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Coordinating the events of the meiotic prophase

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Meiosis is a specialized type of cell division leading to the production of gametes. During meiotic prophase I, homologous chromosomes interact with each other and form bivalents (pairs of homologous chromosomes). Three major meiotic processes – chromosome pairing, synapsis and recombination – are involved in the formation of bivalents. Many recent reports have uncovered complex networks of interactions between these processes. Chromosome pairing is largely dependent on the initiation and progression of recombination in fungi, mammals and plants, but not in *Caenorhabditis elegans* or *Drosophila*. Synapsis and recombination are also tightly linked. Understanding the coordination between chromosome pairing, synapsis and recombination lends insight into many poorly explained aspects of meiosis, such as the nature of chromosome homology recognition.

Introduction

Upon entry into meiosis, the diploid nucleus contains two homologous copies of each chromosome, one inherited from the father and the other from the mother. During meiotic prophase I (see Glossary), homologous chromosomes, previously distributed throughout the nucleus, identify each other, enter into an intimate contact and form bivalents (Glossary; Figure 1). At the same time, double-strand DNA breaks (DSBs) are generated in chromosomal DNA and repaired, resulting in meiotic recombination (Glossary). Meiotic prophase I combines events that are biochemical in nature, such as processing of meiotic DSBs, with those that also involve the physical three-dimensional structure of chromosomes, such as co-alignment or juxtapositioning of homologous chromosomes. These events can be categorized as three processes: (1) chromosome pairing (i.e. an interaction between homologous chromosomes that results in their juxtapositioning and formation of bivalents. It includes a step in which homologs get into physical proximity with each other and a subsequent step of the identification of homology between the partners; Glossary), (2) synapsis (i.e. installation of the proteinaceous synaptonemal complex (SC) structure between the two chromosomes in a bivalent that stabilizes the initial pairing interaction; Glossary), and (3) meiotic recombination (which spans the period from the formation of meiotic DSBs to the completion of their repair, including reciprocal chromosome arm exchange). These processes show high complexity, yet, at the same time, they require error-free completion. Errors in meiosis are costly; in humans, they lead to infertility, miscarriage during pregnancy and severe birth defects.

Many individual components involved in chromosome pairing, synapsis and recombination have been identified

Glossary

Bivalents: pairs of chromosomes that form as a result of chromosome pairing and synapsis interactions. They form during zygotene and persist until metaphase I.

Crossover: a reciprocal exchange of chromosome arms and one of the alternative outcomes of meiotic recombination. In late meiotic prophase I, crossovers are sites of chiasmata, cytological structures that link non-sister chromatids of homologous chromosomes and hold bivalents together until metaphase I.

Meiotic prophase I: the longest and most complex stage of meiosis. Subdivided into five substages (Figure 1) based on the changes in chromosome morphology and the progression of pairing and synapsis. In **leptotene**, the decondensed chromatin is organized into chromosomes by the assembly of a proteinaceous core (the axial element). Meiotic recombination is initiated at this step by DNA double-strand breaks (DSBs) that are formed on chromosomes. During **zygotene**, homologous chromosomes pair and synapse, when the central region of the synaptonemal complex (SC) is installed between the paired homologous chromosomes. In **pachytene**, SC formation is complete and meiotic recombination between homologs is resolved. In **diplotene**, the SC disassembles and chiasmata, which are responsible for holding the homologs together, are visible. Finally, in **diakinesis**, the chromosomes undergo a final stage of condensation.Figure 1

Meiotic recombination: the process of formation of DSBs in chromosomal DNA in early meiotic prophase I and their subsequent repair. Meiotic recombination results in formation of crossover and non-crossover products.

Pairing: interactions between HOMOLOGOUS_ chromosomes that result in their juxtaposition. The mechanism of chromosome pairing is not known. However, pairing must include a step in which homologs get into physical proximity with each other and a subsequent step involving the identification of homology between the partners (homology search). By definition, only interactions between homologous chromosomes are designated as 'pairing'. Chromosome pairing is followed by synapsis and leads to the formation of bivalents, i.e., stable pairs of homologous chromosomes.

Synapsis: the process of installation of the proteinaceous synaptonemal complex (SC) structure between the two homologous chromosomes in a bivalent that stabilizes the initial pairing interaction. The presence and progression of synapsis are usually inferred experimentally with electron microscopy or immunolocalization of SC component proteins. Synapsis follows chromosome pairing and usually occurs between homologous chromosomes. However, in certain situations (e.g. in haploid cells or in mutants defective in homologous chromosome pairing) synapsis can take place between non-homologous chromosomes.

Synaptonemal complex (SC): a tripartite proteinaceous structure installed between two chromosomes in the process of synapsis. SCs consist of two lateral elements connected by a central region. The lateral elements form as axial elements (AEs, also called the chromosome axis) in leptotene. The central region assembles following chromosome pairing during zygotene. The Zip1 protein forms the central region of the SC in *S. cerevisiae*.

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in the past two decades. However, it is only recently that we have begun to understand the mechanisms responsible for coordination of these processes. Here, we review recent reports that seek to explain how the different meiotic processes are indeed coordinated with each other.

Interaction between homologous chromosome pairing and meiotic recombination

Homologous chromosome pairing includes a step in which the homologs overcome spatial separation within the nucleus and get into close physical proximity with each other and a step in which sequence homology is compared between the interacting partners. The mechanism of chromosome pairing is one of the least-understood aspects of meiosis. It is likely that several different processes contribute to homolog pairing, including associations of homologous chromosomes that exist before meiosis [1,2]. Among the various mechanisms proposed to explain chromosome pairing, a link between meiotic recombination and pairing has been suggested to play a major role.

In *Saccharomyces cerevisiae* and in the mouse, chromosome homology search and pairing have been shown to require proteins involved in initiation and progression through the early steps of meiotic recombination [3–6]. A similar situation has been suggested to exist in plants [7–9], although this has not yet been demonstrated directly. By contrast, pairing is independent from recombination in *C. elegans* and in *Drosophila* females, where chromosomes pair normally in mutants that do not initiate meiotic recombination [10,11]. In fact, in wild-type female *Drosophila*, chromosome pairing precedes the initiation of meiotic recombination [12].

DSB formation and repair

Meiotic recombination is universally initiated by the introduction of DSBs into chromosomal DNA by the recombination protein Spo11 [13] (Box 1). The DSBs are then resected from 5′ to 3′ by a complex of recombination proteins containing Rad50, Mre11 and others [14]. Single-stranded DNA ends created in this way subsequently invade homologous double-stranded DNA. This process is facilitated by another complex of recombination proteins containing two RecA homologs – Rad51 and its meiosis-specific cousin Dmc1 (described below). Later, DSB repair is channeled through two or more [15] alternative pathways that lead to formation of either crossover (Glossary) or non-crossover products [16–18]. The presence of separate pathways leading to crossovers and non-crossovers was first detected in *S. cerevisiae* [16,17], but a similar situation might also exist in *Arabidopsis* [19]. Initial experiments to define these two pathways suggested that they branch no later than the single-strand invasion step [17,18].

Although chromosome pairing in many species is linked to proteins involved in the initiation of meiotic recombination, the nature of this interaction has not been fully elucidated. In *Saccharomyces cerevisiae* and *Coprinus cinereus*, chromosome pairing, as measured with fluorescent *in situ* hybridization (FISH) probes to specific chromosomal loci, requires the presence of the Spo11 protein but does not require the formation of DSBs [20,21]. However, when pairing was measured with a site-specific recombination system in living *S. cerevisiae* cells [3,4], the presence of DSBs was required for pairing. It is not entirely clear why the two approaches for measuring homologous chromosome pairing in yeast gave contradictory results, although different genetic backgrounds of the mutant strains have been suggested as the reason [4].

Role of the Rad51–Dmc1 protein complex in pairing

Several recombination proteins acting downstream from Spo11 are also involved in chromosome pairing. An involvement for Rad51 and Dmc1 in pairing has been proposed in *S. cerevisiae*, mouse and maize, based on analyses of *rad51*- and *dmc1*-defective mutants and analyses of dynamic changes in distribution of Rad51 foci during meiosis [2,7,9,22,23]. In addition, the claim of Rad51 and Dmc1 involvement in chromosome pairing is supported by biochemical data, which indicate that Rad51 and Dmc1 can promote efficient homologous interactions between kilobase-long DNA substrates [24,25]. This ability might provide the basis of the proposed involvement of these proteins in chromosome pairing.

Rad51 and Dmc1 form protein complexes [26], which appear on chromosomes in early meiotic prophase I. These complexes interact with other proteins, such as Hop2 [27–32]. In yeast, absence of Hop2 allows non-homologous chromosome interactions that partially replace homologous pairing and lead to non-homologous synapsis [33], suggesting that this protein is required for the fidelity of chromosome pairing. Hop2 binds to double-stranded DNA and does this before the Rad51–Dmc1 complex is loaded onto chromosomes, suggesting that, during single-strand invasion, it acts on the donor DNA strand, which does not contain DSBs [27,33]. Hop2 also interacts with Mnd1, which requires Hop2 for loading onto chromosomes [32,34]. Tsubouchi and Roeder [30], based on results from *S. cerevisiae*, recently proposed a model in which Rad51 and Dmc1 perform the homology search by acting in two parallel pathways. One of these pathways relies solely on Rad51. In the second pathway, Rad51 is first loaded on chromosomes and then recruits Dmc1, which requires additional factors, including Hop2 and Mnd1, for efficient homology recognition [26,30]. *C. elegans* and *Drosophila* do not have Dmc1 and also lack Hop2 and Mnd1, implying that the entire Dmc1-based pathway has been lost in these species and suggesting that they must rely on a different mechanism to perform the homology search. These mechanisms are unlikely to involve recombination proteins as chromosome pairing in *C. elegans* and *Drosophila* precedes recombination.

Zierhut *et al.* [35] proposed an alternative model of Mnd1–Hop2 function in which these two proteins primarily act on chromatin structure rather than directly at the strand invasion site. These authors discovered that a prophase arrest in yeast *Mnd1* knockouts can be alleviated by deleting *Red1* and *Hop1*, which both encode components of the chromosome axis [35]. They also observed that Mnd1 does not localize directly to the sites of DSBs. Consequently, they suggested that Hop2–Mnd1 might act globally, for example, by making chromatin

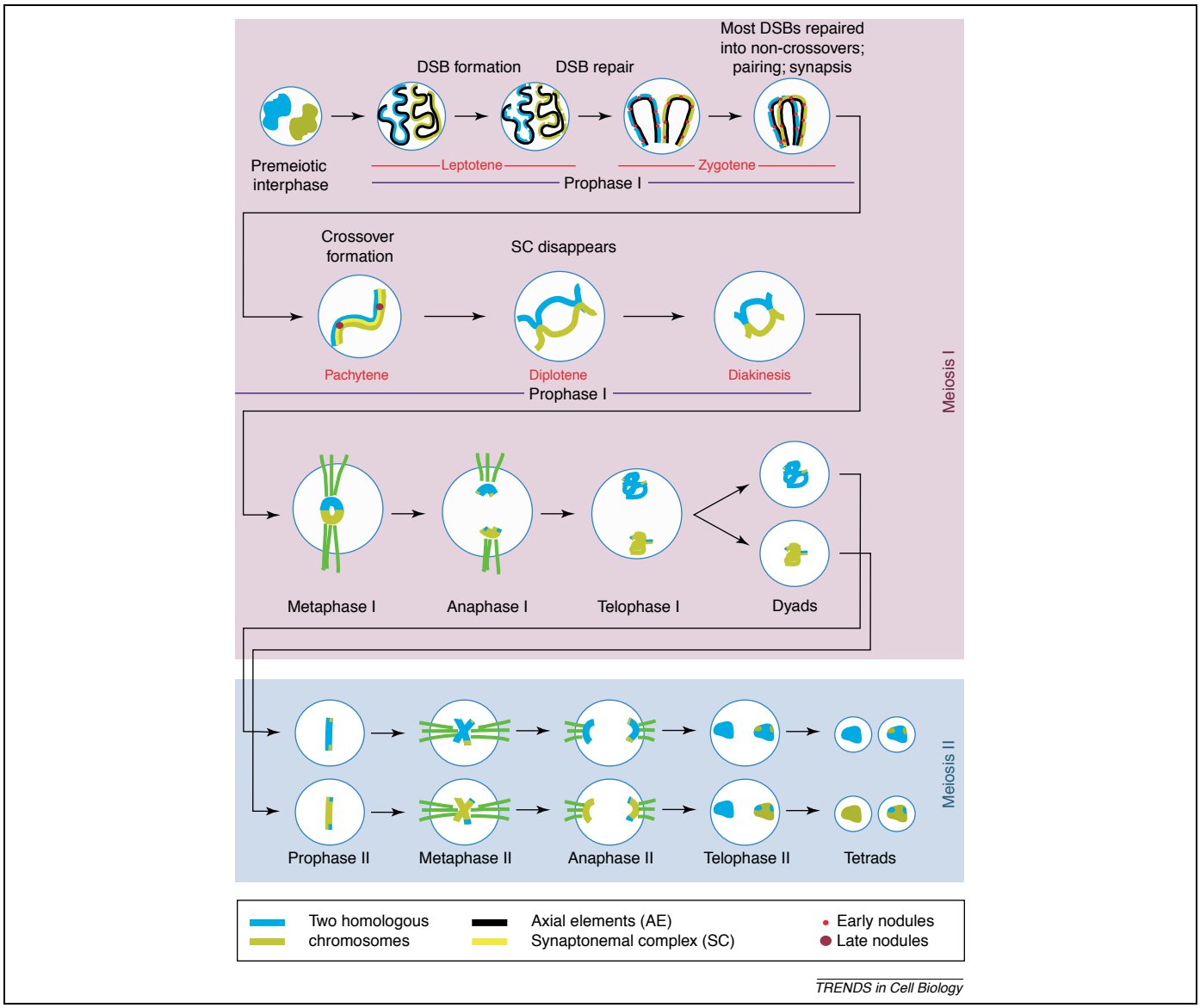

Figure 1. Diagram showing the stages and main events in meiosis. Only one pair of chromosomes is shown, and each homolog is depicted in a different color. Early and late recombination nodules are depicted as dots of different size. The two upper panels show the extended meiotic prophase I. Major events during prophase I are depicted, including DNA double-strand break (DSB) formation and repair, crossover formation, homologous chromosome pairing and synapsis. Interactions between homologous chromosomes during prophase I lead to formation of homolog pairs (bivalents) and reciprocal exchanges of chromatid arms, as a result of crossing-over. Homologous chromosomes segregate in anaphase I. During the second division of meiosis (meiosis II), the chromatids segregate, much like during a normal mitotic division.

more accessible to proteins involved in chromosome pairing and recombination.

Recently, another RecA homolog in addition to Rad51 and Dmc1, Rad51C, has been shown in *Arabidopsis* to act in chromosome pairing, in addition to its role in meiotic recombination [36]. Rad51C is closely related to Rad51 but, interestingly, its function in chromosome pairing is not identical with the function of Rad51. A Rad51C homolog also has been shown to play a role in *Drosophila* female meiosis, although it is unknown whether it is involved also in pairing [37].

Other recombination proteins

Other recombination enzymes might also be involved in pairing of homologs, but the nature of these interactions is not fully understood. For example, in *S. cerevisiae*, *mre11S*, a mutation in the Mre11 protein involved in DNA strand resection, results in a significant frequency of non-homologous chromosome synapsis [38].

In contrast to genes regulating early recombination steps, mutations in genes encoding recombination proteins involved in the formation of crossovers, such as *msh4* or *msh5*, do not affect chromosome pairing [3,4]. This observation suggests that the commitment to pairing is already made at the time when crossovers are formed or that pairing depends mostly on the non-crossover pathway.

Interaction between synapsis and recombination

The relationship between synapsis and meiotic recombination varies among species. In species that require recombination for pairing, such as *S. cerevisiae*, *Sordaria*, *Coprinus*, mouse and *Arabidopsis*, synapsis, which normally follows pairing, also requires DSB formation and

Box 1. Key recombination proteins

Spo11: a meiosis-specific recombination protein belonging to the topoisomerase family and responsible for creating DNA double-strand breaks (DSBs) in chromosomal DNA in meiotic prophase I.

Rad50 and **Mre11:** recombination proteins that form a complex acting downstream of Spo11 in the meiotic recombination pathway. Involved in 5′ to 3′ resection of the meiotic DSBs generated by Spo11.

Rad51 and **Dmc1:** RecA homologs involved in repair of meiotic DSBs. Rad51 and Dmc1 act downstream from Rad50–Mre11 and Spo11. The proteins cover single-stranded DNA ends created by the Rad50–Mre11 complex, forming a nucleoprotein filament. The nucleoprotein filament invades the corresponding region in the homologous double helix in a process called single-strand invasion. Rad51 and Dmc1 form foci on meiotic chromosomes at the sites of meiotic DSBs (see Figure 2) and are components of early recombination nodules. Rad51 is also involved in the repair of somatic DNA breaks. Dmc1 is specific to meiosis.

Hop2 and Mnd1: recombination proteins interacting with Rad51 and Dmc1. Hop2 and Mnd1 are required for homologous chromosome pairing (the *hop2* mutant in yeast shows a high frequency of associations between non-homologous chromosomes) and meiotic recombination. They most likely act during the single-strand invasion step of recombination on the DNA donor strand, which does not contain DSBs.

progression through early stages of the recombination pathway [2,5,6,20,22,23,38–45]. The situation is obviously different in *C. elegans* and *Drosophila*, in which the chromosomes pair and synapse in the absence of DSBs [10,11]. However, even in the latter two species, synapsis and recombination are not completely independent. For instance, proper assembly of the SC is required in *C. elegans* and *Drosophila* for the completion of recombination [46,47].

Temporal coordination

The link between synapsis and recombination is not well understood mechanistically, but most likely lies in the process of the initiation of synapsis. In *S. cerevisiae*, synapsis initiates at distinct sites along each chromosome pair. By contrast, in many plants, synapsis starts primarily at telomeres [48]. Initiation of synapsis is linked to the presence of recombination nodules, which are cytological structures detectable by transmission electron microscopy and implicated in recombination processes [49,50]. Two types of recombination nodules have been observed: early and late nodules. Both types are known to contain recombination enzymes (Figure 2). Early nodules are more numerous, contain Rad51 and Dmc1, and are thought to be the sites of initial single-strand invasions [51]. Late nodules might form from a subset of early nodules or might arise *de novo* later in meiosis [52]. They are few in number, contain recombination enzymes such as Mlh1 and Msh4 instead of Rad51 and Dmc1, and mark the sites of crossovers [52–54]. Several lines of evidence suggest that late recombination nodules also mark the sites of SC initiation [53,55]. In plants, late nodules are located primarily near telomeres, where synapsis is initiated [48]. In yeast, the Zip3 protein is the key component of SC initiation sites. It promotes synapsis by recruiting other SC proteins, such as Zip1 and Zip2 [53]. Zip3 interacts with Msh4 and Msh5, which localize to late recombination nodules. Interestingly, Zip3 also interacts

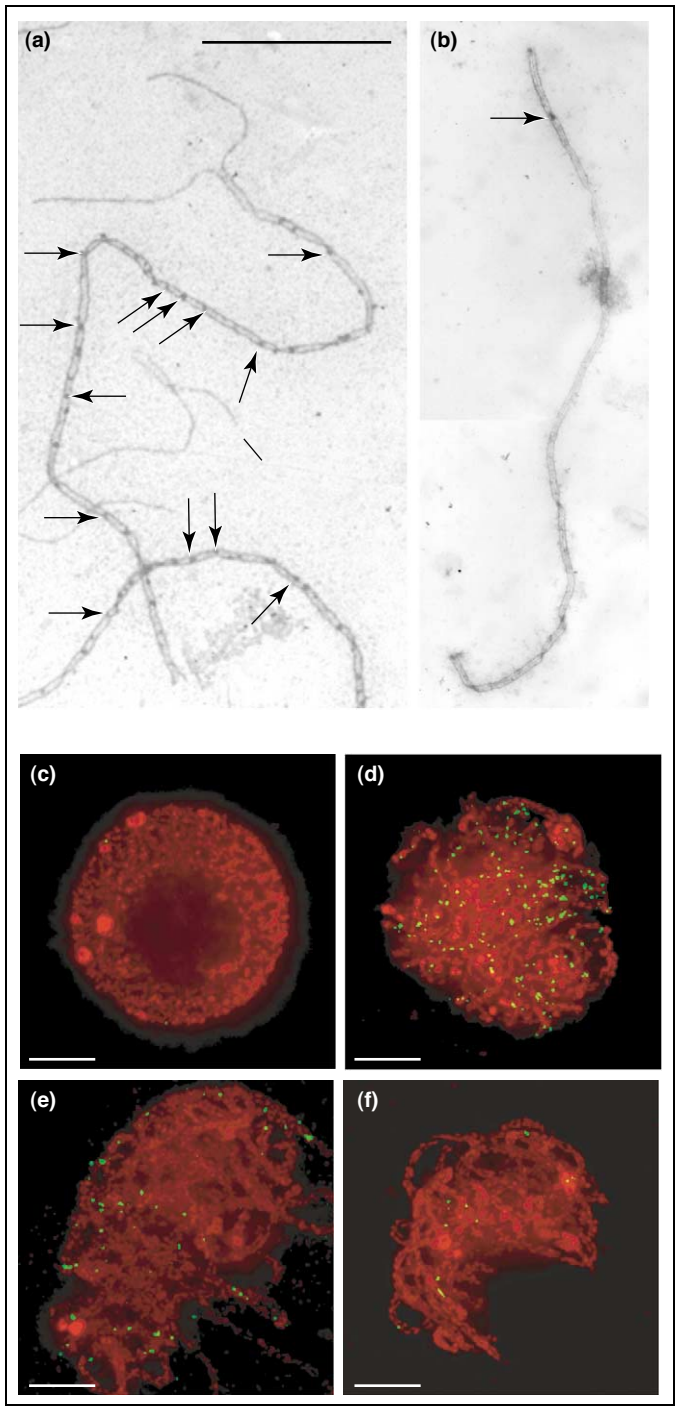

Figure 2. Recombination in the context of the synaptonemal complex (SC) and the chromosomes. **(a,b)** SC spreads of tomato showing recombination nodules. Stained are the lateral elements of the SC. (a). Early nodules in zygotene. Arrows indicate several nodules. (b) A late nodule in pachytene indicated by an arrow. Bar, 5 μm. Images courtesy of L. Anderson and S. Stack, Colorado State University, USA. **(c–f)** Meiotic chromosomes of maize with foci of the Rad51 recombination protein, a component of early recombination nodules. (c) Leptotene. (d) Zygotene. (e) Early pachytene. (f) Late pachytene. Rad51 foci appear on maize chromosomes in early zygotene and their number reaches a peak of ~500 foci per nucleus in mid zygotene. In late pachytene, the number of Rad51 foci drops to ~20 per nucleus, roughly corresponding to the average number of crossovers in maize. DAPI-stained chromatin is shown in red; Rad51 is shown in green. Images are flat projections from several consecutive optical sections through three-dimensional nuclei. Bars, 5 μm.

with Rad51, which is a component of early nodules [53]. This and other evidence suggests that Zip3 might define the fraction of early nodules that subsequently become late nodules – that is, sites that correspond to early

recombination events destined to become crossovers [48,53,55,56]. Not surprisingly, increasing the number of crossovers in yeast leads to a higher number of SC initiation sites [56] and decreasing the number of crossovers leads to a lower number of SC initiation sites [55]. These observations suggest a role for the recombination pathway leading to crossovers in the initiation of synapsis.

In species that require the initiation of recombination for synapsis, the timing of synapsis is also tightly linked to the progression of meiotic recombination. In mutants that exhibit stalled or delayed DSB repair (and non-homologous chromosome associations in place of homologous pairing), such as *hop2* in yeast [33] and *phs1* in maize [8], completion of synapsis is delayed. Conversely, in the *sgs1* mutant in *S. cerevisiae*, which shows increased rates of crossing-over, the completion of synapsis is accelerated in comparison with that of wild-type cells [56].

Spatial coordination

A key feature of meiotic recombination, as compared with somatic recombination, is that DSB repair preferentially uses homologous chromosomes rather than sister chromatids as templates. While crossovers between sister chromatids are not completely inhibited, in *S. cerevisiae* they are ~10-fold less frequent than recombination between homologous chromosomes [57]. This phenomenon is crucial for the formation of chiasmata, which are cytological representations of crossovers, necessary to hold homologous chromosomes together as bivalents in later stages of meiotic prophase I following disassembly of the SCs. Generating the recombination bias towards the homologous chromosome appears to be one of the functions of the lateral element of the SC.

Three axial and lateral element proteins in *S. cerevisiae*, Hop1, Red1 and Mek1, have been proposed to interact with recombination proteins to ensure that crossovers occur between homologous chromosomes rather than sister chromatids [58]. Red1 and Hop1 are required for activation of Mek1. Mek1, in turn, acts to prevent the use of sister chromatids for DSB repair and enables the Dmc1-mediated DSB repair, which employs the homologous chromosome as a template [58–60]. Recently, proteins with similar functions have also been identified in *Drosophila* and *C. elegans*, suggesting that these species might have analogous mechanisms to ensure the homologous chromosome recombination bias, even though they lack Dmc1. In *Drosophila*, the ORD protein, which has been proposed to act in meiotic sister-chromatid cohesion and SC formation, was found to be involved in maintaining the homolog bias by stimulating interhomolog crossovers [61]. In *C. elegans*, a similar role is played by Him-3 [62]. Him-3, an axial/lateral element component, also appears to be involved in the spatial reorganization of chromosomes in the nucleus during early meiotic prophase I and in the initial alignment of homologous chromosomes [62]. This suggests that the homolog bias might be achieved through spatial constraints that make homologous chromosomes more accessible than sister chromatids for reciprocal interactions. These specific spatial constraints might, for example, result from local destabilization of the chromosome axis after the introduction of DSBs [63].

Crossover interference

The crossover pathway eventually leads to the formation of chiasmata, which are essential for proper segregation of chromosomes at anaphase I. Not surprisingly, the number of crossovers per chromosome is tightly regulated. Most eukaryotes, regardless of their genome size or chromosome length, form only one crossover per chromosome or chromosome arm, and the presence of a crossover discourages additional crossovers in its vicinity. This phenomenon is known as crossover interference. The mechanism of crossover interference is not completely understood. However, it appears that interference might be yet another manifestation of coordination between meiotic recombination and synapsis. It is not our intention to discuss the mechanisms of interference in this review. We will instead focus on the aspects of chromosome interference that might involve coordination between meiotic processes.

Crossover interference has long been linked to the presence of SCs [64,65]. However, recent results suggest that interference precedes synapsis. Fung *et al.* [66] studied the Zip2-containing SC initiation sites (that may be marked by late recombination nodules, see the 'Temporal coordination' section) in yeast and found that they already exhibit an uneven distribution and interference, even though they precede synapsis. Studies of recombination intermediates also suggest that, at least in yeast, synapsis requires interference, and not the other way around [18]. Results of theoretical predictions of the mechanical properties of chromosomes and empirical observations of meiotic protein distribution in different chromatin domains along chromosomes indicate that internal physical forces play a major role in chromosome function [67,68]. These analyses also suggest that the internal mechanical forces might be responsible for creating crossover interference. This conclusion, based mostly on studies in *S. cerevisiae*, is also supported by results of a study of chromosome fusions in *C. elegans* by Hillers and Villeneuve [69]. *C. elegans* normally has only one crossover per chromosome. The fusion products consist of two or three whole chromosomes. Yet, they behave as single chromosomes and mostly exhibit a single crossover per bivalent. Analyses of different types of chromosome fusions suggested that crossover interference in *C. elegans* relies on the presence of a continuous chromosome axis [69].

Synapsis and pairing

Both chromosome pairing and synapsis involve intimate associations between chromosomes. However, they are two very different processes. Pairing is an interaction between homologous chromosomes, which is based on homology recognition. Synapsis is a process of cementing an association of two chromosomes by installation of the SCs. In normal meiosis, synapsis follows pairing and binds homologous chromosomes together. However, in mutants and other abnormal situations, such as meiosis in haploid cells, synapsis can be uncoupled from pairing. Extensive

synapsis has been documented in haploid yeast and plants, which obviously lack homologous chromosome pairs [70,71]. Specific proteins, whose absence results in a high frequency of non-homologous synapsis, have also been identified. In *hop2* knockouts in yeast, ~60% of all synapsis is between non-homologous chromosome segments [33]. In maize, a mutant in the *phs1* gene has an even more extreme phenotype, showing ~95% non-homologous synapsis [8]. Hop2 and PHS1 are not SC components but both appear to play a role in linking chromosome pairing and recombination. Hop2 homologs so far have been found in mouse [28], plants [29] and in *Schizosaccharomyces pombe* [72], which lacks SCs, and have been found to perform similar functions in these species. In *hop2* and *phs1* mutants, synapsis is delayed. This suggests that synapsis might be based only on proximity, while sequence homology between the synapsing partners is irrelevant. As a result, synapsis might stabilize any type of intimate chromosome association if homologous pairing is not established in time, as is the case in the *hop2* and *phs1* mutants. It is likely that there are mechanisms in normal meiosis that prevent premature synapsis of any closely positioned chromosome fragments. However, Hop2 and PHS1 are probably not elements of such mechanisms as, if they were, one would expect to see earlier rather than delayed synapsis in the *hop2* and *phs1* mutants. Contrary to the data suggesting independence of synapsis from homologous pairing, a study by Crackower *et al.* [73] described synapsis between nonhomologous chromosome segments that was caused by a mutation in the SC protein Fkbp6 in the mouse. This indicates that perhaps some aspects of synapsis might still depend on homology.

In yeast, independence of pairing from synapsis is also evident from the fact that chromosomes pair in the absence of Zip1, a component of the central region of SCs [4,64]. By contrast, in *C. elegans*, synapsis-dependent mechanisms do contribute to chromosome pairing, and the central SC element is required to stabilize pairing along the entire lengths of chromosomes [74]. This observation might be another indication that the chromosome pairing mechanisms operating in *C. elegans* are different from the ones in yeast.

Concluding remarks

Chromosome interactions during meiotic prophase I occur in the form of pairing, synapsis and recombination. These three processes are not separate from each other but show tight coordination. An extensive amount of data suggests that meiotic recombination is linked to chromosome pairing and to synapsis. Improving understanding of these interactions is of major importance as they lie at the heart of several poorly understood aspects of meiosis, such as the mechanisms of homologous chromosome recognition and crossover interference.

Several meiotic recombination proteins have been postulated to affect chromosome pairing. However, in most cases, understanding of this interaction at the mechanistic level is lacking. It is not entirely clear whether the link between recombination and pairing is mediated by dual-function proteins (i.e. proteins that act in both pairing and recombination), as has been proposed for Spo11, or through the recombination pathway DNA intermediates that act in the chromosome homology search, or both. The best genetic and biochemical evidence exists so far for the case of the involvement of Rad51, Dmc1 and proteins that interact with them, such as Hop2 and Mnd2, in chromosome pairing.

It is still unknown to what extent recombination affects homologous chromosome pairing. It is conceivable that other mechanisms, in addition to the recombination-dependent homology search, are necessary for efficient pairing, especially in species with large and complex genomes that contain large fractions of repetitive DNA. However, regardless of how this question is resolved, the current data point to the existence of a continuous coordination between the progression of meiotic recombination and the progression of chromosome pairing.

Similarly to recombination and pairing, a strong link exists between recombination and synapsis/the synaptonemal complex. Recombination nodules, the sites of meiotic recombination, are likely involved in the initiation of synapsis, while the lateral elements are involved in generating the recombination bias towards the sister chromatid. Crossover interference, a phenomenon that limits the number of crossovers per chromosome, links recombination with synapsis and the chromosome axis. Nevertheless, synapsis is largely independent from pairing and sometimes proceeds regardless of whether proper pairing is established.

The observations of strong links between recombination and pairing, and between recombination and synapsis, suggest that recombination plays a key role in unifying meiotic processes. In yeast, plants and mammals, meiotic recombination starts in early leptotene [8,75,76] and proceeds during most of the meiotic prophase I through a series of distinct steps. Coordinating other meiotic processes, such as pairing and synapsis, to the progression of recombination might be a way to accurately time their initiation, progression and completion. Understanding the intricate interactions between meiotic processes will certainly be one of the hallmarks of meiosis research in the next few years.

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References

1 McKee, B.D. (2004) Homologous pairing and chromosome dynamics in meiosis and mitosis. *Biochim. Biophys. Acta* 1677, 165–180
2 Weiner, B.M. and Kleckner, N. (1994) Chromosome pairing via multiple interstitial interactions before and during meiosis in yeast. *Cell* 77, 977–991
3 Peoples-Holst, T.L. and Burgess, S.M. (2005) Multiple branches of the meiotic recombination pathway contribute independently to homolog pairing and stable juxtaposition during meiosis in budding yeast. *Genes Dev.* 19, 863–874
4 Peoples, T.L. *et al.* (2002) Close, stable homolog juxtaposition during meiosis in budding yeast is dependent on meiotic recombination, occurs independently of synapsis, and is distinct from DSB-independent pairing contacts. *Genes Dev.* 16, 1682–1695
5 Baudat, F. *et al.* (2000) Chromosome synapsis defects and sexually dimorphic meiotic progression in mice lacking Spo11. *Mol. Cell* 6, 989–998

6 Loidl, J. *et al*. (1994) Homologous pairing is reduced but not abolished in asynaptic mutants of yeast. *J. Cell Biol.* 125, 1191–1200
7 Franklin, A.E. *et al*. (1999) Three-dimensional microscopy of the Rad51 recombination protein during meiotic prophase. *Plant Cell* 11, 809–824
8 Pawlowski, W.P. *et al*. (2004) Coordination of meiotic recombination, pairing, and synapsis by PHS1. *Science* 303, 89–92
9 Pawlowski, W.P. *et al*. (2003) Altered nuclear distribution of recombination protein RAD51 in maize mutants suggests involvement of RAD51 in the meiotic homology recognition. *Plant Cell* 15, 1807–1816
10 Dernburg, A.F. *et al*. (1998) Meiotic recombination in *C. elegans* initiates by a conserved mechanism and is dispensable for homologous chromosome synapsis. *Cell* 94, 387–398
11 McKim, K.S. *et al*. (1998) Meiotic synapsis in the absence of recombination. *Science* 279, 876–878
12 Jang, J.K. *et al*. (2003) Relationship of DNA double-strand breaks to synapsis in *Drosophila*. *J. Cell Sci.* 116, 3069–3077
13 Keeney, S. *et al*. (1997) Meiosis-specific DNA double-strand breaks are catalyzed by Spo11, a member of a widely conserved protein family. *Cell* 88, 375–384
14 Smith, K.N. and Nicolas, A. (1998) Recombination at work for meiosis. *Curr. Opin. Genet. Dev.* 8, 200–211
15 Argueso, J.L. *et al*. (2004) Competing crossover pathways act during meiosis in *Saccharomyces cerevisiae*. *Genetics* 168, 1805–1816
16 Allers, T. and Lichten, M. (2001) Differential timing and control of noncrossover and crossover recombination during meiosis. *Cell* 106, 47–57
17 Hunter, N. and Kleckner, N. (2001) The single-end invasion: An asymmetric intermediate at the double-strand break to double-Holliday junction transition of meiotic recombination. *Cell* 106, 59–70
18 Borner, G.V. *et al*. (2004) Crossover/noncrossover differentiation, synaptonemal complex formation, and regulatory surveillance at the leptotene/zygotene transition of meiosis. *Cell* 117, 29–45
19 Higgins, J.D. *et al*. (2004) The *Arabidopsis* MutS homolog AtMSH4 functions at an early step in recombination: evidence for two classes of recombination in *Arabidopsis*. *Genes Dev.* 18, 2557–2570
20 Celerin, M. *et al*. (2000) Multiple roles of Spo11 in meiotic chromosome behavior. *EMBO J.* 19, 2739–2750
21 Cha, R.S. *et al*. (2000) Progression of meiotic DNA replication is modulated by interchromosomal interaction proteins, negatively by Spo11p and positively by Rec8p. *Genes Dev.* 14, 493–503
22 Yoshida, K. *et al*. (1998) The mouse RecA-like gene *Dmc1* is required for homologous chromosome synapsis during meiosis. *Mol. Cell* 1, 707–718
23 Rockmill, B. *et al*. (1995) Roles for two RecA homologs in promoting meiotic chromosome synapsis. *Genes Dev.* 9, 2684–2695
24 Eggler, A.L. *et al*. (2002) The Rad51-dependent pairing of long DNA substrates is stabilized by replication protein A. *J. Biol. Chem.* 277, 39280–39288
25 Sung, P. *et al*. (2003) Rad51 recombinase and recombination mediators. *J. Biol. Chem.* 278, 42729–42732
26 Bishop, D.K. (1994) RecA homologs Dmc1 and Rad51 interact to form multiple nuclear complexes prior to meiotic chromosome synapsis. *Cell* 79, 1081–1092
27 Enomoto, R. *et al*. (2004) Positive role of the mammalian TBPIP/HOP2 protein in DMC1-mediated homologous pairing. *J. Biol. Chem.* 279, 35263–35272
28 Petukhova, G.V. *et al*. (2003) The Hop2 protein has a direct role in promoting interhomolog interactions during mouse meiosis. *Dev. Cell* 5, 927–936
29 Schommer, C. *et al*. (2003) AHP2 is required for bivalent formation and for segregation of homologous chromosomes in *Arabidopsis* meiosis. *Plant J.* 36, 1–11
30 Tsubouchi, H. and Roeder, G.S. (2003) The importance of genetic recombination for fidelity of chromosome pairing in meiosis. *Dev. Cell* 5, 915–925
31 Petukhova, G.V. *et al*. (2005) The Hop2 and Mnd1 proteins act in concert with Rad51 and Dmc1 in meiotic recombination. *Nat. Struct. Mol. Biol.* 12, 449–453
32 Chen, Y.K. *et al*. (2004) Heterodimeric complexes of Hop2 and Mnd1 function with Dmc1 to promote meiotic homolog juxtaposition and strand assimilation. *Proc. Natl. Acad. Sci. U. S. A.* 101, 10572–10577
33 Leu, J.Y. *et al*. (1998) The meiosis-specific Hop2 protein of *S. cerevisiae* ensures synapsis between homologous chromosomes. *Cell* 94, 375–386
34 Tsubouchi, H. and Roeder, G.S. (2002) The Mnd1 protein forms a complex with Hop2 to promote homologous chromosome pairing and meiotic double-strand break repair. *Mol. Cell. Biol.* 22, 3078–3088
35 Zierhut, C. *et al*. (2004) Mnd1 is required for meiotic interhomolog repair. *Curr. Biol.* 14, 752–762
36 Li, W. *et al*. (2005) The *AtRAD51C* gene is required for normal meiotic chromosome synapsis and double-stranded break repair in *Arabidopsis*. *Plant Physiol.* 138, 965–976
37 Abdu, U. *et al*. (2003) The *Drosophila spn-D* gene encodes a RAD51C-like protein that is required exclusively during meiosis. *Genetics* 165, 197–204
38 Nairz, K. and Klein, F. (1997) *mre11S* – a yeast mutation that blocks double-strand-break processing and permits nonhomologous synapsis in meiosis. *Genes Dev.* 11, 2272–2290
39 Li, W. *et al*. (2004) The *Arabidopsis AtRAD51* gene is dispensable for vegetative development but required for meiosis. *Proc. Natl. Acad. Sci. U. S. A.* 101, 10596–10601
40 Gerecke, E.E. and Zolan, M.E. (2000) An mre11 mutant of *Coprinus cinereus* has defects in meiotic chromosome pairing, condensation and synapsis. *Genetics* 154, 1125–1139
41 Grelon, M. *et al*. (2001) AtSPO11-1 is necessary for efficient meiotic recombination in plants. *EMBO J.* 20, 589–600
42 Romanienko, P.J. and Camerini-Otero, R.D. (2000) The mouse *Spo11* gene is required for meiotic chromosome synapsis. *Mol. Cell* 6, 975–987
43 Tesse, S. *et al*. (2003) Localization and roles of Ski8p protein in *Sordaria* meiosis and delineation of three mechanistically distinct steps of meiotic homolog juxtaposition. *Proc. Natl. Acad. Sci. U. S. A.* 100, 12865–12870
44 Bishop, D.K. *et al*. (1992) DMC1: A meiosis-specific yeast homolog of *Escherichia coli* recA required for recombination, synaptonemal complex formation, and cell cycle progression. *Cell* 69, 439–456
45 Pittman, D.L. *et al*. (1998) Meiotic prophase arrest with failure of chromosome synapsis in mice deficient for Dmc1, a germline-specific RecA homolog. *Mol. Cell* 1, 697–705
46 Colaiacovo, M.P. *et al*. (2003) Synaptonemal complex assembly in *C. elegans* is dispensable for loading strand-exchange proteins but critical for proper completion of recombination. *Dev. Cell* 5, 463–474
47 Manheim, E.A. and McKim, K.S. (2003) The Synaptonemal complex component C(2)M regulates meiotic crossing over in *Drosophila*. *Curr. Biol.* 13, 276–285
48 Stack, S.M. and Anderson, L.K. (2002) Crossing over as assessed by late recombination nodules is related to the pattern of synapsis and the distribution of early recombination nodules in maize. *Chromosome Res.* 10, 329–345
49 Carpenter, A.T. (1975) Electron microscopy of meiosis in *Drosophila melanogaster* females: II. The recombination nodule – a recombination-associated structure at pachytene? *Proc. Natl. Acad. Sci. U. S. A.* 72, 3186–3189
50 Anderson, L.K. *et al*. (2003) High-resolution crossover maps for each bivalent of *Zea mays* using recombination nodules. *Genetics* 165, 849–865
51 Anderson, L.K. *et al*. (1997) RecA-like proteins are components of early meiotic nodules in lily. *Proc. Natl. Acad. Sci. U. S. A.* 94, 6868–6873
52 Moens, P.B. *et al*. (2002) The time course and chromosomal localization of recombination-related proteins at meiosis in the mouse are compatible with models that can resolve the early DNA–DNA interactions without reciprocal recombination. *J. Cell Sci.* 115, 1611–1622
53 Agarwal, S. and Roeder, G.S. (2000) Zip3 provides a link between recombination enzymes and synaptonemal complex proteins. *Cell* 102, 245–255
54 Anderson, L.K. *et al*. (1999) Distribution of crossing over on mouse synaptonemal complexes using immunofluorescent localization of MLH1 protein. *Genetics* 151, 1569–1579
55 Henderson, K.A. and Keeney, S. (2004) Tying synaptonemal complex initiation to the formation and programmed repair of DNA double-strand breaks. *Proc. Natl. Acad. Sci. U. S. A.* 101, 4519–4524
56 Rockmill, B. *et al*. (2003) The Sgs1 helicase regulates chromosome synapsis and meiotic crossing over. *Curr. Biol.* 13, 1954–1962

57 Schwacha, A. and Kleckner, N. (1994) Identification of joint molecules that form frequently between homologs but rarely between sister chromatids during yeast meiosis. *Cell* 76, 51–63
58 Wan, L. *et al*. (2004) Mek1 kinase activity functions downstream of RED1 in the regulation of meiotic double strand break repair in budding yeast. *Mol. Biol. Cell* 15, 11–23
59 Schwacha, A. and Kleckner, N. (1997) Interhomolog bias during meiotic recombination: meiotic functions promote a highly differentiated interhomolog-only pathway. *Cell* 90, 1123–1135
60 Bishop, D.K. *et al*. (1999) High copy number suppression of the meiotic arrest caused by a dmc1 mutation: REC114 imposes an early recombination block and RAD54 promotes a DMC1-independent DSB repair pathway. *Genes Cells* 4, 425–444
61 Webber, H.A. *et al*. (2004) The cohesion protein ORD is required for homologue bias during meiotic recombination. *J. Cell Biol.* 164, 819–829
62 Couteau, F. *et al*. (2004) A component of *C. elegans* meiotic chromosome axes at the interface of homolog alignment, synapsis, nuclear reorganization, and recombination. *Curr. Biol.* 14, 585–592
63 Storlazzi, A. *et al*. (2003) Meiotic double-strand breaks at the interface of chromosome movement, chromosome remodeling, and reductional division. *Genes Dev.* 17, 2675–2687
64 Sym, M. *et al*. (1993) ZIP1 is a synaptonemal complex protein required for meiotic chromosome synapsis. *Cell* 72, 365–378
65 Tung, K.S. and Roeder, G.S. (1998) Meiotic chromosome morphology and behavior in zip1 mutants of *Saccharomyces cerevisiae*. *Genetics* 149, 817–832
66 Fung, J.C. *et al*. (2004) Imposition of crossover interference through the nonrandom distribution of synapsis initiation complexes. *Cell* 116, 795–802
67 Blat, Y. *et al*. (2002) Physical and functional interactions among basic chromosome organizational features govern early steps of meiotic chiasma formation. *Cell* 111, 791–802
68 Kleckner, N. *et al*. (2004) A mechanical basis for chromosome function. *Proc. Natl. Acad. Sci. U. S. A.* 101, 12592–12597
69 Hillers, K.J. and Villeneuve, A.M. (2003) Chromosome-wide control of meiotic crossing over in *C. elegans*. *Curr. Biol.* 13, 1641–1647
70 Loidl, J. *et al*. (1991) Meiotic chromosome synapsis in a haploid yeast. *Chromosoma* 100, 221–228
71 De Jong, J.H. *et al*. (1991) Synapsis and chiasma formation in a ditelo-substituted haploid of rye. *Genome* 34, 109–120
72 Nabeshima, K. *et al*. (2001) A novel meiosis-specific protein of fission yeast, Meu13p, promotes homologous pairing independently of homologous recombination. *EMBO J.* 20, 3871–3881
73 Crackower, M.A. *et al*. (2003) Essential role of Fkbp6 in male fertility and homologous chromosome pairing in meiosis. *Science* 300, 1291–1295
74 MacQueen, A.J. *et al*. (2002) Synapsis-dependent and -independent mechanisms stabilize homolog pairing during meiotic prophase in *C. elegans*. *Genes Dev.* 16, 2428–2442
75 Mahadevaiah, S.K. *et al*. (2001) Recombinational DNA double-strand breaks in mice precede synapsis. *Nat. Genet.* 27, 271–276
76 Padmore, R. *et al*. (1991) Temporal comparison of recombination and synaptonemal complex formation during meiosis in *S. cerevisiae*. *Cell* 66, 1239–1256