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Meiosis: Recombination and the Control of Cell Division

8

Eric Jenczewski, Raphael Mercier, Nicolas Macaisne, and Christine Mézard

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8.1 Introduction

Meiosis is a key step in the reproduction of many species, halving ploidy levels to produce haploid gametes, which are then restored by fertilization. The reduction in ploidy in meiosis results from one cycle of replication followed by two cell divisions (Fig. 8.1). During the first division, which is very specific to meiosis, the homologous chromosomes segregate to opposite poles. The second division during which the sister chromatids separate, is a modified version of mitosis. Thus a diploid cell produces four haploid spores.

However, depending on species-specific mechanisms for sporocyte maturation, it is possible that not all spores become gametes. For example, in *Arabidopsis thaliana* four spores are obtained from female meiosis but only one matures to produce an embryo sac containing an egg cell, while in male meiosis, all four spores give rise to pollen grains.

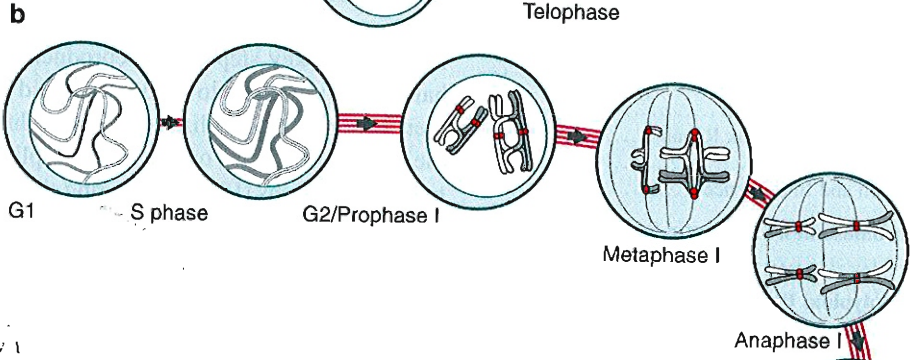
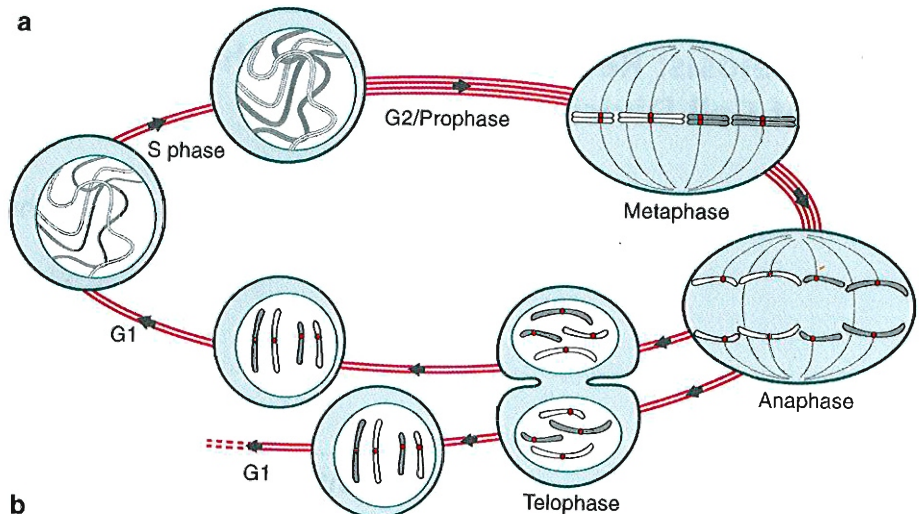
During the first meiotic division, homologous chromosomes recombine producing mosaic chromosomes that are harmonious patchworks of the original genetic material contained in the meiocytes. The underlying molecular mechanisms for these recombination events are very well conserved among species even if each species has shown some specificity in regulation of the pathways or the molecular actors involved. Recombination is initiated by the formation of programmed DNA double strand breaks (DSBs) (Fig. 8.2a). These breaks are repaired using mainly the homologous chromosome as a template. The repair process leads either to a crossover (CO, i.e., reciprocal exchange of a large fragment of the chromosome) or a gene conversion not associated with a CO (non-reciprocal exchange of small DNA fragments, i.e., a non-crossover, NCO)(see Fig. 8.2).

In this review we summarize and discuss recent findings concerning the main steps of chromosome recombination and segregation during meiosis and the control of cell division in diploid and polyploid plants. Several excellent

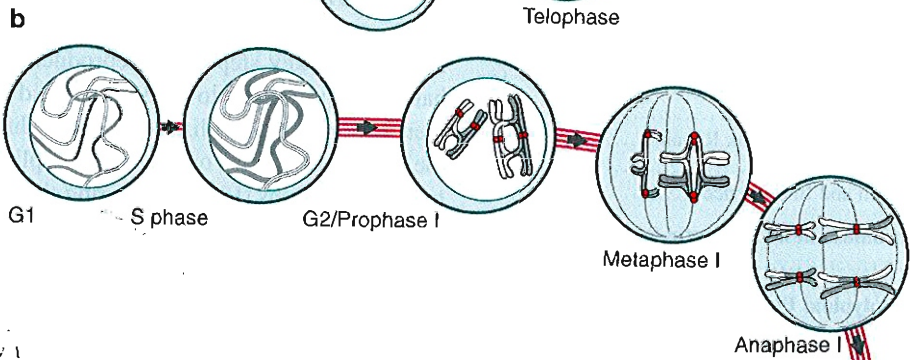
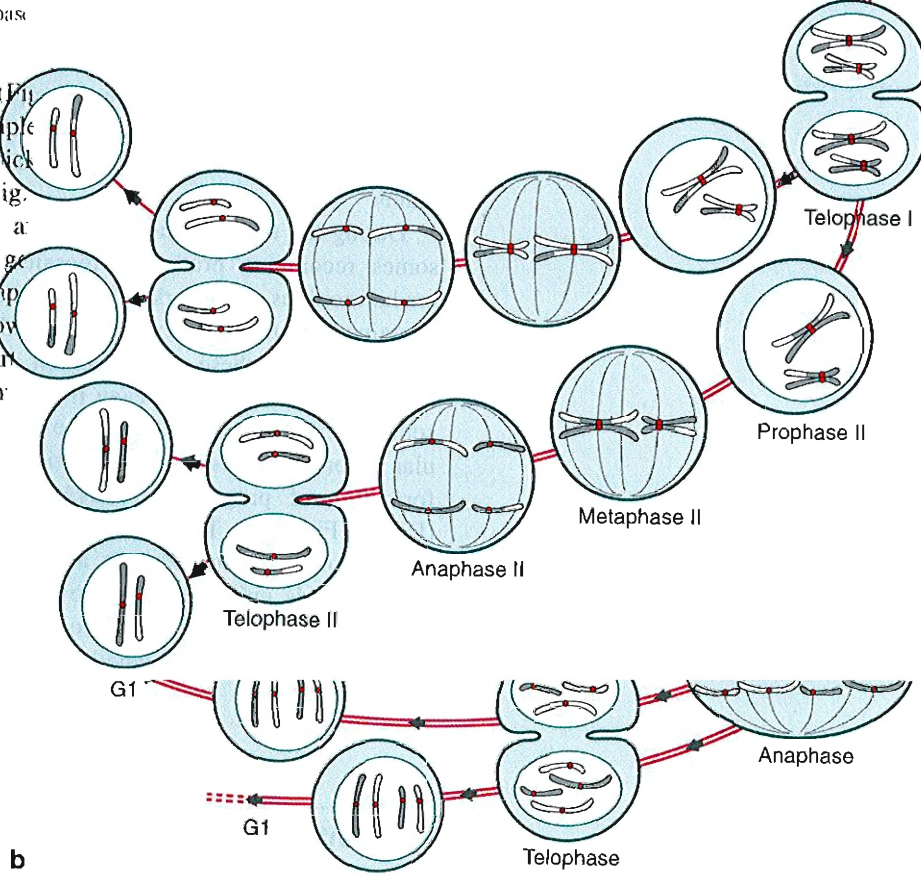
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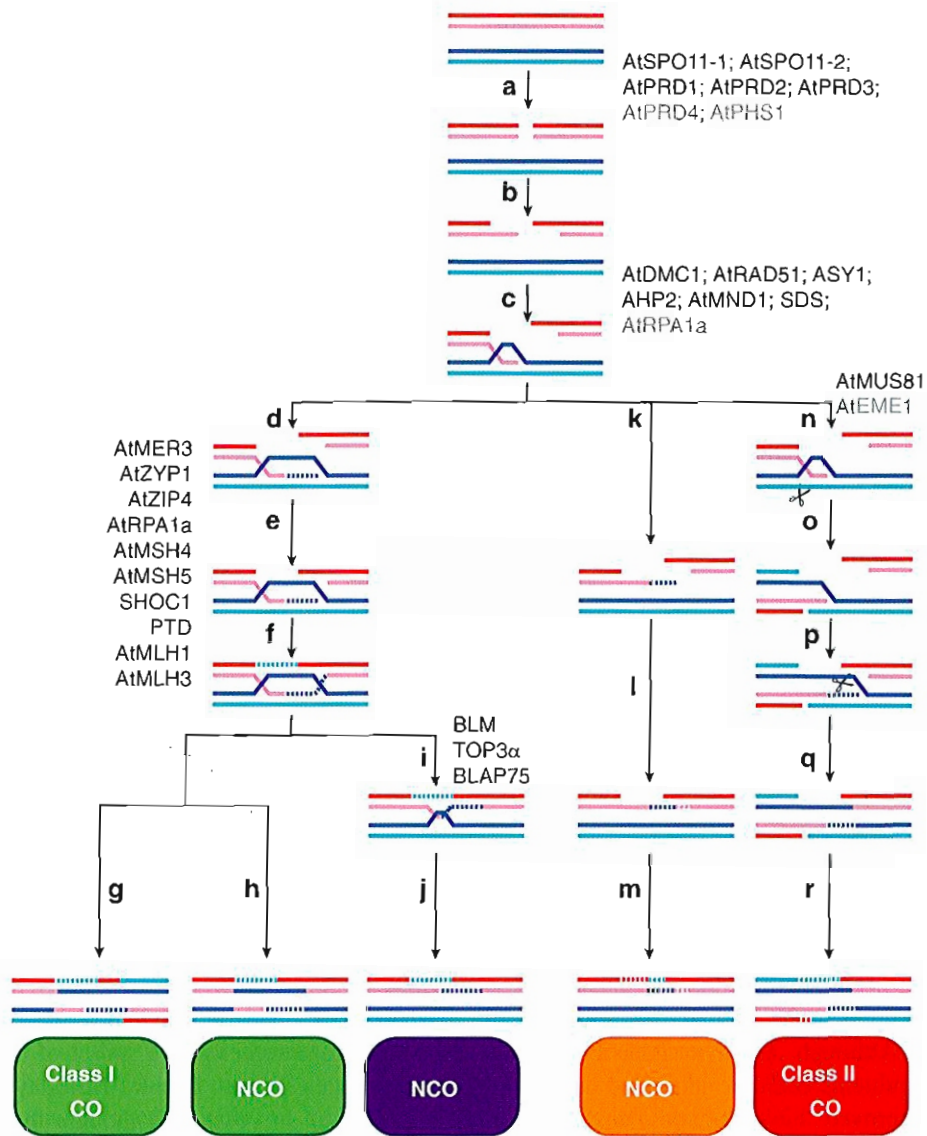


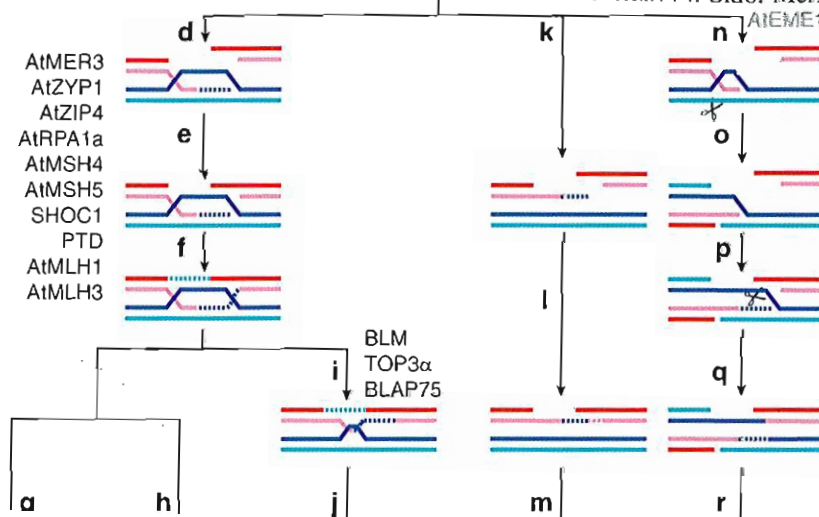
Fig. 8.2 A simplified view of the meiotic recombination mechanisms. (a) Recombination is initiated by the programmed formation of DNA double strand breaks (DSBs). (b) DSBs are then processed to produce 3' single stranded DNA ends. (c) Next, DNA ends invade allelic sequences on the homologous chromosomes. (d–f) A subset of these recombination intermediates form double Holliday junctions (dHJs). Resolution of dHJs leads either to class I crossovers (CO) (g) or to non-crossovers (NCOs) (h). (i, j) On the other hand, decatenation of dHJs produces

NCOs. (k, l, m) Nascent DSB partner complexes shown in (c) may also be processed by Single Strand Annealing (SSA). After DNA invasion and replication, the extended end is displaced from the template (k) and anneals with its partner (l) producing a NCO (m). (n–q) Class II COs are produced via a single Holliday Junction. *Arabidopsis* proteins known (*black characters*) or thought to be (*grey characters*) involved are indicated at their presumed step of action

8.2 Meiotic Recombination

8.2.1 Initiation of Meiotic Recombination

A. thaliana, whereas AtSPO11-3 is not (Stacey et al. 2006). In rice, functional analysis of OsSPO11-1 demonstrated its role in DSB formation (Yu et al. 2010). In *Saccharomyces cerevisiae* (budding yeast), six other meiotic proteins (*Rec102 Rec104 Rec114. Ski8. Mer2 and Mei4*) and three



Rec10, *Rec15*, *Rec24*) (Keeney 2007). In plants as in other eukaryotes, several screens (forward or reverse, see Mercier and Grelon 2008) were developed to identify genes that control this DSB formation step. It appears that only a few of these additional DSB-forming proteins are conserved in other kingdoms and even when they show sequence similarities their function in DSB formation may not be entirely conserved. For example, in *A. thaliana*, the DSB processing role of Rad50 and Mre11 is only conserved in vegetative cells and not in meiotic DSB formation (Bleuyard et al. 2004; Puizina et al. 2004). The *Arabidopsis* Ski8 ortholog does not appear to play a role in DSB formation (Jolivet et al. 2006). Nevertheless, two plant DSB formation genes were successfully identified in forward screens: *AtPRD1* in *Arabidopsis* and *PAIR1* in rice (Nonomura et al. 2004; De Muyt et al. 2007).

To improve the identification of new genes involved in DSB formation in *A. thaliana*, a very efficient high throughput analysis forward screen was designed (De Muyt et al. 2009b). A collection of 55,000 mutant lines was successively screened for (1) a reduction in fertility (1,280 lines) then (2) meiotic defects (80 lines) and finally (3) meiotic DSB formation defect-like phenotypes (28 lines). Following fine localization, out of the nine loci identified, three new genes *AtPRD2*, *AtPRD3* (ortholog of *PAIR1* in rice) and *AtPRD4* (Mathilde Grelon, personal communication) were obtained that are involved in DSB formation. Several mutant alleles of each gene were identified, suggesting that screen saturation has been reached and that all genes required for DSB formation have been identified in *Arabidopsis* (unless there is gene duplication, preventing its identification by forward genetics). Although at first sight no obvious orthologs for these proteins could be identified outside the plant kingdom, improved bioinformatics analysis then showed that *AtPRD2* could be the ortholog of Mei4 in mice and yeast (Kumar et al. 2010). For *AtPRD3* and *AtPRD4* as yet no significant homology has been identified outside the plant kingdom.

The *PHS1* gene was identified in maize and appears to be involved in DSB repair but not formation and to prevent synapsis between non-homologous chromosomes (Pawlowski et al. 2004). When the *Arabidopsis* *PHS1* homolog is inactivated, nuclear import of the DSB repair protein Rad50 is dramatically decreased. However, surprisingly, chromosomal fragmentation was not reported, which is in contrast to the phenotype of the single *rad50* mutant (Bleuyard et al. 2004; Ronceret et al. 2009). A recent report in mice suggested that *PHS1* is an ortholog of the Rec114 protein (see above; Kumar et al. 2010). In *S. cerevisiae*, Rec114 interacts with Mei4 and both proteins are involved in DSB formation (Keeney 2007). In mice, the role of Mei4 in DSB formation as well as its interaction with Rec114 is conserved suggesting that its function in DSB formation may also be conserved.

It would be interesting to reanalyse the *phs1* mutants in maize and *Arabidopsis* with regards to these new data obtained in mice concerning Mei4 and Rec114.

8.2.2 Meiotic DNA Double-Strand Break Repair

DSBs are then processed to produce 3' single stranded DNA ends (Fig. 8.2b). In yeast, this single stranded DNA interacts with RPA, a heterotrimeric protein that helps the recombinase activity of Rad51 (reviewed in Sung et al. 2003). *Arabidopsis thaliana* has five and *Oryza sativa* (rice) has three homologs of the large subunit RPA1. Analyses of the meiotic proteome of *Brassica oleracea*, a close relative of *Arabidopsis*, showed that *AtRPA1a*, one member of the *AtRPA1* family, is potentially a meiotically-expressed gene (Sanchez-Moran et al. 2005). *OsRPA1a* has the most amino acid sequence similarities with *AtRPA1a* and belongs to the same phylogenetic clade (Chang et al. 2009). However, chromosomal defects in the corresponding mutants are very different. A mutation in *OsRPA1a* leads to severe fragmentation of meiotic chromosomes in male meiocytes consistent with a similar role in rice and yeast. In contrast, no fragmentation is observed in *atrpal* but crossover (CO) rates are dramatically lower (see below) (Osman et al. 2009) suggesting that this protein functions later in the DNA repair process. Thus, different RPA complexes in rice and *Arabidopsis* could perform the various RPA tasks during meiotic recombination (Chang et al. 2009).

Next, DNA ends invade allelic sequences on the homologous chromosomes and a subset of these recombination intermediates forms double Holliday junctions (dHJs) (Fig. 8.2c–f). In yeast, it is thought that the meiotic dHJs are mainly resolved toward the formation of COs (Hunter 2007). However, in *Arabidopsis*, recent results suggest that some of the meiotic dHJs could mature via a different pathway (Chelysheva et al. 2008; Hartung et al. 2008). A protein complex known as BTB in mammals and RTR in yeast has anti-CO activity through the dissociation of dHJ (or potentially aberrant dHJ) (Raynard et al. 2006). This complex contains a RecQ-like helicase (BLM for Bloom in Human, Sgs1 in yeast), a topoisomerase (Top3 α) and a third protein Blap75/Rmi1/Nce4, identified through its interaction with either BLM or Sgs1. However, limited data are available on the role of this complex in meiosis. In *Arabidopsis*, a mutation in BLAP75 or a hypomorphic mutation in Top3 α results in extensive fragmentation of meiotic chromosomes, which depends on meiotic DSB formation, and an unusual arrest at the end of telophase I (Chelysheva et al. 2008; Hartung et al. 2008). The activity of BLM and RTR *in vitro* and in vegetative cells suggests that at least in *Arabidopsis*, and potentially in all species,

BLM/RTR could decatenate a subset of normal dHJs or aberrant recombination intermediates containing dHJs toward NCOs.

DNA DSBs are then repaired using either the homologous chromosome or the sister chromatid as a template. In meiosis, it is thought that there is a bias in the choice of template and that repair is mainly directed toward the homolog. In *A. thaliana*, AtDMC1 the meiotic recombinase, is one of the major actors facilitating this bias (Couteau et al. 1999; De Muyt et al. 2009b). Three other proteins also play a role in this process (De Muyt et al. 2009b): ASY1, an axis associated protein related to yeast Hop1 (Sanchez-Moran et al. 2007); AtHP2, a homolog of yeast Hop2 which was suggested to mediate the activity of the yeast Dmc1 protein in a complex with AtMND1 (Chen et al. 2004; Vignard et al. 2007); and SDS, an *Arabidopsis* cyclin that interacts with several Cyclin Dependant Kinases (CDKs) (Azumi et al. 2002). The role of PAIR2, the rice homolog of ASY1, in this process remains to be elucidated (Nonomura et al. 2006).

The *PAIR3* gene was also identified in rice in a large-scale screen of a population of T-DNA insertional mutants for partial or complete sterility (Yuan et al. 2009). The protein has no similarity with any known proteins and no known motifs except a coil-coiled domain. A preliminary characterization of *pair3* mutants found that synapsis between homologous chromosomes at prophase I was absent. Additional studies are needed to determine the role of PAIR3 in meiosis.

The *AtXRI1* gene is highly transcribed in response to gamma rays (Dean et al. 2009). Detailed characterization of *atxri1* mutants showed that its chromosomes displayed extensive fragmentation that did not depend on SPO11-induced DSBs. Thus, *AtXRI1* could play an important role in the S-phase of meiosis together with two other proteins which when depleted cause a similar phenotype, MEI1 and CDC45 (Grelon et al. 2003; Stevens et al. 2004). *AtXRI1* could also function in meiotic DSB repair by interacting with MIP1, which in turn interacts with the AtMND1 protein partner of AtHP2 (see above). Thus *AtXRI1* could be involved in various aspects of homologous replication: repair of collapsed replication forks and post-replication repair pathways. Finally, *AtXRI1* is also involved in the post-meiotic stages of pollen development.

8.2.3 Crossover Distribution

DSBs can be repaired either as COs or NCOs (Fig. 8.2). In plants, as in many higher eukaryotes, it is thought that the number of NCOs largely exceeds the number of COs. However only indirect evidence supports this supposition, no direct test to measure NCO rates is presently available in plants (reviewed in De Muyt et al. 2009a).

The number of COs per chromosome and per meiosis is tightly controlled. In most species, there is a need for one obligatory CO per pair of homologous chromosomes. Moreover, the distribution of COs along chromosomes is not homogenous. Interference (see below) plays a role in both controlling and constraining the final CO distribution but additional factors are also important in localizing COs. In all species with an available genetic map, the CO rate drops in centromeric regions with estimated decreases between five- to more than 200-fold depending on organisms (Talbert and Henikoff 2010). Nevertheless, intriguing recent results in maize suggest that centromeres are not inert for meiotic recombination. In a mapping population, two gene conversion events not associated with COs were mapped in 53 inbred lines giving a theoretical rate of 10^{-5} conversion events per marker and per generation. This suggests that CO formation in centromeric regions is not prohibited through recombination abolition (e.g., prevention of DSB formation) but by specific control of the DSB repair process. A precise analysis of the frequency and distribution of NCOs is clearly needed to better understand their rate of formation and localization in plant genomes.

GC content is positively correlated with high CO rates in many species such as rat, mice, human, zebra finch, honeybee, maize, even at a broad scale (Jensen-Seaman et al. 2004; Beye et al. 2006; Gore et al. 2009; Backström et al. 2010), although the underlying mechanisms responsible for this correlation are still under discussion (see Duret and Arndt 2008; Marsolier-Kergoat and Yeramian 2009). To add a piece to the puzzle, in *Arabidopsis*, the variation in CO rate of a male-female averaged recombination map was negatively correlated to GC content (Drouaud et al. 2006). Moreover, on the five *Arabidopsis* chromosomes, CO rates negatively correlate with GC content in female meiosis but not in male meiosis (Laurène Giraut, personal communication). Variation in CO rates also correlate with several other genomic features such as transposable elements, the CpG ratio, gene density, nucleotide polymorphisms or chromosome architecture properties like distance to telomeres or centromeres (Petes 2001; Nachman 2002; Jensen-Seaman et al. 2004; Myers et al. 2005; Sainenac et al. 2009). Nevertheless, none of these other characteristics are systematically correlated with CO rate variation across every species. Thus the various features that correlate with non-homogeneity in CO rates may have causal relationships or may be incidentally related.

CO rates and distribution can vary between male and female meiosis in the same species. Haldane (1922) suggested that the heterogametic sex had a lower CO rate as a consequence of selection against recombination between the sex chromosomes. However, this hypothesis, referred to as the Haldane and Huxley rule, has since been called into question. Less recombination in the homogametic sex than

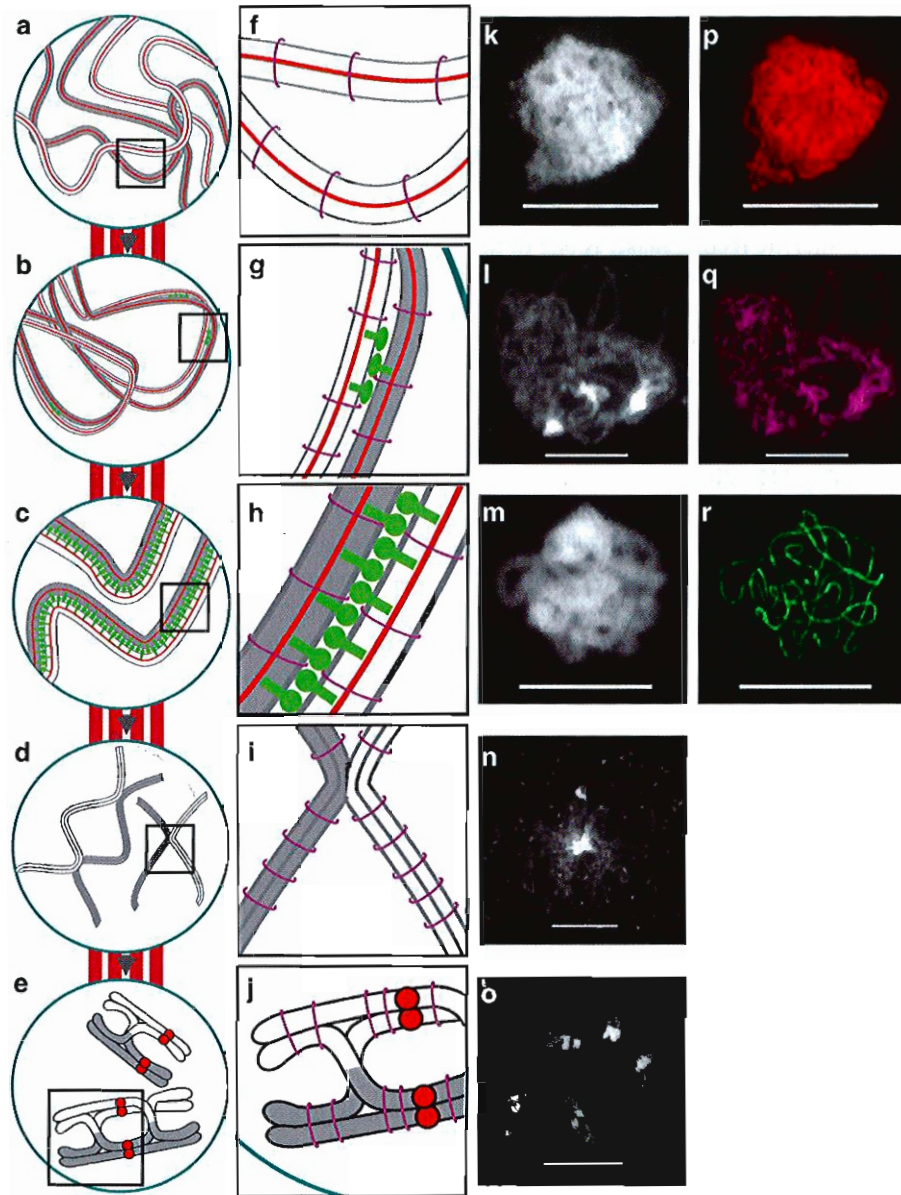
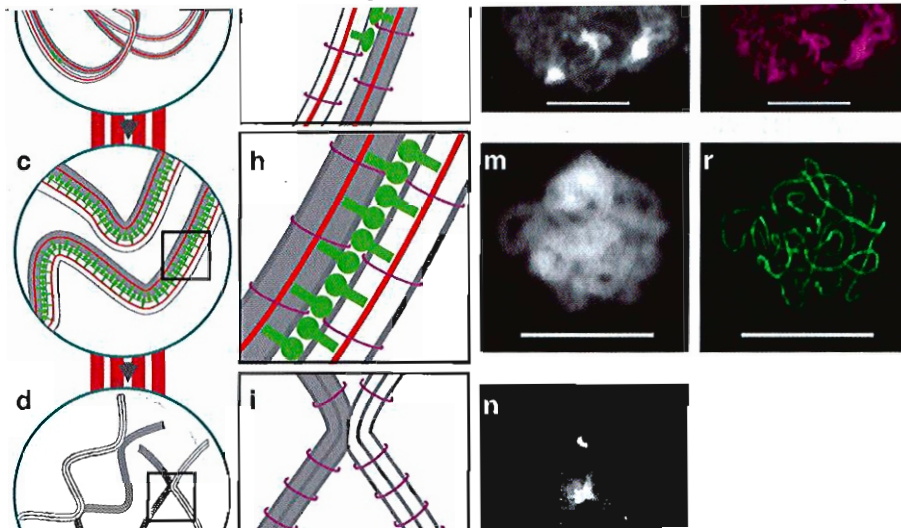


Fig. 8.3 Prophase of the first meiotic division. Leptotene (a, f, k, p): chromosomes begin to condense and the axial element (red line) along chromosomes is formed (a, f); purple structures = cohesin complexes; red line: axial elements. (k) DAPI staining of an *Arabidopsis* meiocyte at leptotene. (p) Immunolocalization of the ASY1 protein associated with the axial element at leptotene. Zygotene (b, g, l, q): homologous chromosomes synapse and the central element between the axial elements, now called lateral elements, is formed to constitute the tripartite structure called the synaptonemal complex (SC) shown in green in (b) and in greater detail in (g). (l) DAPI staining of an *Arabidopsis* meiocyte at

zygotene. (q) Immunolocalization of the cohesin SCC3 protein at zygotene. Pachytene (c, h, m, r): synapsis between homologous chromosomes is complete (c, h). (m) DAPI staining of an *Arabidopsis* meiocyte at pachytene. (r) Immunolocalization of the Zyp1 protein in the synaptonemal complex at pachytene. Diplotene (d, i, n): chromosomes decondense and the SC is disassembled (d, i). (n) DAPI staining of an *Arabidopsis* meiocyte at diplotene. Diakinesis (e, j, o): chromosomes condense; bivalents individualize; homologous chromosomes remain physically attached through chiasmata and sister chromatid cohesion (e, j). (o) DAPI staining of an *Arabidopsis* meiocyte at diakinesis

the heterogametic one has been observed in some species

2007) but none satisfactorily explain the variations in



correlation between the mean CO number per chromosome and the SC length (Laurène Giraut and Christine Mézard, personal communication). Moreover, several studies have shown that CO number and SC length vary coordinately, even in situations where DNA length is constant (Kleckner et al. 2003). For example, in human meiosis, males have about half the CO number and total SC length compared with females (Wallace and Hulten 1985). This correlation was also reported in male and female meiocytes in the flatworm *Dendrocoelum lacteum* (Croft and Jones 1989) and zebrafish (Singer et al. 2002; Wallace and Wallace 2003) and in many other species with various individuals of the same population (Fox 1973; Quevedo et al. 1997; Tease and Hulten 2004). The reasons for this correlation are still poorly understood.

8.2.4 Crossover Formation and Interference

In many species, at least two CO pathways coexist (Fig. 8.2). Class I COs are sensitive to interference whereas Class II are not. These two pathways also exist in plants (Copenhaver et al. 2002). The phenomenon of interference was first described at the beginning of the twentieth century as a lower frequency of double COs in disjoint chromosomal intervals than was expected if they occurred independently (Sturtevant 1915). One of the consequences is that the physical distance between adjacent COs increases. When interference is total as in *Caenorhabditis elegans*, only one CO occurs per pair of homologous chromosomes. The mechanism that mediates interference is still poorly understood. Nevertheless, many molecular actors that are involved in this Class I pathway have been identified. In the yeast *S. cerevisiae*, interfering COs depend on the ZMM proteins (Zip1, Zip2, Zip3, Zip4, Msh4, Msh5 and Mer3), Mlh1 and Mlh3 whereas non-interfering COs need the Mus81-Mms4 complex (reviewed in Lynn et al. 2007). In *A. thaliana*, homologs of many of these genes have been characterized: *AtMSH4*, *AtMSH5*, *AtMER3*, two *AtZYP1*, *AtZYP4*, *AtMLH3*, *AtMLH1* and *AtMUS81* (Fig. 8.2). Since a detailed description of these genes was recently reviewed elsewhere (Mercier and Grelon 2008; De Muyt et al. 2009a), here we will only discuss the main conclusions.

In rice, a mutant in the *MER3* homolog displays a similar phenotype to the *Arabidopsis mer3* mutants described (Wang et al. 2009). The *SHOC1* gene is also a likely functional homolog of Zip2 (Macaisne et al. 2008). *SHOC1* interacts with PTD, an Ercc1 homolog, suggesting a role for a XPF-Ercc1 complex in Class I CO formation (Nicolas Macaisne, personal communication). Two Mms4 homologs were identified in *Arabidopsis* and the corresponding proteins interact with AtMus81 (Geuting et al. 2009). However, the meiotic phenotype of corresponding

mutants was not reported. As yet, no Zip3 homolog has been identified. In *zmm* mutants, CO rates drop down to a minimum of 15% of the wild type level and residual COs do not display interference, suggesting the co-existence of two CO pathways. Even in the absence of both the ZMM and AtMUS81 proteins, and as observed in *S. cerevisiae*, some COs (5–7%) are still detected suggesting either the existence of a third CO formation pathway or the activation of a pathway only active when the two main ones are absent. Unlike observations in yeast, *zmm* mutants in *Arabidopsis* do not show defects in synapsis between homologous chromosomes suggesting that synapsis depends on precocious recombination intermediates rather than Class I COs. The *Arabidopsis* genome contains two *Zip1* orthologs, *AtZYP1a* and *AtZYP1b*. Plants where both *ZYP1* genes have been downregulated using interfering RNAs undergo synapsis between non-homologous chromosomes and form aberrant multivalents whereas chiasmata labelled by the MLH1 proteins are only slightly reduced (Higgins et al. 2005). The *Zip1* homolog of rice, ZEP1 also shows some specificity compared with other organisms (Wang et al. 2010a). In its absence, chromosomes align along their entire length but the SC is not formed and the number of COs may increase slightly suggesting a role later in meiosis.

In maize, a statistical approach was developed to analyse the position of late recombination nodules, which are electron dense structures thought to designate all Class I and Class II COs (Falque et al. 2009). This analysis demonstrates that (1) both Class I and Class II coexist in maize; (2) the proportion of Class II COs varies from 6% to 23% (with an average of 15%) depending on the chromosomes. A similar proportion of non-interfering COs was identified in two other plants: 30% in tomato (Lhuissier et al. 2007) and 28% in rice (Wang et al. 2009). These values, together with the approximately 15% found in *Arabidopsis*, seem to be in the same range as the values found in *S. cerevisiae* (7–12%) and mice (5–11%) (Broman et al. 2002; Malkova et al. 2004; Guillon et al. 2005).

8.3 Dynamics of Chromosomes, Chromatin Structure and Meiosis

During meiosis, chromosomes undergo a series of dramatic structural changes. They condense, exchange DNA segments, pair, synapse, decondense and move in the nucleus. Probably due to this complexity, meiosis is a relatively long process compared to mitosis. It takes from two (in *Triticum aestivum*) to nine times longer (in *Trillium erectum*) in some species (Bennett 1971). In *Arabidopsis*, the meiotic process is three times longer than the mitotic cell cycle (8.5 h) (Armstrong et al. 2003). Prophase of the first

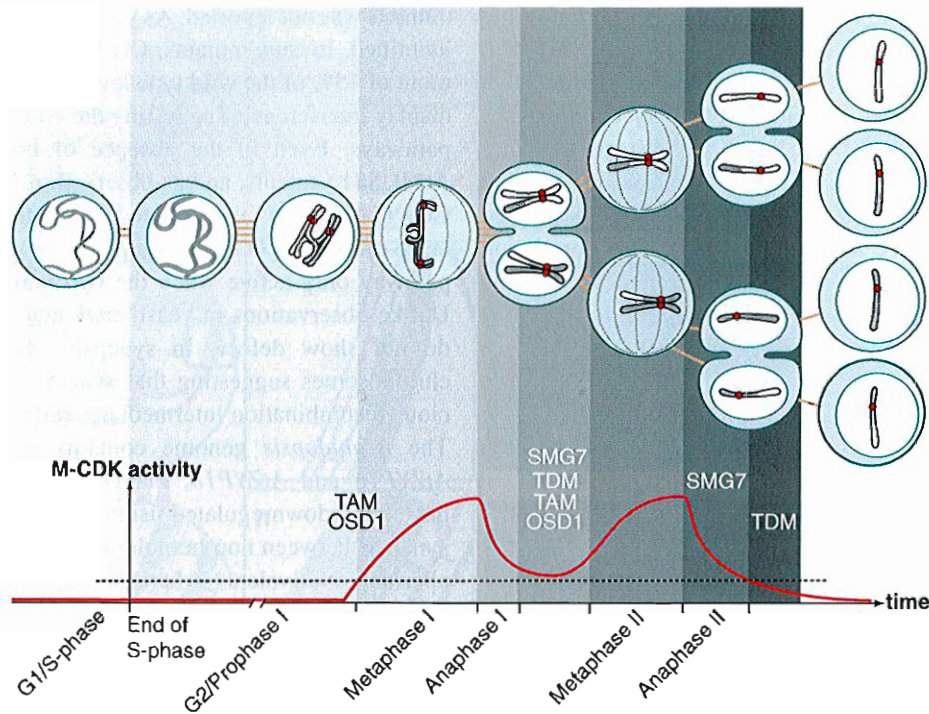


Fig. 8.4 Model of the control of meiosis progression. The red line represents a not yet identified cyclin-cyclin dependent kinase (CDK) activity that controls meiosis progression. This activity must reach a certain level to allow the G2/prophase to metaphase I transition and reach a peak at metaphase I and metaphase II. The metaphase to anaphase

transitions are ensured by a rapid decrease in CDK activity. However, at the end of anaphase I, a certain level of cyclin-CDK activity must be maintained to allow entry into meiosis II and to avoid premature meiosis exit. *Arabidopsis* genes involved in the control of meiosis progression are indicated above the graph at their presumed time(s) of action

meiotic division (Figs. 8.3 and 8.4) is the longest stage reflecting its complexity (21.3 h), the remaining stages occur relatively rapidly (2.7 h).

In leptotene (Fig. 8.3a, f, k, p) chromosomes begin to condense and the axial element along the chromosomes is installed. At zygotene (Fig. 8.3b, g, l, q), homologous chromosomes synapse and the central element between the axial elements, now called lateral element, is formed to constitute the tripartite structure called the SC (see above).

Synapsis is complete at pachytene (Fig. 8.3c, h, m, r). In most species, telomeres cluster during early zygotene at a single site on the nuclear envelope and this structure, called the “bouquet” resumes at the beginning of pachytene. Recombination is initiated by the formation of DSBs in leptotene, thus before synapsis, and is completed during pachytene. At diplotene (Fig. 8.3d, i, n), the SC disappears but homologous chromosomes remain linked to each other by COs and sister chromatid cohesion (a proteinaceous) structure deposited on chromosomes after replication that

Thus chromosomal movement across the nucleus is essential for recombination, pairing and synapsis. Live observations in *S. pombe* and *S. cerevisiae* have provided evidence of unexpected vigorous chromosome motility during prophase I. In *S. pombe*, before karyogamy, telomeres cluster tightly beneath the spindle pole body (SPB) while centromeres detach from the SPB. During karyogamy, the two telomere clusters fuse and after karyogamy, the diploid nucleus elongates about three times and initiates violent oscillations from one end to the other forming the “horsetail” nucleus that will remain throughout prophase I. This movement is driven by microtubules coming from the SPB and telomeres clustering beneath the SPB located at the leading edge of the moving nucleus (reviewed in Ding and Hiraoka 2007). In *S. cerevisiae*, chromosomal dynamics were visualized using a SC protein tagged with green fluorescent protein (GFP) (Scherthan et al. 2007; Koszul et al. 2008). SCs exhibit dramatic and continuous movements, crossing relatively large distances in the nucleus and changing shape.

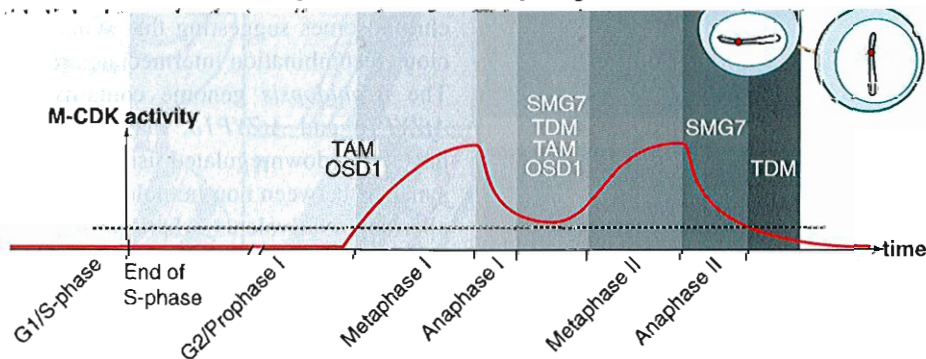


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Pawlowski 2009). Similar to the observations in yeasts, maize chromosomes move extensively during zygotene and pachytene with dynamic deformation of the nuclear envelope. Chromosome motility is dependent upon the actin and tubulin cytoskeletons. It has been proposed that these chromosome movements either promote pairing of homologous chromosomes and/or eliminate unwanted connections (Ding and Hiraoka 2007; Koszul et al. 2008; Sheehan and Pawlowski 2009).

Chromatin structure has an important role to play in the meiotic process. The most striking evidence has come recently from mice and *S. cerevisiae* where a link between trimethylation of the histone H3 at lysine 4 (H3K4) and the formation of DSBs was demonstrated (Borde et al. 2009; Baudat et al. 2010; Myers et al. 2010; Parvanov et al. 2010). In both species, this trimethylation, which is associated with an open chromatin structure, occurs before the formation of DSBs (Borde et al. 2009; Buard et al. 2009). Set1 ensures it in yeast. In mice, Prdm9 does the job: it is a meiosis-specific protein containing a Set1-like domain and a series of Zinc fingers that gives it sequence specificity for H3K4 trimethylation and thus DSB formation. No clear orthologs of these proteins exist in plants and the similarity of mechanisms remains to be demonstrated. However, recently, in maize, based on the parallel between Mu transposon insertion sites and regions with high recombination rates, it was suggested that meiotic recombination occurs in regions marked with open chromatin features in vegetative cells such as a high level of trimethylated H3K4, trimethylated H3K36, acetylated H3K9 and low level of trimethylated H3K27 (Liu et al. 2009). Whether this correlation holds true when DSB forming regions are looked at more precisely remains to be confirmed and whether the mechanisms are similar to those described in budding yeast and mice needs to be elucidated.

In *S. pombe* (fission yeast), a mutation in the Set1 homolog that severely reduces the level of trimethylated H3K4 does not affect sporulation and thus probably not the global level of DSBs (Noma and Grewal 2002). However in fission yeast, histone acetylation plays a role in meiotic recombination (Yamada et al. 2004). Histone acetylation is also correlated with meiotic recombination in *S. cerevisiae* (budding yeast) (Mieczkowski et al. 2007) even if it is now clear that it is not the main player linked to DSB formation. Recent results obtained in *A. thaliana* suggest that histone acetylation plays a role in the meiotic process (Perella et al. 2010). In a mutant line over-expressing the GCN5-related histone N-acetyltransferase, the distribution of meiotic COs appeared to be altered. Overall, the number of COs per meiotic cell was similar to wild type but the number of COs per chromosome was altered with less COs on the longest chromosome 1 and more COs on the shortest chromosome 4. Sister chromatid separation during the second meiotic division was also

disrupted suggesting that histone hyperacetylation may have a profound effect on global chromatin structure affecting different aspects of the meiotic process.

8.4 Meiotic COs in Polyploid Plants

It has now been clearly established that *all* flowering plants have experienced at least one, and usually more, rounds of whole genome duplication (i.e., polyploidy events) during their evolution (Soltis et al. 2009; Van de Peer et al. 2009; Fawcett et al. 2013, this volume). Nearly 30% of extant flowering plants, including most of the world's important crops, are polyploids (Wood et al. 2009) while all other angiosperms have been impacted by ancient polyploidy events (they are *palaeopolyploid* species; Jiao et al. 2011).

One immediate consequence of polyploidy is an increase in the number of chromosomes that can compete for pairing, synapsis and recombination at meiosis. In newly-formed synthetic or natural polyploids, the presence of more than two partners usually leads to abnormal meiosis with multiple or illegitimate chiasma associations that result in chromosome missegregation, aneuploidy and partial fertility (Ramsey and Schemske 2002). By contrast, extant wild and cultivated polyploids display a clear tendency towards a diploid-like meiotic behaviour. In autopolyploid species, which are derived from within a single species (see Soltis et al. 2010 for details), this results from an increased number of bivalents forming at meiosis I, to the detriment of multivalents, between any pair of homologs (resulting in polysomic inheritance). In allopolyploid species, which usually arise via hybridization between different species followed by chromosome doubling, regular meiosis requires a non-random assortment of chromosomes into pairs with COs being exclusively formed between homologous rather than homoeologous chromosomes (i.e., inherited from different progenitors). Several reviews have examined diploidization in polyploids from a cytological, genetic, agronomic and evolutionary point of view (Jenczewski and Alix 2004; Able and Langridge 2006; Hamant et al. 2006; Able et al. 2009; Moore and Shaw 2009; Cifuentes et al. 2010a; Yousafzai et al. 2010a). We reiterate here that suppression of COs between homoeologous chromosomes is usually under polygenic control, with one locus having a greater influence than the others and frequent gene-dosage effects.

8.4.1 Changes in CO Distribution

An unexpected result that has emerged from comparisons of CO formation in allopolyploid species and their diploid progenitors is that COs sometimes get a boost in polyploids.

For example, Brubaker et al. (1999) compared the genetic map of allotetraploid cotton with that of its diploid parents and observed that allotetraploidy in *Gossypium* has been accompanied by an increase in CO rates. However we do not yet know if this observation holds true for polyploids in general or if it only illustrates genotypic variation in the propensity to form COs within the diploid species (i.e., it is possible that the true parents of the allopolyploid cotton formed more COs than the diploid plants used to build the diploid genetic maps). Nevertheless, recent analyses in *Brassica* which directly addressed this concern have confirmed the trend observed in cotton. Leflon et al. (2010) analysed the extent of CO variation in a set of related diploid AA, allotriploid AAC and allotetraploid AACC *Brassica* hybrids which were produced using exactly the same genotypes. Combining immunolocalization of MLH1 and genetic analyses, the authors observed that the number of COs in the allotriploid AAC hybrid was higher than in the diploid AA hybrid, with the allotetraploid AACC showing intermediate behaviour (Leflon et al. 2010). Although the precise mechanisms involved are not presently known, these results point towards an unexpected interplay between increased ploidy and enhanced recombination. This in turn may tentatively explain why increased and more variable recombination rates are observed in plants, which have been repeatedly impacted by polyploidy, compared with animals (Gaut et al. 2007; Kejnovsky et al. 2009).

8.4.2 Genetic Control of CO Formation

8.4.2.1 Wheat

At present, most continuing efforts to identify genes involved in the genetic control of recombination in polyploids are focusing on wheat (Crismani et al. 2006; Boden et al. 2007; de Bustos et al. 2007; Lloyd et al. 2007; Khoo et al. 2008; Boden et al. 2009; Bovill et al. 2009; Perez et al. 2010), and most notably on recombination between homoeologous chromosomes (Griffiths et al. 2006; Al-Kaff et al. 2008; Yousafzai et al. 2010b).

A number of these studies have aimed to identify wheat orthologs of key recombination genes including *Asy1* (Boden et al. 2007), *Msh7* (Lloyd et al. 2007), *Mre11* (de Bustos et al. 2007) and *Rad50* (Perez et al. 2010). The homoeologous copies of *Mre11* and *Rad50* in wheat are highly conserved but have slightly different expression levels (de Bustos et al. 2007; Perez et al. 2010); yeast two-hybrid assays revealed that the products of the *Rad50* and *Mre11* genes show a great affinity for one another that does not depend on their genome of origin (Perez et al. 2010). This example demonstrates that genetic redundancy in recent (<10,000 year-old) polyploids provides a buffer effect for crucial functions.

Another approach has specifically aimed to identify novel candidate meiotic genes. Crismani et al. (2006) produced and analysed a large-scale transcriptomics dataset across a

meiotic time series in bread wheat and identified ~1,350 transcripts that were temporally-regulated during the early stages of meiosis. Some of these candidates shared sequence similarity with genes involved in chromatin condensation, SC formation and recombination while most others showed no sequence similarities with genes in the databases. Functional characterization of these candidates has now to be pursued.

CO suppression between homoeologous chromosomes is one expected additional constraint that an allopolyploid species has to contend with during meiosis (compared to a diploid species). In wheat, this control is ensured by a multi-genic system (for review: Sears 1976; Jenczewski and Alix 2004), with the *Ph1* locus (Wall et al. 1971) localized on the long arm of chromosome 5B, having the most influence (Riley and Chapman 1958; Sears and Okamoto 1958). This system is efficient in both natural and synthetic wheats (Mestiri et al. 2010) even when suppressors are present as have been found in some genotypes of *Aegilops speltoides* (Dvorak et al. 2006).

A 50-year quest was necessary to characterize the *Ph1* locus at the molecular level (see Yousafzai et al. 2010b for a review of the cloning efforts). *Ph1* has been defined as a region containing a cluster of seven genes related to cyclin-dependant kinases (CDK) (see Sect. 8.5 for details about these proteins) interrupted by a segment of heterochromatin (Griffiths et al. 2006). This makes it distinct from its homoeologs, which contain five (on chromosome 5A) and two (on chromosome 5D) cdk-like genes, respectively (Al-Kaff et al. 2008). Detailed bioinformatics and *in silico* analyses has recently indicated that one of the *Ph1* cdk-like genes shares many functional attributes with human CDK2 (Yousafzai et al. 2010a). Human CDK2 promotes the timely entry into premeiotic DNA replication and the first nuclear division; it also induces transcription of a number of early meiosis-specific genes including *Hop1*, which encodes a component of the lateral element of the SC and plays an important role in pairing of meiotic chromosomes (Szwarcwort-Cohen et al. 2009). Expression profiling has revealed that one 5A cdk-like and five of the *Ph1* cdk-like genes from the 5B locus are transcribed, including two apparent pseudogenes (Al-Kaff et al. 2008). By contrast, transcription of most functional cdk-like genes from 5A and 5D is detected only when the 5B copies are deleted. G. Moore et al. have thus proposed that deletion of *Ph1* could result in a higher level of overall functional cdk-like proteins, which may be responsible for the observed meiotic phenotypes of *ph1* mutants (Al-Kaff et al. 2008). If this hypothesis holds true, then over-expression of cdk2-like target genes would be expected in these mutants. Indeed, this is exactly what Boden et al. (2009) observed; they showed that absence of *Ph1* correlates with increased transcription of *TaASY1*, a gene with significant sequence and functional similarity to *Hop1*. Likewise, Knight et al. (2010) showed that okadaic acid, a potent protein serine/threonine phosphatase inhibitor that activates CDKs, promotes intergenomic recombination in

wheat \times rye interspecific hybrids, thereby phenocopying the absence of *Ph1*. Even if direct functional evidence is still required to demonstrate that wheat *Ph1* is a functional analogue of human *CDK2*, all current results indicate that it is likely to be so (Yousafzai et al. 2010b). A major challenge of the future will be to reconcile this function with all the meiotic defects that have been observed in *ph1* mutants: non-resolution of incorrect and multiple early associations between chromosomes (Holm and Wang 1988), CO formation between non-homologous chromosome segments (Luo et al. 1996), defects in chromosome condensation and/or scaffold organization (Mikhailova et al. 1998), and asynchronous chromatin remodelling between homologs (Prieto et al. 2004; Colas et al. 2008).

8.4.2.2 *Brassica napus*

Over the last decade, *Brassica napus* has become a second model for deciphering how COs between homoeologous chromosomes are genetically suppressed. In this species, a major locus, named *PrBn* for *Pairing regulator in B. napus*, was shown to regulate CO formation between non-homologous chromosomes in allohaploid plants produced from different varieties (Jenczewski et al. 2003). Comparative analyses between the meiotic phenotype of 363 allohaploids produced from 29 accessions and the maternal origins of the same 29 accessions recently indicated that these different levels of CO suppression between homoeologs in *B. napus* allohaploids were the result of repeated polyploidy in this species (Cifuentes et al. 2010b). Actually *PrBn* shows incomplete penetrance (Cifuentes et al. 2010b) and four to six additive and epistatic QTLs have been detected, which contribute to the meiotic behaviour of *B. napus* haploids (Liu et al. 2006). *PrBn* has also been shown to determine the frequency, but not the distribution of COs between homoeologous chromosomes during meiosis of *B. napus* haploids and also to affect homologous recombination in allotriploid AAC hybrids (Nicolas et al. 2009). By contrast, genotypes with differing *PrBn* activities at the haploid level do not change the rate of CO formation between homologous chromosomes in allotetraploid AACC hybrids (Nicolas et al. 2009) suggesting that the effect of *PrBn* on recombination is dosage-dependent. Experiments are ongoing to characterize the *PrBn* locus at the molecular and phenotypic levels.

8.4.2.3 Cotton

Although it is clear that natural selection has certainly favored the evolution of mechanisms that promote exclusive bivalent formation in allopolyploids, it remains to be understood if the CO suppression between homoeologous chromosomes is paralleled by a similar effect on the other product of meiotic recombination, i.e., NCO or gene conversion events. Recent investigations in allotetraploid cotton have provided very

interesting information on this pending question (Salmon et al. 2010). Tetraploid cotton is almost a strictly bivalent-forming species (Kimber 1961) and displays disomic inheritance (Reinisch et al. 1994; Brubaker et al. 1999) indicating that COs are almost exclusively formed between homologous chromosomes. Irrespective of this control, Salmon et al. (2010) used a vast EST dataset to demonstrate that non-reciprocal recombination events have occurred between homoeologous sequences throughout polyploid divergence and speciation in cotton. The authors first identified ESTs in the allopolyploids derived from one parental EST but that displayed at least one homoeoSNP from the other parent. They subsequently sequenced *de novo* genomic DNA corresponding to 20 putative recombination events and validated 14 of these chimeric sequences. Six were sequences from the D genome that have experienced conversion by the A homoeolog, whereas four others exhibited the reciprocal situation. Cloning and sequencing homoeologous copies from a total of five allopolyploid cotton species demonstrated that not a single recombination event was shared among species, which indicated that these events occurred sporadically after allopolyploid speciation.

8.5 The Meiotic Cell Cycle in Plants

Modification of the somatic cell cycle is one of the key features of meiosis (N.B. meiosis is not a cycle, the products of meiosis cannot undergo another round of meiosis, but by analogy with mitosis we use the term cell cycle to describe the control of progression through meiosis) (Figs. 8.1 and 8.4). The most prominent difference between meiosis and the canonical mitotic cell cycle is that two divisions follow a single replication at meiosis whereas replication and division strictly alternate during mitotic proliferation. The meiotic cell cycle follows the same phases as mitosis: G1, which precedes replication; S, the replication phase; G2, between replication and nuclear membrane break-down; and a mitotic phase during which the chromosomes contract and align (prophase to metaphase) and separate (anaphase). But meiosis differs from mitosis in several aspects of the cell cycle. Firstly, the G2 phase is dramatically longer and is the scene of chromosomal pairing and recombination. Secondly, while mitosis follows (G1 – S – G2 – metaphase – anaphase – G1) n cycles, meiosis follows a strikingly different pattern that leads to halving of the chromosomal content, G1 – S – G2 – metaphase I – anaphase I – interphase – metaphase II – anaphase II (Fig. 8.4). Two phases of division follow each other, without an intervening S phase, but just a short interphase without DNA replication.

Precisely how the mitotic machinery is modified for the purpose of meiosis is still poorly understood. Most of the knowledge currently available originates from studies

carried out in unicellular fungi, *Xenopus laevis* or mouse oocyte systems (Marston and Amon 2004). Cyclins and CDKs form complexes that are essential for progression through both the mitotic and meiotic cell cycles. High CDK activity is required for entry and progression into metaphase and rapid decrease of CDK activity, mediated by the Anaphase Promoting Complex (APC), is required for induction of anaphase and exit from the division phases. The transition from meiosis I to meiosis II requires a fine balance in cyclin-CDK activity: it must be sufficiently low to exit meiosis I but must nonetheless be maintained at a level sufficiently high to suppress DNA replication and promote entry into meiosis II (Marston and Amon 2004; Pesin and Orr-Weaver 2008).

While only a few years ago nothing was known about the control of meiotic progression at the molecular level in plants this is an exciting time for the field. Recently, CDKA activity was shown to indeed oscillate throughout the course of plant meiosis (Bulankova et al. 2010) and several genes involved in crucial transitions were functionally characterized in *Arabidopsis* (*OSD1*, *TAM*, *SMG7*, *TDM*).

Two of these genes, *TAM* and *OSD1* are required for the transition from meiosis I to meiosis II. Null *osd1* and *tam* mutants fail to enter the second division in both male and female meiosis and exit meiosis after anaphase I, leading to the production of functional $2n$ gametes (d'Erfurth et al. 2009, 2010; Wang et al. 2010b). Interestingly, male meiocytes lacking both *OSD1* and *CYCA1;2/TAM* fail to enter meiotic division I, producing tetraploid spores directly after prophase (d'Erfurth et al. 2010). This shows that in addition to their crucial function in driving the meiosis I to meiosis II transition, these two genes are involved in the prophase to metaphase I transition (Fig. 8.4). This suggests that they both contribute to an activity, most likely mediated by CDK, which promotes entry into metaphase I and into metaphase II. The molecular function of *OSD1* is currently unknown, however, by analogy to fission yeast *Mes1*, it may inhibit APC activity, thus promoting CDK activity (d'Erfurth et al. 2009). The cyclin *TAM/CYCA1;2*, may directly or indirectly promote the CDK activity controlling cell cycle progression.

The two other genes, *SMG7* and *TDM*, appear to have opposite effects on cell cycle progression from the above genes in the meiotic cycle. In *smg7*, meiosis arrests at late anaphase II and cells do not exit from meiosis (Fig. 8.4). *SMG7* is a nonsense-mediated mRNA decay factor suggesting an unappreciated link between the cell cycle machinery and RNA processing (Riehs et al. 2008). Mutants in the *TDM* gene have an even more spectacular phenotype: meiosis progresses normally up to the end, performing the two divisions, but then an aberrant third round of division takes

place, without replication (Ross et al. 1997; Glover et al. 1998) (Fig. 8.4). *TDM1* has limited similarity with *Xe-p9*, a regulatory subunit of CDK. Genetic interaction studies revealed complex interactions between these genes. *tdm* is epistatic to *smg7*, suggesting that the anaphase II arrest of *smg7* depends (directly or indirectly) on the presence of *TDM* (Bulankova et al. 2010). Strikingly, double *tam-2/tdm* and *tam-2/smg7* mutants exhibit the *tdm* and *smg7* phenotype, respectively (Bulankova et al. 2010). Thus, the absence of either *TDM* or *SMG7* removes the requirement for *TAM* for entry into meiosis II (Fig. 8.4). Remarkably, while *osd1* and *tam* single mutants have very similar phenotypes (d'Erfurth et al. 2010), the double *osd1/tam* mutant shows the *osd1* phenotype with meiotic exit at the end of meiosis I (Raphaël Mercier et al., unpublished data). This suggests that *OSD1* and *TAM* act differently on the progression of meiosis. Altogether, these recent studies highlight the existence of a very complex network (not yet well understood!) to regulate the meiotic process.

Two other genes may also affect the meiotic cell cycle, *AtPS1* and *JASON* (d'Erfurth et al. 2008; Erilova et al. 2009). Both mutants produce diploid spores because of a defect in spindle orientation at the second division in the case of *Atps1* and through an as yet unclear mechanism in the case of *jas*. In both cases it is reasonable to suggest that a defect in cell cycle/phase identity could generate the observed phenotype. Interestingly, *AtPS1* possesses a PINc domain that is present in proteins involved in RNA processing, suggesting that, like *SMG7*, there is a link between RNA decay and the meiotic cell cycle.

The identification of a series of genes involved in meiotic progression and the striking effect of their disruption alone or in combination, provides a unique opportunity to decipher the meiotic cell cycle. Study of the meiotic cell cycle machinery will certainly help to decipher general cell cycle mechanisms, mirroring the massive contribution of meiosis research to the understanding of DNA recombination mechanisms in somatic cells (Szostak et al. 1983; Paques and Haber 1999).

Interestingly cell cycle machinery genes, beyond their function in controlling meiotic progression, appear to have been recruited to control other key features of meiosis such as meiotic recombination. Indeed, the *SDS* gene, which clearly encodes a cyclin, controls the choice of template (e.g., homologous versus sister chromatid) during recombination (De Muyt et al. 2009b) (see above). Similarly, the wheat *Ph1* locus that controls homoeologous recombination (see above) contains CDK-like genes.

Conclusion

This is an exciting time with an international effort in progress to better understand the molecular processes

involved in meiosis in a large variety of higher eukaryotes. In plants, thanks to powerful genetic studies and the development of new efficient molecular tools, these studies have enjoyed a boom in the last 10 years with more than 50 genes identified mainly in *Arabidopsis thaliana* but also in rice, maize, and wheat. Results obtained in plants demonstrate that there is both conservation in the underlying molecular mechanisms but also some specificity compared to other eukaryotic kingdoms. There is now an opportunity when analysing plants to decipher the impact of genome structure on the meiotic process.

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