In Favor of Establishment: Regulation of Chromatid Cohesion in Plants

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In eukaryotic organisms, the correct regulation of sister chromatid cohesion, whereby sister chromatids are paired and held together, is essential for accurate segregation of the sister chromatids and homologous chromosomes into daughter cells during mitosis and meiosis, respectively. Sister chromatid cohesion requires a cohesin complex comprised of structural maintenance of chromosome adenosine triphosphatases and accessory proteins that regulate the association of the complex with chromosomes or that are involved in the establishment or release of cohesion. The cohesin complex also plays important roles in the repair of DNA double-strand breaks, regulation of gene expression and chromosome condensation. In this review, we summarize progress in understanding cohesion dynamics in plants, with the aim of uncovering differences at specific stages. We also highlight dissimilarities between plants and other eukaryotes with respect to the key players involved in the achievement of cohesion, pointing out areas that require further study.

Keywords: cell division, CTF7, WAPL, PDS5, transposons, meiosis, recombination, DNA repair

INTRODUCTION

In eukaryotes, DNA faithfully duplicates during the S phase of the cell cycle to produce sister chromatids. The newly duplicated sister chromatids are then tethered and held together by the cohesin complex until they segregate into new daughter cells (Uhlmann and Nasmyth, 1998). The cohesin complex is also involved in the repair of DNA double-strand breaks (DSBs), the regulation of gene expression and chromosome condensation (Guacci et al., 1997; Sjögren and Nasmyth, 2001; Onn et al., 2008; Nasmyth and Haering, 2009; Yuan et al., 2011; Lopez-Serra et al., 2013; Mehta et al., 2013; da Costa-Nunes et al., 2014).

In eukaryotic organisms, the cohesin core complex comprises four structural proteins: two structural maintenance of chromosome (SMC) adenosine triphosphatases (ATPases), SMC1 and SMC3; the α-kleisin sister chromatid cohesion protein 1 (SCC1); and the SCC3 subunit. The interaction of cohesin with chromosomes is regulated by the genes *PRECOCIOUS DISSOCIATION OF SISTERS 5* (*PDS5*) and *WINGS APART-LIKE* (*WAPL*). In animal cells, Sororin helps promote the stable association of cohesin with chromatin (Peters and Nishiyama, 2012). Tripartite rings are formed via the association of the SMC1-SMC3 heterodimer with SCC1 (Anderson et al., 2002; Haering et al., 2002). Different models have been proposed to explain the functional interaction of the complex

with chromatin. The simplest model suggests that the ring entraps the two sister chromatids (Haering et al., 2008) (**Figure 1**). In other models, the interaction between different cohesin complexes can promote sister chromatid tethering (Eng et al., 2015). SCC1 also directly or indirectly associates with SCC3, PDS5, and WAPL (Haering et al., 2002).

Other SMC complexes exist, such as the condensin (SMC2/4) and SMC5/6 complexes, and their function is required in different contexts (Hirano, 2006). Condensins are multisubunit protein complexes that play a crucial role in the structural and functional organization of chromosomes (Ono et al., 2003). The majority of eukaryotes, including Drosophila possess two condensin complexes that participate in gene regulation, DNA repair and cell fate determination (Ono et al., 2003; Klebanow et al., 2016), while in Arabidopsis the condensin II complex is also important for conferring tolerance to excess soil Boron (Sakamoto et al., 2011). In addition to the SMC2/4 subunits, each complex may feature three non-SMC subunits, namely CAP-D2, CAP-G, and CAP-H for condensin I and CAP-D3, CAP-G2, and CAP-H2 for condensin II (Hirano, 2012). Arabidopsis CAP-D2 and CAP-D3 are required for pollen fertility and for preventing the association of centromeric repeats (Schubert et al., 2013). The eukaryotic SMC5/6 complex is primarily involved in DNA repair, replication fork stability, and possibly in the control of DNA topology (Verver et al., 2016). It consists of two SMC proteins and several non-SMC proteins (Andrews et al., 2005), which may interact with the ATPase head domain of SMC5 and SMC6 (Pebernard et al., 2004; Palecek et al., 2006). In Arabidopsis, the SMC5/SMC6 subunit AtMMS21 has been shown to regulate maintenance of root stem cells during embryogenesis and postembryonic stages (Xu et al., 2013). Given the evolutionary conservation of these complexes, it seems that their spatial organization and topology are very important to define their functionality (Gligoris and Löwe, 2016).

In this review, we summarize recent progress in understanding cohesion dynamics in plants, highlight differences at specific stages, key points of divergence between plant cohesin complexes and those from yeast and metazoans, and point out areas that require further study.
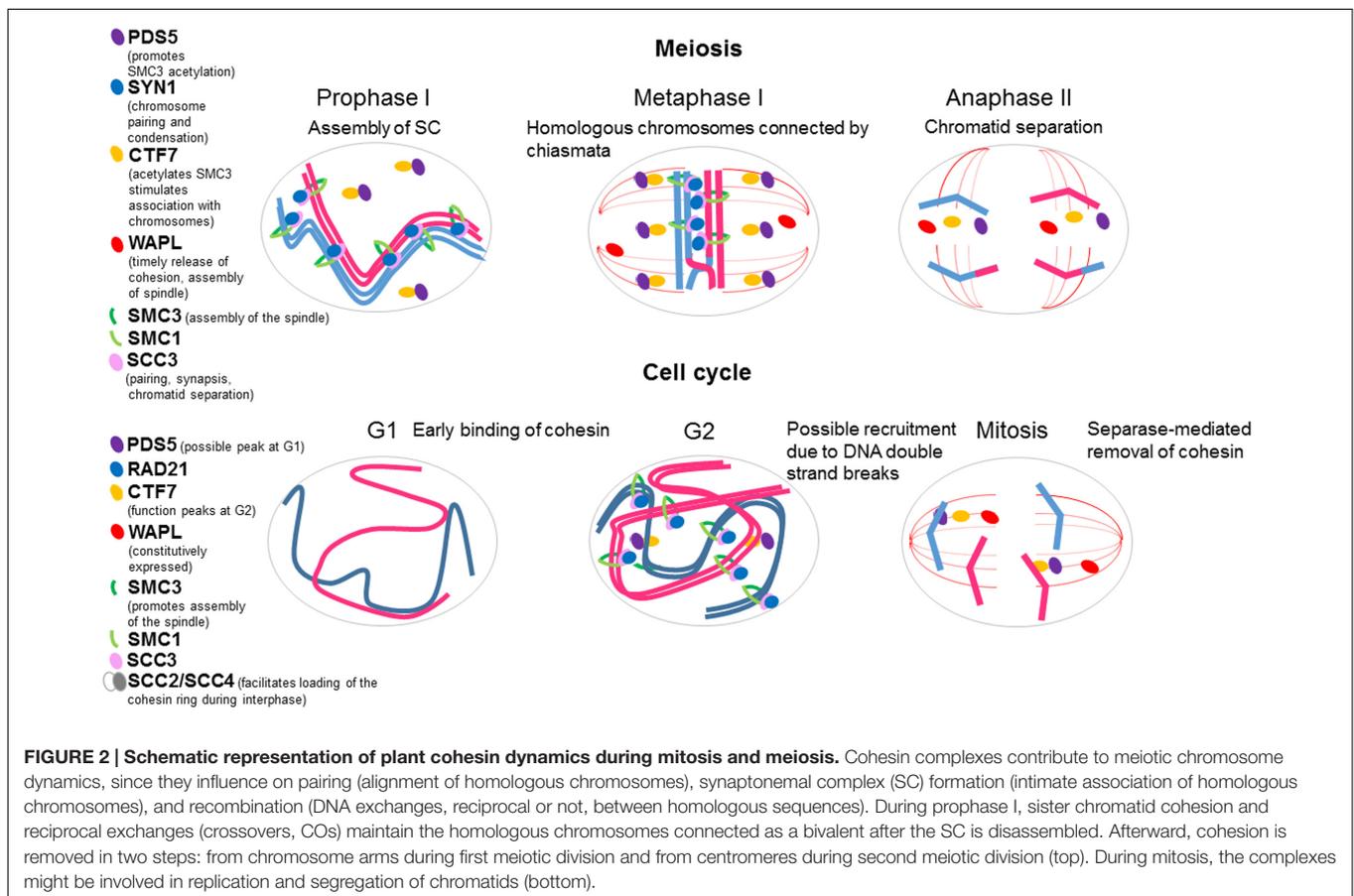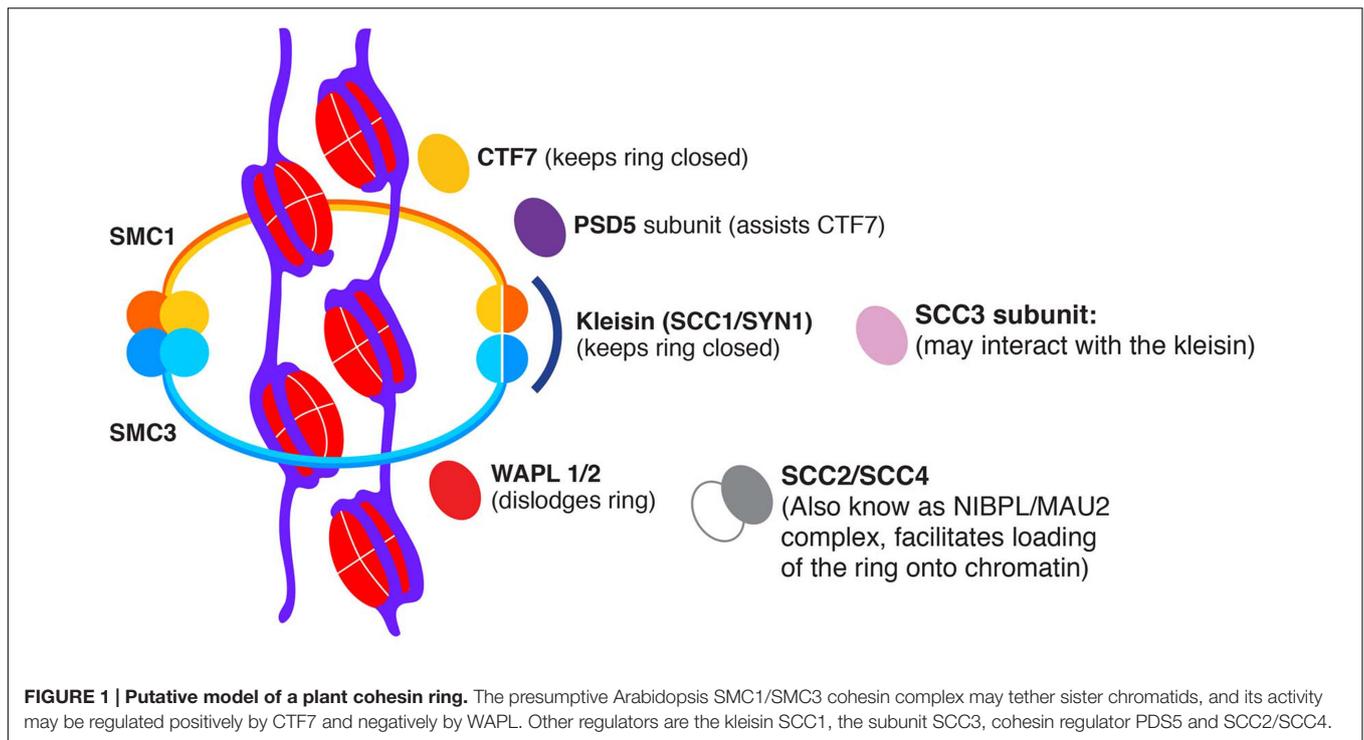
THE CORE COHESIN COMPLEX

In Arabidopsis, cohesion is mediated by the cohesin complex, consisting of two subunits of the SMC protein family, SMC1 and SMC3 (Liu et al., 2002). Both SMC1 and SMC3 are present in the Arabidopsis genome as single-copy genes (Liu et al., 2002). SMC1 and SMC3 are highly conserved among plant species and share the same characteristics: an N-terminal ATP binding domain, two large antiparallel coiled-coil regions separated by a hinge region, and a C-terminal DA box (Liu et al., 2002). The homozygous T-DNA knockouts of *SMC1* (*titan8-1* and *titan8-2*) and *SMC3* (*titan7-1 and titan7-2*) show developmental defects in both embryo and endosperm that result in an early arrest in seed development (Liu et al., 2002).

Structural maintenance of chromosome 3 is found in both the cytoplasm and nucleus, bound to the nuclear matrix of somatic cells and in meiocytes (Lam et al., 2005). Specifically, it is localized from interphase to anaphase during mitosis, from premeiotic G_2 to anaphase I during meiosis I, and in metaphase II centromeres during meiosis II (**Figure 2**). Strikingly, the protein is also present in the mitotic and meiotic spindle, so SMC3 may have additional roles in plant cells other than sister chromatid cohesion (Lam et al., 2005). No reports of Arabidopsis SMC1 have been published. In tomato, this protein, as well as SMC3, localizes along the axial elements (AEs), the precursors of the lateral elements (LEs) of the synaptonemal complex (SC), the tripartite structure that links homologous chromosomes in zygotene-pachytene meiocytes; but whether it is present in the cytoplasm and localizes to the spindle is unclear because studies were not conducted on whole cell mounts (Lhuissier et al., 2007).

Four orthologs of the kleisin subunit SCC1/radiation sensitive 21 (RAD21) have been detected in Arabidopsis and rice, and several *SCC1/RAD21* genes are present in other plant species (Golubovskaya et al., 2006). During the first meiotic division, the mitotic kleisin subunit SCC1 is replaced by RECOMBINATION 8 (REC8), (Klein et al., 1999) which plays a role during meiosis that SCC1/RAD21 cannot support (Watanabe and Nurse, 1999). In maize, the ortholog of *REC8* is *ABSENCE OF FIRST DIVISION 1* (*AFD1*) (Golubovskaya et al., 2006). AFD1 is essential for the elongation of AEs and immunolocalization studies revealed that it localizes to the LEs of the SC. The AFD1 protein is also required for RAD51 distribution on the chromosomes and is also important for homologous chromosome pairing (Golubovskaya et al., 2006). In the rice genome, the putative *REC8* ortholog is thought to be *RAD21-4*. RNA knock-down of this gene resulted in multiple aberrations during male meiosis, which included severe chromosome condensation, precocious segregation of homologous chromosomes and chromosome fragmentation (Zhang et al., 2006).

In the Arabidopsis genome, the *REC8* ortholog is *SYN1/DIF1* (Peirson et al., 1997; Bai et al., 1999; Bhatt et al., 1999; Cai et al., 2003). T-DNA *syn1* mutants are sterile in both male and female gametophytes, but the protein is dispensable for somatic development; vegetative growth appears normal in the mutants (Bai et al., 1999; Bhatt et al., 1999; da Costa-Nunes et al., 2006). Male meiocytes show severe defects in sister chromatid cohesion, homologous chromosome pairing, and chromosome condensation that result in the fragmentation of chromosomes and formation of polyads (Peirson et al., 1997; Bai et al., 1999; Bhatt et al., 1999; Cai et al., 2003). Transmission electron microscopy of chromosomes in *syn1* meiocytes show short stretches of SC surrounded by condensed chromatin in late pachytene, which suggests that SYN1 is essential for SC formation (Zhao et al., 2006). In the *syn1* mutant, the recombination machinery is partially functional since some recombination spots were seen in chromosomes (Zhao et al., 2006). Immunolocalization studies showed that SYN1 first appears on meiotic chromosomes beginning in late interphase. SYN1 antibody labels the developing chromosome axes beginning at early leptotene and lines the chromosome axes of paired chromosomes (Cai et al., 2003). A large portion of SYN1 dissociates from the chromosome arms during diplotene and diakinesis and by metaphase I the signal is only associated

FIGURE 1 | Putative model of a plant cohesin ring. The presumptive Arabidopsis SMC1/SMC3 cohesin complex may tether sister chromatids, and its activity may be regulated positively by CTF7 and negatively by WAPL. Other regulators are the kleisin SCC1, the subunit SCC3, cohesin regulator PDS5 and SCC2/SCC4.

FIGURE 2 | Schematic representation of plant cohesin dynamics during mitosis and meiosis. Cohesin complexes contribute to meiotic chromosome dynamics, since they influence on pairing (alignment of homologous chromosomes), synaptonemal complex (SC) formation (intimate association of homologous chromosomes), and recombination (DNA exchanges, reciprocal or not, between homologous sequences). During prophase I, sister chromatid cohesion and reciprocal exchanges (crossovers, COs) maintain the homologous chromosomes connected as a bivalent after the SC is disassembled. Afterward, cohesion is removed in two steps: from chromosome arms during first meiotic division and from centromeres during second meiotic division (top). During mitosis, the complexes might be involved in replication and segregation of chromatids (bottom).

with the centromeres. SYN1 signal is not typically detected at late metaphase I and early anaphase I. Similar to Arabidopsis SYN1, yeast REC8 dissociates from chromosome arms and by metaphase I the signal is localized only at centromeres (Klein et al., 1999; Watanabe and Nurse, 1999).

Arabidopsis has three other kleisin genes, *SYN2/AtRAD21.1*, *SYN3/AtRAD21.2,* and *SYN4/AtRAD21.3*, which are expressed throughout the plant (Dong et al., 2001; Jiang et al., 2007). SYN3 plays an important role in the nucleolus of both somatic and meiotic cells and is also indispensable for megagametogenesis (Jiang et al., 2007), while *SYN2/AtRAD21.1* and *SYN4/AtRAD21.3* play roles in DNA repair and may represent mitotic cohesins (Dong et al., 2001; da Costa-Nunes et al., 2006). Plants homozygous for mutations in *AtRAD21.1* and *AtRAD21.3* showed a decrease in sister chromatid alignment in somatic cells, suggesting that they may represent the mitotic cohesins (da Costa-Nunes et al., 2006). *AtRAD21.1* has been shown to play a critical role in recovery after DNA damage during seed imbibition before germination (da Costa-Nunes et al., 2006), whereas *AtRAD21.3* appears to play a role in somatic DNA DSB repair (da Costa-Nunes et al., 2014).

In contrast to mammals, *SCC3* is present as a single-copy gene in Arabidopsis. The corresponding protein is 1,098 amino acids long and exhibits 21% sequence identity and 40% sequence similarity to its yeast homolog. The transcript is expressed strongly in roots, mature leaves, buds, and plantlets (Cromer et al., 2013). In general, T-DNA insertional mutations of *SCC3* result in embryo lethality; however, a weak allele, *scc3-1*, hypothesized to express a truncated protein, confers both mitotic and meiotic defects and homozygous *scc3-1* plants are dwarf and sterile (Chelysheva et al., 2005). Microscopy analysis revealed few dividing cells in root tips as compared with the wild type (WT), and male meiotic chromosomes showed defects in chromosome condensation, chromosome pairing and synapsis and presented early sister chromatid separation. During meiosis, SCC3 appears to localize at the chromosome axes until anaphase I, but during mitosis it is present throughout the entire cell cycle. Moreover, SYN1 binds normally to meiotic chromosomes in *scc3-1* plants, but in *syn1-1* plants, SCC3 localizes incorrectly to meiotic chromosome axes (Chelysheva et al., 2005). Whether the two proteins interact is still unknown.

LOADING OF THE COHESIN COMPLEX

Before DNA replication, SCC2 and SCC4 (also known as the NIBPL/MAU2 complex) mediate the recruitment of cohesin to chromosomes in *Saccharomyces cerevisiae*, *Caenorhabditis elegans*, and humans (Ciosk et al., 2000; Gillespie and Hirano, 2004; Watrin et al., 2006; Onn et al., 2008; Nasmyth and Haering, 2009). However, these proteins are not required to maintain cohesion after the completion of DNA replication. In fact, large-scale mapping in several organisms such as *S. cerevisiae* and *Schizosaccharomyces pombe* has demonstrated that the cohesin complex and SCC2 bind non-randomly to chromosomes and that the respective binding loci may not overlap (Blat and Kleckner, 1999; Glynn et al., 2004; Lengronne et al., 2004; Weber

et al., 2004; D'Ambrosio et al., 2008; Schmidt et al., 2009). Cohesin is enriched in regions around centromeres and at sites of convergent transcription, whereas SCC2 and SCC4 localize with transfer RNA genes (Glynn et al., 2004; D'Ambrosio et al., 2008). Cohesin may first associate with SCC2/SCC4, then relocate to sites of convergent transcription through the action of RNA polymerases (Lengronne et al., 2004; Hu et al., 2011; Fernius et al., 2013). The specific function of SCC2/SCC4 during loading of the cohesin complexes is unclear, but they may activate or prime the ATPase activity of SMC proteins, somehow allowing cohesin rings to entrap chromosomes (Haering et al., 2002; Arumugam et al., 2003; Gruber et al., 2003, 2006; Seitan et al., 2006). This behavior has been inferred from mutant SMC1 or SMC3 proteins that cannot hydrolyze ATP. These mutations lead to a phenotype that resembles that of *scc2* or *scc4* mutants in which cohesin rings are formed but fail to associate with chromosomes (Arumugam et al., 2003). Alternatively, it has been proposed that SCC2/SCC4 subunits might have a role in the remodeling of chromatin to facilitate the binding of cohesin (Hakimi et al., 2002; Huang et al., 2004; Ritchie et al., 2008).

In addition to SCC2/SCC4, other factors are required for the association of cohesin with chromosomes. For example, in *Xenopus* egg extracts, the CDC7/DRF1 kinase (DDK), a component of pre-replication complexes (pre-RCs), is essential for loading both SCC2/SCC4 and cohesin onto chromatin (Gillespie and Hirano, 2004; Takahashi et al., 2004, 2008; Ström et al., 2007). However, SCC2/SCC4 complexes have not been found associated with pre-RCs in yeast (Uhlmann and Nasmyth, 1998). In some instances, the kinetochore, transfer RNA transcription factors or proteins related to epigenetic mechanisms also participate in SCC2/SCC4-mediated loading of cohesin (Nonaka et al., 2002; Weber et al., 2004; D'Ambrosio et al., 2008). Nonetheless, although SCC2 and SCC4 are essential for cohesin loading, they are dispensable for cohesin maintenance and resolution during the S and G_2 stages (Ciosk et al., 2000; Lengronne et al., 2006).

Functional characterization indicated that SCC2/SCC4 is essential for establishing sister chromatid cohesion in Arabidopsis (Sebastian et al., 2009). T-DNA insertional mutations in SCC2 and SCC4 lead to defects in embryo and endosperm development (Sebastian et al., 2009). Additionally, RNAi knockdown of *SCC2* leads to defects during male and female meiosis, including chromosome clumping, chromosome fragmentation, loss of chromatid cohesion, SCC3 mis-distribution and defects in segregation (Sebastian et al., 2009). The predicted protein sequence of Arabidopsis *SCC2* reveals a putative plant homeodomain (PHD) finger, a domain involved in chromatin organization and regulation of gene expression (Sebastian et al., 2009). Cytological analyses of T-DNA insertional lines *Atscc2-2*, *Atscc2-3*, *Atscc4-1* and *Atscc4-1* indicates that in these lines 25% of all embryos develop only up to the heart stage and show loss of bilateral symmetry, cell over-proliferation in the suspensor, and in the case of *Atscc2-2*, over-proliferation of the endosperm (Minina et al., 2017). In *Atscc4-1* and *Atssc2-2* analysis of the distribution of the auxin-response reporter *DR5rev::3xVENUS-N7* indicates that most of the reporter is confined to the basal cells of the

suspensor, which is the opposite to the wild type, suggesting the existence of: (a) alterations in the embryogenic potential of the suspensor in the mutants, and (b) a role for both SCC4 and SCC2 in embryonic cell fate determination (Minina et al., 2017). It was also found that SCC4 interacts stably with the N-terminus of SCC2 *in planta* and in baker's yeast, but this interaction is not required for proper localization of SCC4 to the plant nucleus in *Atscc2-2* (Minina et al., 2017). The authors interpreted both this finding and the colocalization of SCC4 with mitotic kleisin *RAD21.3/SYN4* during interphase as an indication that Arabidopsis SCC4 may play a special role in the determination of sites for cohesin loading on chromatin (Minina et al., 2017). Taken together all these results indicate that in Arabidopsis the SCC2 protein plays an important role during meiosis (Sebastian et al., 2009), while the SCC2/SCC4 complex regulates embryo and endosperm development with additional functions that are specific for each subunit (Minina et al., 2017).

COHESION ESTABLISHMENT AND MAINTENANCE

In yeast, sister chromatid cohesion is established during the S phase of the cell cycle by the activity of Establishment of cohesion 1/Chromosome transmission fidelity 7 (Eco1/Ctf7) acetyltransferase soon after cohesins are recruited to chromosomes (Skibbens et al., 1999; Tóth et al., 1999; Onn et al., 2008; Nasmyth and Haering, 2009; Yuan et al., 2011). Eco1/Ctf7 acetylates lysine residues in the Smc3 subunit, close to its ATPase domain (K112 and K113). These residues are highly conserved among eukaryotes and are also acetylated in human cells by two proteins, establishment of sister chromatid cohesion N-acetyltransferase 1 (ESCO1) and ESCO2 (Hou and Zou, 2005; Zhang et al., 2008). Then the acetylated Smc3 protein interacts stably with Scc1 and counteracts the activity of the Rad61/Wpl1 (Wapl) complex, which is thought to promote the disassociation of cohesin from chromosomes (Rolef Ben-Shahar et al., 2008; Unal et al., 2008; Zhang et al., 2008; Rowland et al., 2009; Woo et al., 2009), possibly by interacting directly with the Ser/Thr phosphatase PP4, which has been shown to target kleisin Rad21 for dephosphorylation (Birot et al., 2017).

Vertebrates express an additional essential cohesion regulator called Sororin (Rankin et al., 2005). This protein associates with cohesin via acetylation and antagonizes WAPL by binding to PDS5 (Nishiyama et al., 2010). PDS5 also promotes SMC3 acetylation (Vaur et al., 2012; Chan et al., 2013). Hence, it integrates an anti-establishment action (by WAPL) with its requirement for cohesion maintenance during the cell cycle progression (Schmitz et al., 2007; Nishiyama et al., 2010). The Arabidopsis genome contains five putative *PDS5* homologs that share similarity with fungal and mammal sequences (Mercier et al., 2001; Pradillo et al., 2015). Compromised expression of several *PDS5* genes leads to a significant reduction in seed production (Pradillo et al., 2015). Depletion of PDS5 proteins alters only slightly meiotic division but alters DNA repair by homologous recombination (HR) (Pradillo et al., 2015).

The establishment of cohesion occurs concomitantly with DNA replication (Uhlmann and Nasmyth, 1998). In addition to Eco1 acetyltransferase, other proteins, related to DNA replication, contribute to the establishment of the SCC. In yeast, Eco1/Ctf7 interacts with DNA replication factors such as proliferating cell nuclear antigen (PCNA, a DNA polymerase processivity factor) (Moldovan et al., 2006), replication factor C (a component of the clamp loader replication factor C) (Mayer et al., 2001), the DNA helix itself (Mayer et al., 2004), and various clamp loader subunits (Petronczki et al., 2004). Inactivation or mutations in Eco1/Ctf7 lead to defects such as chromosome mis-organization, mis-distribution of the cohesin complex and activation of cell cycle checkpoints (Skibbens et al., 1999; Tóth et al., 1999; Milutinovich et al., 2007). Deletions or mutations in *Rad61/Wpl1, Pds5, Smc3* and *Scc3* may suppress the effect of deletions in *Eco1/Ctf7*, which suggests a degree of functional redundancy in the activity of Eco1/Ctf7 or that other factors can modify cohesin to counteract the activity of Eco1/Ctf7 during the establishment of cohesion (Warren et al., 2004; Rolef Ben-Shahar et al., 2008; Rowland et al., 2009; Sutani et al., 2009; Chen et al., 2012).

Experimental evidence indicates that Arabidopsis ECO1/CTF7 can functionally replace its yeast ortholog (Jiang et al., 2010; Bolaños-Villegas et al., 2013; Singh et al., 2013). Arabidopsis CTF7 lacks an N-terminal extension common in other organisms but features a PCNA-interacting protein (PIP) box, a C_2H_2 zinc finger motif and an acetyltransferase domain (Jiang et al., 2010). Similar to other species, Arabidopsis CTF7 appears to have a dosage-dependent function. Heterozygous *ctf7* plants exhibit defects in the development of female gametophytes, with no obvious defects in microsporogenesis. Vegetative growth is normal in these plants, but siliques contain fewer seeds than in WT plants and many show embryonic developmental defects. Inactivation of Arabidopsis CTF7 typically results in embryo lethality; however, homozygous *ctf7* mutant plants, which are completely sterile, can be obtained at very low frequencies. These plants show a more drastic phenotype: they are dwarf and feature fewer epidermal cells per area. Also, cell cycle progression is defective (Bolaños-Villegas et al., 2013). Furthermore, *ctf7* mutant plants exhibit a severe loss of sister chromatid cohesion during mitosis and meiosis as well as significantly reduced localization of cohesin onto chromosomes (Bolaños-Villegas et al., 2013). The absence of ECO1/CTF7 impairs cytosine methylation, especially CG methylation (Bolaños-Villegas and Jauh, 2015). In addition, genes involved in HR are upregulated, which suggests defects in DNA repair (Bolaños-Villegas et al., 2013). Similar phenotypes were observed in plants transformed with a dexamethasone-inducible *CTF7*-RNAi construct. Finally, overexpression of the *CTF7* genomic sequence leads to ovule arrest at female gametophyte 1 stage (Liu and Makaroff, 2015).

Extensive studies in different species have shown that WAPL controls mitotic sister chromatid cohesion and takes part in the removal of cohesin (Kueng et al., 2006). In Drosophila, WAPL has an important role in the organization of heterochromatin (Vernì et al., 2000). The *WAPL* genomic sequence features a conserved C-terminus that may be a determinant of cohesin and a divergent N-terminal domain that in humans contains a PDS5

binding domain (Chatterjee et al., 2013; Ouyang et al., 2013). Although the effect of inactivation of WAPL during mitosis has been studied in several organisms (Cunningham et al., 2012; Chatterjee et al., 2013; Ouyang et al., 2013), much less is known about its role during meiosis.

The Arabidopsis genome contains two *WAPL* genes that appear to have a significant role in the removal of cohesin in the prophase (De et al., 2014). Arabidopsis plants homozygous for either of the *wapl* mutations have no obvious phenotype, but double homozygous plants show reduced fertility and severe defects in male meiosis, including defective organization of heterochromatin regions during prophase I, altered pairing of homologous chromosomes and delayed cohesin release during the first meiotic division. Assembly of the meiotic spindle is also severely impaired in double mutants. These problems may lead to the formation of chromosome bridges, broken chromosomes, uneven segregation of chromosomes and aneuploid gametes (De et al., 2014). In contrast, cohesin complexes appear to be removed normally in somatic cells (De et al., 2014). Hence, Arabidopsis *WAPL* genes may play a critical role during meiosis, and mechanisms involved in the removal of cohesin during prophase may vary between mitosis and meiosis in plants. Additionally, inactivation of the two Arabidopsis *WAPL* genes can suppress the lethal phenotype produced by the lack of CTF7 (De et al., 2016) and allows for normal vegetative growth and production of a reduced number of viable seeds (De et al., 2016). Immunolocalization of SYN1 in meiocytes confirmed that the release of cohesin during diakinesis is recovered in *wapl1 wapl2 ctf7* triple homozygous mutant plants (De et al., 2016). However, comet assay experiments in vegetative tissues revealed that both WAPL1/2 and ECO1/CTF7 are important for the repair of DNA DSBs during the cell cycle in Arabidopsis (De et al., 2016). In addition, flow cytometry revealed a high level of aneuploidy in vegetative tissues of the triple mutant (De et al., 2016). All these results demonstrate that WAPL1/2 is important for the timely release of cohesion during meiosis and that inactivation of WAPL1/2 most-likely abrogates the requirement for SMC3 acetylation by CTF7 during mitosis (De et al., 2016). These plants are still able to develop and reproduce, which suggests the presence of an alternative cohesion pathway that awaits proper identification and functional characterization.

The Arabidopsis SMC-like gene *SWITCH* (*SWI1*), also known as *DYAD*, also plays a role in meiotic chromosome structure, maintenance and cohesion. The name is due to its function as a master controller of the switch from mitosis to meiosis (Mercier et al., 2001; Schubert, 2009). The corresponding mutant exhibits 10 univalents (instead of 5 bivalents) at the end of prophase I. Subsequently, chromatids lose their cohesion and their appear individually at metaphase I (Mercier et al., 2001, 2003). *SWI1* is a plant-specific gene that has been characterized in several species. The maize homolog is *AMEIOTIC1* (*AM1*). In *am1* mutants premeiotic cells undergo mitosis instead of meiosis and meiotic-specific cohesins are not installed on chromosomes (Pawlowski et al., 2009). In rice, *OsAM1* is required for meiotic progression and the mutant fails to load OsREC8 on chromosome axes (Che et al., 2011).

Cohesion establishment and maintenance is also controlled by several posttranslational modifications. In addition to the acetylation mentioned previously, phosphorylation and SUMOylation play an essential role during cohesion establishment. Indeed, cohesin SUMOylation is indispensable for the entrapment of sister chromatids (Almedawar et al., 2012). In this sense, SUMO accumulates at DNA damage sites in S/G_2-phase human cells in a cohesin-dependent manner. This modification affects SCC1 and promotes DNA repair by sister chromatid exchange by antagonizing WAPL (Wu et al., 2012).

COHESIN DISSOCIATION

During cell division, cohesin needs to be removed for segregation of sister chromatids. The dissociation of cohesin is tightly regulated and takes place during two phases that involve different factors (Sumara et al., 2000; Waizenegger et al., 2000; Peters and Nishiyama, 2012). During the mitotic prophase and prometaphase stages, most cohesins are removed from chromosome arms, but those at the centromere stay. However, shortly before the onset of mitotic anaphase, all remaining chromosome-bound cohesin (mainly at centromeres) is removed when SCC1 is cleaved by Separase (Uhlmann et al., 1999; Sumara et al., 2000; Tomonaga et al., 2000; Waizenegger et al., 2000; Losada et al., 2002).

In vertebrates, Sororin is targeted for phosphorylation by cyclin-dependent kinase 1 (CDK1)/Cyclin B, which facilitates the action of PDS5–WAPL. This complex takes part in the release of cohesin from the chromosome arms (Schmitz et al., 2007; Nishiyama et al., 2010). The fraction of cohesin that remains at centromeres is protected by Shugoshin 1 protein (SGO1), which mediates the recruitment of Phosphatase 2A to protect cohesin against phosphorylation and hinder its release (Kitajima et al., 2004; Tang et al., 2006; Rivera and Losada, 2009). Other proteins such as Haspin (a histone H3 kinase) and Prohibitin 2 have been found involved in the protection of cohesion at centromeres (Dai et al., 2006).

The bi-orientation of chromosomes at metaphase is possible because cohesin is preserved at centromeres. Before metaphase, the anaphase-promoting complex (APC/C) remains inactive and Separase is inhibited by Securin and Cyclin B (Stemmann et al., 2001; Toyoda et al., 2002; Musacchio and Salmon, 2007). This pathway is regulated by the spindle assembly checkpoint (SAC). At the onset of anaphase, the SAC is disrupted and APC/C becomes active and targets Securin and Cyclin B for ubiquitylation and destruction (Uhlmann et al., 1999; Hauf et al., 2001; Musacchio and Salmon, 2007). Free from its inhibitors, Separase is released and activated (Nasmyth, 2000). At the same time, SGO1 is released from the centromere and SCC1 is phosphorylated. Separase then proceeds to cleave SCC1 and remove cohesin from sister chromatids (Nasmyth, 2000; Hauf et al., 2001). Finally, SMC3 is deacetylated by the histone lysine deacetylase 1 for reuse in the next cycle (Rivera and Losada, 2010).

During meiosis, cleavage along chromosome arms is pivotal for disjunction of homologous chromosomes at anaphase I, but

it must not occur at centromeres, because cohesion of sister chromatids is indispensable for their correct bi-orientation at metaphase II (Bai et al., 1999). REC8, and other meiotic-specific factors such as SMC1β (SMC1) or Stromal Antigen 3 (SCC3) work in concert to protect centromeric cohesion during anaphase I and interkinesis (Dong et al., 2001; Prieto et al., 2001; Revenkova et al., 2001).

In Arabidopsis, the protection of meiotic centromeric cohesion depends on several proteins including SGO1 and SGO2, which are required at anaphase I, and PATRONUS 1 (PANS1), which is required at interkinesis and meiosis II and is presumably targeted by the APC/C complex (Cromer et al., 2013; Zamariola et al., 2013). In sgo1 sgo2 double mutant plants, immunolabeling for REC8/SYN1 suggested that this protein is not present at metaphase II (Cromer et al., 2013). The pans1 mutant features up to 10 single chromatids at each metaphase II plate and no REC8/SYN1 signal at metaphase II in chromatids (Cromer et al., 2013). PANS1 may protect REC8 or may inhibit cohesin release by WAPL inactivation (Cromer et al., 2013; Zamariola et al., 2013).

The predicted Arabidopsis Separase protein (extra spindle pole bodies 1, ESP1) is significantly longer than the corresponding proteins from yeast, worm, and fly, but is similar to the mammalian protein (Liu and Makaroff, 2006). ESP1 proteins from different organisms show high similarity in the C-terminus, which features a C-50 peptidase domain (Liu and Makaroff, 2006). The ESP1 peptidase domain shares approximately 20% sequence identity with the mammalian enzyme. However, the Arabidopsis ESP1 peptidase domain is considerably longer than those found in other organisms (700 vs. ~400–470 amino acids) (Liu and Makaroff, 2006). Moreover, this domain consists of a predicted 2Fe-2S-Ferredoxin domain that is not present in other organisms. ESP1 in Arabidopsis contains an EF-hand/calcium-binding domain, which is also present in budding yeast, where it is important for initiation or maintenance of its association with the spindle (Jensen et al., 2001; Liu and Makaroff, 2006). The calcium-binding domain may have the same function in plants, but this has not yet been proven. Analysis of T-DNA insertional mutants suggests that ESP1 is an essential gene in that no homozygous plants from two different alleles could be obtained (Liu and Makaroff, 2006). Moreover 25% of the seeds from heterozygous plants for the T-DNA insertions showed enlarged endosperm nuclei and nucleoli, a failure of the endosperm to cellularize, and embryo arrest at the globular stage, indicating that the protein is essential for embryo development (Liu and Makaroff, 2006). The radially swollen 4 (rsw4) mutant is a temperature-sensitive line that contains a mis-sense mutation in ESP1 (Wu et al., 2010); replicated chromosomes fail to disjoin in roots. In addition, the roots of rsw4 accumulate high levels of the mitotic-specific Cyclin B1 and show disorganized cortical microtubules. However, how inactivation of ESP1 specifically affects Cyclin B1 remains to be determined (Liu and Makaroff, 2006).

The role of ESP1 in Arabidopsis mitosis and meiosis has also been investigated by means of an RNAi construct driven by the 35S and meiotic-specific DMC1 promoters (Yang et al., 2009). The inability to recover RNAi plants containing the

35S promoter suggested that ESP1 is an essential gene during mitosis. RNAi plants containing the DMC1 promoter showed entangled and stretched chromosomes during anaphases I and II (Yang et al., 2009). In addition, chromosome bridges and DNA fragmentation were observed, which suggested that ESP1 is an essential gene for HR as well as chromosome segregation during both meiotic divisions (Liu and Makaroff, 2006; Yang et al., 2009). SYN1 and SMC3 signals persisted along the chromosome arms and the centromeres throughout meiosis in DMC1-ESP1-RNAi plants. ESP1 RNAi knockdown during meiosis induced non-homologous association of centromeres, disruption of the radial microtubule system after telophase II, and disruption of the nuclear cytoplasm, which resulted in multinucleate microspores (Yang et al., 2009). Thus, ESP1 appears to function beyond the removal of cohesin in plant cells. Despite the importance of ESP1, little is known about the mechanism of its regulation in plants (Yang et al., 2009). Analysis of plant genomes has failed to identify a putative plant homolog of Securin, and no experimental work has been conducted on the activation of the Separase pathway.

ROLE OF COHESIN IN REPAIR OF DSBs

Cohesin is important for postreplicative repair of DSBs in both mitosis and meiosis (Klein et al., 1999; Cortés-Ledesma and Aguilera, 2006). The essential function of cohesin in DNA repair is to allow a DSB on one sister to be repaired using the undamaged sister as a template. Thus, it brings the two sister chromatids into close proximity to facilitate the repair by HR. In budding yeast, cohesin is removed from the chromatin at DSB sites to promote DSB resection and repair (McAleenan et al., 2013).

As discussed above, SYN2/AtRAD21.1 and SYN4/AtRAD21.3 have been shown to play roles in DNA repair (da Costa-Nunes et al., 2006, 2014). Further, results from the characterization of ctf7 and wapl1 wapl2 ctf7 single and triple mutants suggested that the failure to establish and regulate cohesion leads to the expression of genes involved in HR and the establishment of cohesion, including ATM, BRCA1, RAD51, PARP2, SMC5, SMC6B, and TOPOII-α in vegetative tissues (Bolaños-Villegas et al., 2013; De et al., 2016). The basis for these changes in gene expression is not well understood and whether alternate error-prone DNA repair mechanisms such as non-homologous end joining (NHEJ) are activated is unclear. In this context, it is worth mentioning that in human cells the cohesin complex contributes to the protection of distinct double-strand ends in the NHEJ DNA repair pathway, helping to avoid genome rearrangements in S/G$_2$ phases (Gelot et al., 2016). It has been also demonstrated that the interaction between BREAST CANCER 2 (BRCA2) and cohesin via PDS5 is important for HR (Brough et al., 2012). In Arabidopsis, PDS5 genes are overexpressed upon exposure to γ-rays. Furthermore, the absence of PDS5 proteins causes hypersensitivity to DNA damaging agents and severely reduced HR, which is probably related to reduced expression of SMC6 genes (Pradillo et al., 2015). The Arabidopsis SMC5/SMC6 complex meliorates sister chromatid alignment after DNA damage, allowing DNA repair by HR (Mengiste et al., 1999;

Watanabe et al., 2009). Conversely, the reduced repair efficiency by HR in *smc6b* mutants may facilitate gene editing (Qi et al., 2013). It has been proposed that cohesin and SMC5/SMC6 have partially overlapping functions and can complement one another if necessary (Tapia-Alveal et al., 2014).

Beyond its function in DNA segregation and repair, cohesin influences other important biological processes such as the regulation of gene expression, duplication of centrosomes and spindle polar bodies, and chromosome condensation (Mehta et al., 2013). In meiosis, cohesin complexes are also important for repairing DSBs. Unlike mitosis, during meiosis the formation of DSBs is programmed and most of them are repaired using non-sister chromatids as templates. Meiotic cohesin complexes also influence chromosome organization to ensure proper chromosome pairing, synapsis, and recombination (Bardhan, 2010; Zamariola et al., 2014). They also have a role in centromere coupling, a mechanism by which non-homologous centromeres pair during prophase I in HR-defective mutants (Tsubouchi and Roeder, 2005) and in bouquet formation, the clustering of telomeres anchored to the nuclear envelope at early meiotic stages (Golubovskaya et al., 2006; Storlazzi et al., 2008).

CONCLUSION

The establishment of chromatid cohesion is crucial for ensuring accurate chromosome dynamics throughout the cell cycle. In plant cells, it is also essential for the development of embryos and seeds and the ability of plants to deal with DNA damage caused by ionizing radiation and faulty DNA replication. During meiosis, cohesin forms a platform for the assembly of the SC, plays an essential role in the exchange between homologous chromosomes and ensures their correct segregation at anaphase I. The regulation of meiotic and mitotic processes has a far-reaching effect on the survival and propagation of a species. Also, for agricultural applications, the study and characterization of genes involved in the establishment of cohesion has potential to enhance the long-term survival, reproduction and adaptation of crops under adverse environmental conditions, including increased UV radiation and the presence of genotoxic agents in soil and water. In addition, cohesin manipulation could be an useful tool to generate clonal seeds by apomixis, a type of asexual reproduction that avoids meiosis. Further work is needed to continue the characterization of plant cohesin complexes, the mechanics of its regulation and to explore its potential application for plant breeding.

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