Review

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Where to cross? New insights into the location of meiotic crossovers

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During meiosis, the repair of induced DNA double-strand breaks (DSBs) produces crossovers (COs). COs are essential for the proper segregation of homologous chromosomes at the first meiotic division. In addition, COs generate new combinations of genetic markers in the progeny. CO localization is tightly controlled, giving rise to patterns that are specific to each species. The underlying mechanisms governing CO location, however, are poorly understood. Recent studies highlight the complexity of the multiple interconnected factors involved in shaping the CO landscape and demonstrate that the mechanisms that control CO distribution can vary from species to species. Here, we provide an overview of the recent findings related to CO distribution and discuss their impact on our understanding of the control of meiotic recombination.

Introduction

Meiosis is a specialized cell division that produces haploid cells that will eventually develop into gametes. It is characterized by two successive chromosomal divisions following one single round of chromosome replication. During the first meiotic division (meiosis I, also called reductional division), homologous chromosomes segregate from each other. During the second division (meiosis II, also called equational division), the sister chromatids of each chromosome separate, resulting in the generation of four haploid cells (see Figure IA in Box 1).

The success of meiosis I relies on the physical association of homologous chromosomes into bivalents. In the vast majority of species, this association is achieved through the combined action of COs (see Glossary) and sister chromatid cohesion. COs are one of the outcomes of meiotic recombination; they establish physical connections between homologous chromosomes by exchanging reciprocal large pieces of chromosome arms from homologous non-sister chromatids (Box 1). In addition to their mechanistic role, COs generate novel combinations of genetic material and therefore represent the physical basis of Mendelian genetic inheritance.

When the study of meiosis became widespread at the beginning of the 20th century, it became quickly evident that CO rate and localization were not homogeneous throughout the genomes. Along the chromosomes of almost all species, domains with high CO rates alternate with domains where CO rates are significantly lower than the genome-wide average. In budding yeast, *Arabidopsis*, wheat, and humans, >80% of the recombination events occur in less than a quarter of the genome (see [1] and references therein). However, each pair of homologous chromosomes shows at least one CO, the so-called 'obligatory CO', required for accurate segregation at meiosis I [2]. More than a century of meiotic studies later, considerable progress has been made in the understanding of the mechanisms that govern meiotic recombination ([3] and Box 1), but our understanding of the factors that shape the CO landscape is still poor. We review here some insights that have recently emerged, highlighting crosstalk between CO localization,

Glossary

Chiasma (plural: chiasmata): the cytological manifestation of crossovers. Together with sister chromatid cohesion, chiasmata connect homologs to one another in a structure called a bivalent (Box 1).
Class I COs: COs that depend on the ZMM group of proteins. These COs show interference (Box 1).
Class II COs: COs that are generated by the MUS81 pathway of recombination (Box 1).
Crossover (CO): one of the products of recombination that yields reciprocal exchanges of large chromosomal fragments between homologous chromosomes.
CO landscape: the number and location of CO events within a chromosome.
Distal CO position: describes a location of CO closer to the telomere ends than to the centromeric region (Figure 1B); contrast with proximal CO position.
Early nodule (EN): proteinaceous complex found in association with the AEs and the SC. ENs have variable sizes from small and round (50 × 50 nm) to large and ellipsoidal (250 × 290 nm) with almost every size in between. They represent sites of DSB repair during meiosis.
Late nodule (LN): proteinaceous complex associated with the central element of SCs from early pachytene through early diplotene. These nodules are larger and more regular in size and shape than ENs. They correspond to CO sites (Box 3).
Non-crossover (NCO): a product of meiotic recombination that results in a local and non-reciprocal replacement of one DNA sequence with a homologous one generating a 3:1 marker segregation (Box 1).
Proximal CO position: describes the location of CO closer to the centromeric region than to the telomere ends; contrast with distal CO position.
Synaptonemal complex (SC): meiosis-specific proteinaceous structure that forms between homologous chromosomes along their entire lengths. The SC is formed when the two lateral elements are linked to each other by the transverse filaments, which lie across the central region in a zipper-like appearance (Box 3).
Synapsis: proteins from the central element of the SC assemble between two homologous axial elements and, by extension, complete the polymerization of the SC. Synapsis initiates at zygotene and is complete at pachytene.

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chromosome structure, chromosome dynamics, and post-translational modifications.

CO formation and location: a brief overview

Meiotic recombination (Box 1) is the consequence of the repair of programmed DNA DSBs [4]. These breaks are preferentially repaired using the homologous chromosome rather than the sister chromatids [Inter Sister (IS) repair] in contrast to DSBs that occur in somatic cells. CO formation is under the control of at least two different pathways. Class I COs are dependent on a group of proteins collectively termed 'ZMM' and are subjected to interference ([3] and Box 2). By contrast, the formation of class II COs depends on the dimer formed by Mus81 and Mms4/Eme1 in several species and is not subjected to interference [3]. The other recombination output of meiotic DSB repair on the homologous chromosome is a gene conversion event not associated with a crossover event, also called a non-crossover event (NCO), which can be generated through multiple molecular pathways [1] (Box 1).

Insight into the control of the distribution of COs during meiosis requires detection of recombination events. Several techniques have been used for that purpose (Box 3), and all have demonstrated that the distribution of recombination events is not homogeneous along chromosomes, regardless of the level of resolution at which the study is conducted. Different patterns of CO distribution are observed depending on the species, and even sometimes within a given species, depending on whether male or female meiosis is examined (see below). A commonly seen pattern is a CO distribution skewed toward the ends of the chromosomes (i.e., distal chiasmata, Figure 1B), as observed in crops and human males for example. The reverse situation, with COs concentrated in proximal regions of the chromosome domains (i.e., close to the centromeres), has also been described. In all the situations investigated so far, the centromeric regions are devoid of COs.

Does the CO landscape mirror DSB activity?

The most straightforward hypothesis to explain the observed heterogeneity in CO landscapes is that it mirrors the heterogeneity in recombination initiation. Indeed, when investigated at low resolution, this assumption is often verified. In mice for example, variations of DSB distributions (as assayed by the presence of γH2AX) correlate with changes in MLH1 foci distribution (Box 3) [5]. Similarly, in humans, female meiocytes form more DSBs (as assayed by RAD51 foci) than male meiocytes as well as more COs [6]. Mice and humans are the only species for which both accurate and genome-wide DSB and CO maps are currently available and can thus be compared at high resolution. In these species, DSB frequencies (as assayed by single-stranded DNA sequencing after chromatin immunoprecipitation) and CO frequencies correlate significantly but nevertheless, only partially [7,8], suggesting that variations in DSB formation only explain a portion of the variability of the genetic maps. In *Caenorhabditis elegans*, where the number of DSBs induced at meiosis is low, CO number and position can be modified when chromosome axis length increases in specific genetic backgrounds, which in turn increases DSB numbers [9], indicating that, in this organism, DSBs can be limiting factors in the process of CO formation. In mice, the small homologous X and Y PAR region of the sex chromosomes shows 10–20-fold higher than average DSBs, likely to ensure the presence of at least one CO [10]. All these data taken together show that variation in recombination initiation probably accounts for an important part of the variation in CO position and frequency, but cannot fully explain it.

In addition, several lines of evidence suggest that the spatiotemporal regulation of recombination initiation can affect CO outcome. It appears that the recombination initiation step can be strongly asynchronous: in both human and barley male meiosis, precocious recombination initiation in subtelomeric chromosomal regions correlates with subtelomeric CO preference [8,11], suggesting that the timing of recombination initiation can be a factor influencing CO formation by favoring the first DSBs to maturate into COs. Interference, which prevents the occurrence of close by COs (Box 2), could reinforce the shape of CO distribution in species with strong spatiotemporal dynamics of recombination initiation.

Even if the step of initiation of meiotic recombination is an important determinant of the overall CO landscape, it clearly does not fully account for it, as the ratio of CO to

Box 1. Meiosis overview and CO formation pathways

Meiosis consists of the succession of two rounds of chromosome segregation after a single round of replication during S phase. In meiosis I, homologous chromosomes associate and exchange DNA through the formation of chiasmata, the cytological representation of crossovers, which allows the correct segregation of homologous chromosomes at anaphase I. In meiosis II, sister chromatids segregate generating four gametes with half of the DNA content of the mother cell (Figure IA).

Meiotic recombination is initiated by the induction of DSBs (Figure IBa) by the Spo11 protein complex [4]. DSBs are then resected (Figure IBb) and strand exchange proteins RAD51 and DMC1 are subsequently loaded onto the resected DNA ends. Both RAD51 and DMC1 play crucial roles in homology search and strand invasion generating joint molecules. Joint molecules can form either with a homologous chromatid (Figure IBc) or with the sister chromatid (Figure IBd) [1]. There is, however, a bias in meiosis toward homolog chromatid invasion. Several proteins including DMC1 and the axis proteins seem to play a crucial role in the establishment of the bias [68]. After strand invasion, recombination intermediates can be processed by a group of proteins called ZMM, forming double Holliday junctions (dHJs) (Figure IBe); the vast majority of which in turn will lead to interfering/class I crossovers (Figure IBf). Alternatively, joint molecules can be processed by the MUS81 protein complex to produce non-interfering/class II COs (Figure IBg) or by several other protein complexes (Figure IBh) to produce NCOs (reviewed in [1]).

The class I CO pathway generates between 70 and 100% of all COs, depending on the species, but there are a few examples like *Aspergillus nidulans* or *Sch. pombe* where only class II COs are formed. The number of COs per meiosis is strictly controlled: at least one per pair of homologous chromosomes and rarely more than one per chromosome arm. The NCO number per meiosis seems to be highly variable from species to species. In *Caenorhabditis elegans* there are almost none, whereas in mice, NCOs largely exceed COs at a series of DSB repair sites. In *A. thaliana* only a few NCOs (1 to 3) are detected per meiosis, but this paucity could be due to the short size of the conversion event that impairs their detection [1].