecules are produced by a rolling-circle mechanism (Gutierrez 1999; Saunders 2008). The viral initiator protein (Rep) is a multifunctional protein with origin-specific DNA binding, homo- and heteroligomerization, and helicase and endonuclease activities (reviewed in Jeske 2009). Interestingly, Rep-binding sites at the replication origin are located in close proximity or partially overlapping the two divergent promoters responsible for early and late viral gene expression (reviewed in Gutierrez 2002). In addition to the rolling-circle replication pathway, a recombination-dependent replication mechanism that does not rely on a sequence-specific replication origin is also used (Jeske 2009).

A rich variety of interactions of viral early proteins with host factors have been identified as necessary for efficient viral DNA replication. These include: (1) inactivation of the retinoblastoma-related pathway (Xie et al. 1995; Kong et al. 2000), the G₂/M transition (Kong and Hanley-Bowdoin 2002; Nagar et al. 2002), and the host antiviral defense and silencing mechanisms (Vanitharani et al. 2005); (2) interaction with cell differentiation transcription factors (Xie et al. 1999; Selth et al. 2005), pathogen response (Ascencio-Ibanez et al. 2008), the ubiquitination (Lai et al. 2009; Zhang et al. 2011), and the sumoylation system (Castillo et al. 2004; Sanchez-Duran et al. 2011); and (3) recruitment of DNA replication factors such as RFC1 (Luque et al. 2002), PCNA (Castillo et al. 2003), RPA2 (Singh et al. 2007), and POLA2 and POLD2 (Lozano-Duran et al. 2011).

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