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Distribution of meiotic recombination events: talking to your neighbors

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Accurate chromosome segregation during meiosis is essential for a species' survival. Therefore, a series of events unfold during meiosis, including pairing, synapsis, and recombination between homologous chromosomes, to ultimately ensure the successful completion of this task. This review will focus on how the regulation of crossover recombination events between homologous chromosomes plays a key role in promoting faithful segregation. Although our understanding of the molecular mechanisms by which crossovers are formed has increased significantly, the mechanisms governing the distribution of crossovers along meiotic chromosomes remain largely mysterious. Here, we review the different levels of apparent control of meiotic crossover formation and distribution.

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Introduction

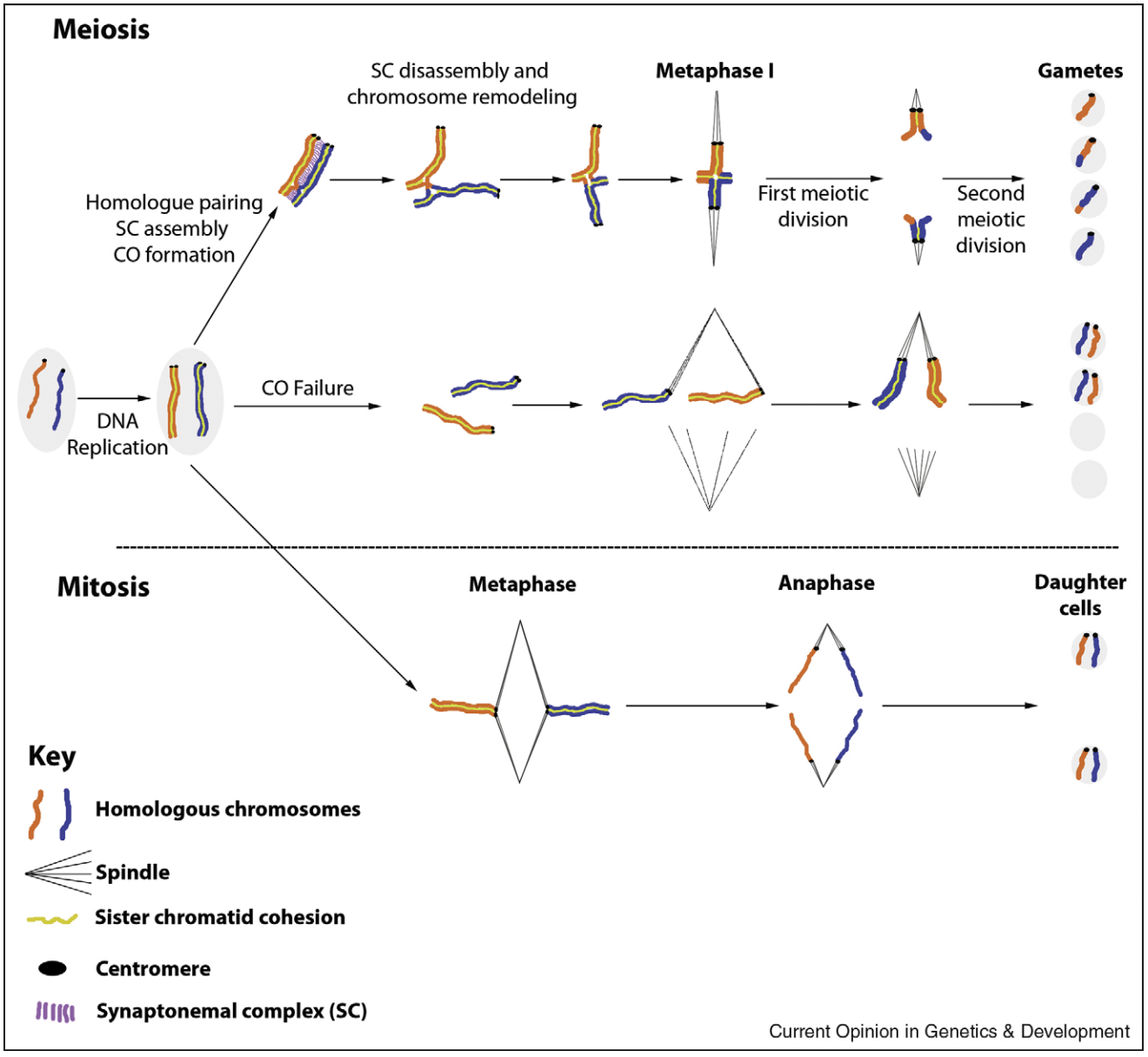
Some aspects of chromosome function, such as the control of gene expression, involve the regulation of small chromosomal domains, while other events require regulatory mechanisms capable of spanning the whole length of a chromosome. A clear example of the latter takes place during meiosis. This is the cell division program in which a single round of DNA replication is followed by two consecutive rounds of chromosome segregation, thereby allowing the formation of haploid gametes from diploid germ cells. The key to this chromosome halving is the separation of homologous chromosomes that occurs during the first meiotic division, a process that requires the recognition and alignment of the homologs (see also Shaw and Moore, this issue), and the formation of crossover (CO) recombination events between them. We will focus on the mechanisms that control the formation and distribution of COs during meiosis.

COs are crucial for faithful meiotic chromosome segregation because they are the basis of the physical linkages that facilitate the correct orientation of the homologs on the first meiotic spindle (Figure 1) [1]. The importance of COs in ensuring correct chromosome segregation during meiosis is exemplified by the fact that most cases of human aneuploidy display alterations in the number and/or distribution of COs [2]. Therefore, the accurate transmission of an intact genome during gamete formation requires that enough COs are correctly placed across the entire genome, so that each homolog pair forms at least one CO (the obligate CO). However, the number of COs is not simply determined by the size of the genome; there can be intra-species differences in recombination rates between male and female meioses [3], and inter-species comparisons demonstrate striking disparities in the number of COs formed per Mb of DNA (Table 1). Furthermore, CO events are not evenly distributed across the genome, most organisms contain recombination hotspots, which are genomic intervals in which COs occur at a much higher frequency. In fact, CO formation is thought to be actively suppressed in certain locations such as near centromeric regions, where COs could compromise proper chromosome segregation [2,4]. This article will review the recent developments in our understanding of CO distribution control, which are revealing a complex interplay between CO-promoting and anti-CO mechanisms superimposed onto meiotic chromosome structure.

How are crossovers made?

Meiotic recombination is initiated via the formation of programmed DNA double-strand breaks (DSBs) by a topoisomerase-like protein known as Spo11, which is present from yeast to humans [5] (Figure 2). The DSBs are then resected in a 5′–3′ orientation, resulting in the formation of 3′ single-stranded DNA overhangs that invade an intact homologous donor template for its repair. This repair involves nonsister chromatids from homologous chromosomes, since a barrier to sister chromatid repair is proposed to be in place during meiosis [6•] (and references therein). The recombination intermediates that form are then resolved, giving rise to either COs, where there is an exchange of flanking markers, or non-crossovers (NCOs) [7].

Figure 1



Segregation of a pair of homologous chromosomes during meiosis and mitosis. For simplification, the diagram shows a pair of telocentric chromosomes (with the centromere located at one of the chromosomal ends) that form a single CO during meiosis. This single CO, together with sister chromatid cohesion, ensures that the homologs remain attached following the disassembly of the synaptonemal complex (SC). SC disassembly is coordinated with a remodeling of meiotic chromosomes. Together, these processes promote the acquisition of a chromosome structure that allows the correct orientation of the homologs on the metaphase I plate. At the onset of anaphase I, the selective release of sister chromatid cohesion allows the segregation of the homologs to different poles of the spindle. This is followed by the second meiotic division in which the sister chromatids are separated (in a manner similar to a regular mitotic division), thereby producing four haploid gametes. The second line of the diagram depicts an example of how the failure to form COs can cause a pair of homologs to missegregate during meiosis. Note how the homologs lacking a CO fail to align properly on the metaphase I plate, and this results in both homologs migrating to the same pole, which ultimately results in the formation of aneuploid gametes (this example displays one of the possible segregation patterns that can occur in the absence of COs). The bottom part of the diagram shows the same pair of chromosomes undergoing a mitotic division. Note how in contrast with meiotic metaphase I, the centromeres of the sister chromatids are oriented toward different poles of the spindle during mitotic metaphase. The complete release of sister chromatid cohesion allows for the separation of the sister chromatids, resulting in the formation of two daughter nuclei with an identical chromosome complement to the mother cell.

Table 1

Number of post-DSB recombination intermediates and COs in different organisms.

Species	Recombination intermediates (RAD51 foci)	COs/meiosis	Number of chromosomes (2*n*)	Genome size (Mb)
S. cerevisiae	44–50 [51]	90.5 [48••] (Microarray)	32	12
C. elegans	5 ± 2 [10]	6[d] (Genetic map)	12	100
Arabidopsis	80–100 [30]	9 [30] (Chiasmata)	10	125
Maize	493 ± 79 [16]	19 ± 1 [52] (Chiasmata)	20	2671
Mice (female)	250–420[a,b]	24.1[a] (Chiasmata)	40	2500
Mice (male)	230–400[a,c]	22.6–23.9[a] (Chiasmata)	40	2500
Human (female)	350–400[a]	60–70[a,e] (MLH-1 foci)	46	2900
Human (male)	91–262[a]	49.6–53.7[a] (Chiasmata)	46	2900

The RAD51 protein binds to the single-stranded DNA that is produced by the processing of meiotic DSBs; thus, RAD51 foci are used as an indirect measurement of DSBs. Since the number of RAD51-positive recombination intermediates detected at any given time does not account for all the DSBs that are made in a single meiosis, counting RAD51 foci most probably results in an underestimation of the actual total number of DSBs formed. In fact, the number of RAD51 foci observed in *S. cerevisiae* is only 44–50 (lower than the number of COs), but the total number of DSBs formed during meiosis must be at least 136, which is the average number of recombination events (COs plus NCOs) detected using high-density microarrays [48••]. In the third column (COs/Meiosis), the method used to estimate the number of COs in each organism is given in parenthesis. COs have been identified cytologically mainly in two ways: first, before the SC is disassembled ZMM-dependent CO sites are marked by the protein MLH-1; second, once the SC is disassembled, COs can be directly visualized as chiasmata, physical connections between the homologs formed by a CO and flanking sister chromatid cohesion (Figure 1). In organisms where both MLH1 foci and chiasmata have been scored, the number of MLH1 foci closely resembles the number of chiasmata.

[a] The references for all these values are given in [7].

[b] These values are the minimum and maximum numbers of RAD51 foci detected in two studies.

[c] These values are the minimum and maximum numbers of RAD51 foci detected between four studies.

[d] http://www.wormbase.org/.

[e] These values represent the averages of MLH1 foci from two studies.

Under circumstances when a homolog is not available for repair, meiotic DSBs can be repaired using the sister chromatids as a template, or even by error-prone mechanisms such as nonhomologous end joining. These two modes of DSB repair do not result in inter-homolog CO formation and therefore do not contribute to accurate homolog segregation.

The distribution of DSBs

DSBs are a prerequisite to COs, therefore their placement across the genome represents an initial mode of control of CO distribution. Early studies showed that DSBs are enriched in specific locations (DSB hotspots) that correlate with nuclease-hyper-sensitive regions [8]. Thus, local chromatin structure appears to be an important determinant of DSB formation. Indeed, histone H3 trimethylation of lysine 4 (H3K4me3), an epigenetic mark associated with active chromatin, seems to mark DSB sites in *S. cerevisiae* [9]. Higher order chromosome structure is also involved in controlling the number and location of DSBs, based on results from mutants for a condensin-related protein in *C. elegans* [10]. The genome-wide mapping of DSBs in *S. cerevisiae* shows that most DSBs tend to occur in intergenic regions containing promoters and in regions 20–120 kb from the telomeres, but are absent from the 20 kb regions adjacent to telomeres [11•]. Surprisingly, DSB hotspots were also found in the CO-depleted pericentromeric regions [11•,12•], which were previously thought to be DSB coldspots. These observations illustrate how DSB placement appears to be controlled both locally (by chromatin structure) as well as by the relative position with respect to chromosomal landmarks such as telomeres. Importantly, a telomere-led mechanism that promotes DSB formation in subtelomeric regions could act to ensure that all chromosomes receive at least one CO, regardless of their size [11•,13].

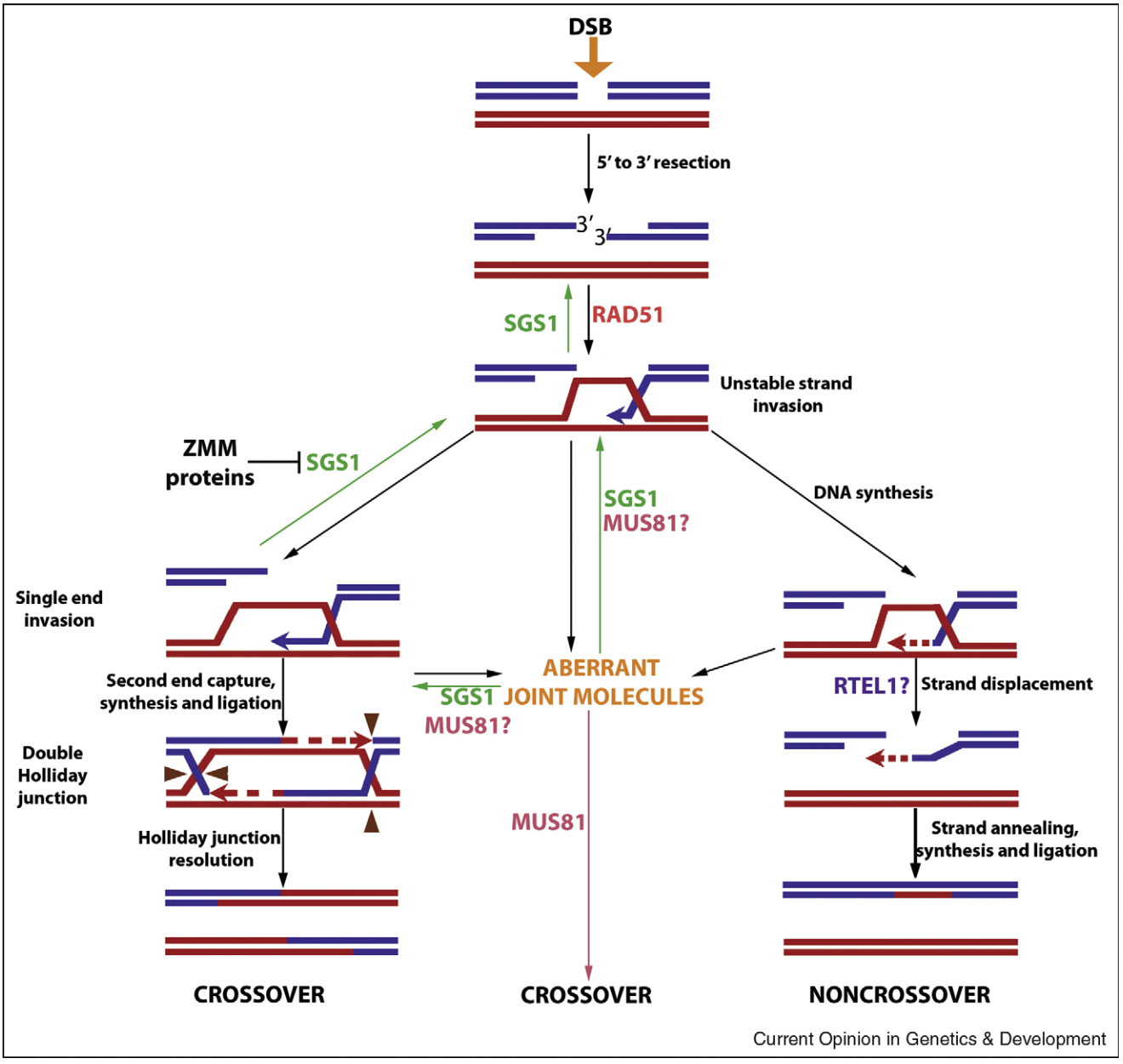
In *S. pombe*, the DSB landscape appears to be mainly controlled locally, with the majority of the prominent DSB hotspots localizing to a discrete class of large intergenic DNA and to loci that express noncoding RNA [14,15]. The expansion of this genome-wide DSB mapping approach to organisms with larger genomes should significantly improve our understanding of DSB distribution.

DSB fates

In the various organisms studied thus far, the number of DSBs seems to far exceed the number of COs. In maize, for instance, up to 560 post-DSB recombination intermediates are observed at early meiotic prophase [16], but only around 20 COs are present at later stages (Table 1). The molecular analysis of CO hotspots in budding yeast, humans, and mice shows that both COs and NCOs arise from the same recombination-rich locations [17–20]. This is consistent with the idea that the CO or NCO fate of a particular DSB is not simply predetermined by its genomic location but is rather the outcome of more complex regulatory mechanisms.

Data from *S. cerevisiae* suggest that the CO fate of a DSB is established as early as the transition from DSB to single-end invasion [17,20,21]. A number of proteins, collectively

Figure 2



Homologous recombination-mediated DSB repair. The diagram shows a single sister chromatid (as a double stranded DNA molecule) from each homolog. After the topoisomerase-like enzyme Spo11 forms a meiotic DSB, the DSB site is processed by removal of the covalently bound Spo11 and resection of the ends in a 5′–3′ orientation. This results in the formation of 3′ single-stranded tails with which the Rad51 and Dmc1 strand-exchange proteins associate. These nucleoprotein filaments proceed to invade a homologous intact template for repair, resulting in the formation of a nascent D-loop structure. These unstable strand invasions can be dismantled by SGS1; however, CO-fated DSBs are protected from the action of SGS1 by the ZMM proteins, which promote the formation of single end invasions. Second end capture, followed by DNA synthesis and ligation, results in the formation of a double Holliday junction (dHJ) intermediate, which is resolved as a CO by an unknown dHJ resolvase. Although not depicted in the diagram, dHJs may also be resolved as NCOs. Nascent D-loops that are not stabilized by the ZMM proteins can be repaired by a mechanism known as synthesis-dependent strand annealing (SDSA). This requires DNA synthesis and the displacement of the invading strand, which might be promoted by RTEL1. Annealing of the displaced strand with the other DSB end is followed by DNA synthesis and ligation, resulting in the formation of NCOs. The anti-recombination activity of SGS1 is needed to prevent the formation of aberrant joint molecules that occur when secondary strand invasions take place. Some of the aberrant joint molecules that are not disassembled by SGS1 are resolved as COs by MUS81. Apart from this late role, MUS81 may also play earlier roles in the resolution of aberrant joint molecules.

known as ZMM, are involved specifically in the formation of COs but not NCOs (Figure 2) [21,22,23•,24]. The analysis of mutants lacking different ZMM components in *S. cerevisiae* and *Arabidopsis* shows that most, but not all, COs are formed by a ZMM-dependent pathway in these organisms [22,25]. Similarly, mice lacking MLH1, a protein involved in the late steps of ZMM-dependent CO formation, display a severe, albeit not complete, reduction of crossovers [26]. Most ZMM-independent COs detected in *S. cerevisiae*, mice, and *Arabidopsis*, appear to be dependent on the endonuclease Mus81 [27–29]. However, residual COs are detected in double mutants defective in the Mus81 and ZMM pathways [27,30], demonstrating that some COs can be formed independently of both the ZMM proteins and Mus81. By contrast, a single CO pathway seems to be responsible for virtually all COs in *C. elegans* and *S. pombe*. Worms use a ZMM-dependent pathway, notably via MSH-4, a ZMM component [31], while in *S. pombe* all COs seem to be dependent on Mus81 [32]. In summary, meiotic DSBs can be repaired in at least three different ways: NCO, ZMM-dependent CO, and ZMM-independent CO.

Anti-crossover activities

The ultimate fate of a DSB is not simply determined by CO-promoting factors but also by the presence of anti-recombination mechanisms. The Sgs1 helicase, a RecQ family member, suppresses mitotic COs, and recent studies show that the anti-CO activity of Sgs1 is also present during meiosis [33••,34••,35,36]. *sgs1* mutants show only a slight increase in COs compared with wild type, but elimination of Sgs1 in mutants defective in any of the ZMM components rescues the CO defect observed in *zmm* mutants [35,36]. This observation has led to a model in which ZMM proteins act at CO-designated sites to stabilize early recombination intermediates from the action of Sgs1.

CO-designated sites also appear to require the anti-recombination activity of Sgs1 to prevent the formation of aberrant multichromatid joint molecules (Figure 2), which lead to the formation of closely spaced COs that can impair homolog segregation [36]. The endonuclease Mus81 appears to collaborate with Sgs1 in promoting the formation of inter-homolog COs by resolving aberrant joint molecules [33••,34••] (Figure 2). The conserved RTEL1 helicase also shows an anti-recombination activity during meiosis [37•]. Worms lacking RTEL1 display elevated numbers of COs, and *in vitro* studies show that human RTEL1 promotes the disassembly of D-loop recombination intermediates [37•]. Thus, during meiosis, RTEL1 could promote the disassembly of early inter-homolog joint molecules, thereby favoring the formation of NCOs (Figure 2). These studies illustrate how the complex and dynamic interactions between CO-promoting and anti-CO mechanisms, affect the outcome of meiotic recombination.

Crossover interference

A remarkable aspect of CO distribution is that COs exhibit 'interference' [38]; this is based on the observation that when two or more COs happen on the same chromosome, they tend not to occur near one another. In *C. elegans*, interference appears to limit COs to one per homolog pair in most meioses [39]. Surprisingly, strains homozygous for a fusion of two chromosomes (that would normally enjoy a CO each), display a single CO on the fused chromosome in most meioses [40]. This demonstrates a chromosome-wide control of CO distribution that can extend over distances greater than that of a regular chromosome length.

Several models have been proposed to explain how CO interference is transmitted (reviewed in [41]). Early models involved transmission along the synaptonemal complex (SC), a proteinaceous structure that holds the cores of the homologs in close proximity during meiotic prophase. Synapsis initiation complexes containing ZMM proteins, however, display interference before SC formation [42]. This demonstrates that CO-designated events can exert interference, and its transmission does not require a mature SC.

The 'stress relief' model proposes a link between CO interference and changes in the physical state of chromosomes: mechanical stress along meiotic chromosomes promotes CO designation, and CO designation is accompanied by structural changes that relieve mechanical stress in flanking regions, thereby inhibiting the occurrence of additional COs nearby [22,43]. Recent studies demonstrate that COs (or CO precursors) induce changes in the organization and molecular composition of the chromosome axes in which they occur [44•,45•,46•,47]. Moreover, in *C. elegans* these changes seem to be established on the basis of the distance between the single CO and the closest telomere [46•], thereby invoking some form of long-range communication along meiotic chromosomes.

An added level of complexity is that only COs formed by the ZMM-dependent pathway seem to display interference. However, in *spo16* mutants (a newly identified ZMM component) the residual COs continue to show interference [23•]. These observations suggest that the capability to induce interference is not intrinsic to all CO events *per se*. Moreover, genome-wide mapping of recombination events has detected evidence for interference between COs and NCOs [48••]. Identifying the specific events capable of triggering interference remains a major challenge in research.

Crossover homeostasis

A recent study in *S. cerevisiae* revealed a nonlinear quantitative relationship between DSBs and COs [49••]. This study took advantage of a *spo11* allelic series, where the levels of DSB formation consisted of ~80%, ~30%, and

~20% of wild-type DSB levels. CO frequencies were then monitored throughout eight intervals spanning three chromosomes. A key observation derived from this analysis was that meiotic CO levels tended to be maintained despite a reduction in the number of initiation events, a phenomenon the authors referred to as 'crossover homeostasis'. However, some genomic regions were less capable, compared with others, of displaying CO homeostasis. Further analysis of both CO and NCO frequencies at the *ARG4* locus (a natural meiotic recombination hotspot) suggested that a decrease in DSB frequencies resulted in a maintenance in CO levels at the expense of NCOs. Moreover, the reduction in DSB levels had little or no effect on either the strength of CO interference or the distance over which it could be detected. Therefore, interference within a given chromosomal interval may be mostly independent of the numbers of DSBs produced in that region. Taken together, this new manifestation of CO control revealed a bias imposed by CO homeostasis toward CO formation, presumably to ensure proper chromosome segregation. This suggests that CO homeostasis may be important in promoting the formation of the obligate CO, and that it may be intertwined with the molecular mechanism resulting in CO interference.

A recent genome-wide analysis of recombination utilizing DNA microarrays allowed for a global correlation between COs and NCOs and provided further support for CO homeostasis in *S. cerevisiae* [50••]. Whereas CO homeostasis was part of normal CO control in wild type, it was reduced in *zip2* and *zip4* mutants, which affect meiotic chromosome synapsis and show reduced CO interference. However, CO homeostasis was not reduced to the same degree as CO interference. Therefore, the correlation between these modes of CO control is not as straightforward as predicted and remains to be explained.

Local regulation within a chromosome: telomeres and centromeres vs. hotspots

The distribution of COs along chromosomes is not uniform. This is exemplified by the enrichment for COs at recombination hotspots in contrast to the reduced levels of recombination observed at either telomeres or centromeres. Previous observations have suggested that COs too near to centromeres can negatively impact chromosome segregation whereas COs too near to the repetitive DNA present at telomeres can result in recombination between nonhomologous chromosomes. The recent advent of microarray-based methods to investigate CO and NCO levels genome wide has allowed for further analysis of the local regulation of COs within a chromosome. In line with previous observations, Mancera *et al.* [48••] observed a complete lack of recombination at all centromeres and low recombination rates in centromere-proximal regions in *S. cerevisiae*. However, results were more variable for regions near telomeres, with some chromosomes completely lacking recombination and others having strong recombination activity near a telomere. By contrast, Chen *et al.* [50••] observed reduced CO levels at both centromeres and telomeres in *S. cerevisiae*. However, NCO levels were maintained at telomere ends despite the ~2-fold reduction in DSB formation in that region, suggesting an alteration in the CO:NCO ratio. Interestingly, the 6-fold repression in CO levels observed within 10 kb from centromeres, was also accompanied by a 6-fold reduction in NCO levels at the same interval. Moreover, their studies revealed that centromeric repression is Zip1-dependent. Thus, regulation of CO levels at centromeres may not stem from alterations in the CO:NCO ratio but instead result from changes from an inter-homolog to an inter-sister mode of repair. Further support for this stems from studies mapping DSB hotspots in budding yeast that suggest an accumulation of unrepaired centromere-proximal DSBs in the absence of Dmc1, a meiotic recombinase involved in both inter-homolog and inter-sister recombination [11•,12•].

Summary

The formation of inter-homolog COs during meiosis is the outcome of a series of decisions that are affected by local factors, such as chromatin structure and the distance with respect to chromosomal landmarks (i.e. centromeres and telomeres), as well as by chromosome-wide mechanisms, namely CO interference. How these aspects of CO regulation are integrated to ensure that COs are placed in an orderly fashion across the genome remains one of the most intriguing aspects of meiosis. Future studies will therefore aim to elucidate the molecular machinery that determines how and when a recombination event is designated to become a CO. Moreover, further studies will examine how this CO-fated event 'talks' to its neighbors thereby affecting both the fate of the listener as well as the chromosomal structures used for this 'conversation'.

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