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Meiotic Recombination: The Essence of Heredity

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The study of homologous recombination has its historical roots in meiosis. In this context, recombination occurs as a programmed event that culminates in the formation of crossovers, which are essential for accurate chromosome segregation and create new combinations of parental alleles. Thus, meiotic recombination underlies both the independent assortment of parental chromosomes and genetic linkage. This review highlights the features of meiotic recombination that distinguish it from recombinational repair in somatic cells, and how the molecular processes of meiotic recombination are embedded and interdependent with the chromosome structures that characterize meiotic prophase. A more in-depth review presents our understanding of how crossover and noncrossover pathways of meiotic recombination are differentiated and regulated. The final section of this review summarizes the studies that have defined defective recombination as a leading cause of pregnancy loss and congenital disease in humans.

MEIOSIS AND THE ROOTS OF RECOMBINATION RESEARCH

The concept of recombination emerged during the early 20th century, following the post-Mendel era of heredity research. Thomas Hunt Morgan's formal theory of gene linkage and crossing-over (Morgan 1913) was a synthesis of three key concepts: "the chromosome theory of inheritance," imparted by Wilhelm Roux, Walther Flemming, Theodor Boveri, and Walter Sutton; "gene linkage," an exception to Mendel's law of independent assortment, first reported by Carl Correns; and the "chiasmatype theory," derived from Frans Janssens' cytological observations of meiotic chromosomes. The first proof of the crossover theory came from Harriet Creighton and Barbara McClintock (Creighton and McClintock 1931), who were able to correlate cytological and genetic exchanges in maize.

Experiments aimed at understanding the mechanism of meiotic recombination became dominated by fungal genetics because of the huge advantage afforded by being able to recover all four meiotic products. These elegant studies culminated in four key concepts that formed the foundation of molecular models of recombination: gene conversion, an exception to Mendel's principle of segregation, signaled a local nonreciprocal transfer of genetic information (Winkler 1930; Lindergren 1953; Mitchell 1955); postmeiotic segregation (PMS) indicated the presence of heteroduplex DNA (Olive 1959; Kitani et al. 1962); polarity gradients of

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gene conversion lead to the idea that recombination initiated from pseudofixed sites (Lissouba and Rizet 1960; Murray 1960); and the strong correlation between gene conversion/PMS events and crossing-over led to the proposal that these processes were mechanistically linked (Kitani et al. 1962; Perkins 1962; Whitehouse 1963).

MOLECULAR MODELS OF MEIOTIC RECOMBINATION

Holliday's classic model reconciled gene conversion, PMS, and crossing-over into a single mechanism with the key features of hybrid (heteroduplex) DNA formed via strand exchange, mismatch correction of hybrid DNA to yield gene conversion, and a four-way exchange junction that could be resolved to yield either crossover or noncrossover duplex products (Holliday 1964). The meticulous testing and revision of models of meiotic recombination ensued over the next 20 years (Haber 2008), culminating in the formulation of the double-strand break repair (DSBR) model of Szostak et al. (1983), which proposed that meiotic recombination is initiated by DNA double-strand breaks and the ensuing strand exchanges result in the formation of double-Holliday junctions (dHJs) (Fig. 1).

Identification of the key DNA intermediates of the DSBR model was enabled by techniques to synchronize meiosis in budding yeast cultures, and a series of Southern blot assays to monitor events at defined recombination sites. These approaches provided direct confirmation that meiotic recombination initiates with double-strand breaks (DSBs) and gives rise to dHJs (Sun et al. 1989; Cao et al. 1990; Schwacha and Kleckner 1994, 1995). These powerful approaches also revealed several important spatial and temporal features of meiotic recombination. DSBs form after bulk chromosome replication and are rapidly processed to form long single-stranded tails with 3′-termini (Padmore et al. 1991; Sun et al. 1991; Zakharyevich et al. 2010). Distinct from the original DSBR model, there is no evidence that a significant gap is formed at the DSB site. Detection of recombination intermediates by Southern analysis was dependent on the fact that DSBs at the assayed loci were confined to very narrow regions or hotspots, a conserved feature that was subsequently shown to apply genome-wide and has been the subject of intense studies (e.g., Baudat and Nicolas 1997; Gerton et al. 2000; Blitzblau et al. 2007; Buhler et al. 2007; Hwang and Hunter 2011; Pan et al. 2011; Smagulova et al. 2011; de Massy 2013, 2014; Pratto et al. 2014).

Formation of metastable one-ended strand-exchange intermediates, called single-end invasions (SEIs), is coincident with chromosome synapsis, that is, the intimate connection of homologs along their lengths by zipper-like structures called synaptonemal complexes (Fig. 2) (Hunter and Kleckner 2001). Given that chromosome pairing and synapsis requires recombination in most organisms, including budding yeast (but not *Drosophila* or *Caenorhabditis elegans*), detected SEIs must be preceded by less stable nascent strand-pairing intermediates (presumably D-loops) that are not readily detected by current approaches. The timing of SEI formation reflects the interdependence between the initiation of synapsis and the initial differentiation of crossover and noncrossover pathways, with SEIs being the earliest detectable crossover-specific joint molecules (see below) (Hunter and Kleckner 2001; Borner et al. 2004; Reynolds et al. 2013; Zhang et al. 2014a). Along the crossover pathway, SEIs give rise to dHJs, which must be resolved exclusively into crossovers, in contrast to the equal mixture of crossovers and noncrossovers originally envisioned by the DSBR model (Allers and Lichten 2001a; Clyne et al. 2003; Zakharyevich et al. 2012).

These findings are incorporated into contemporary models of meiotic recombination that propose early differentiation of crossover and noncrossover pathways, with a majority of noncrossovers arising from D-loops via synthesis-dependent strand annealing, and crossover-designated events going on to form stable dHJs (Fig. 1) (McMahill et al. 2007; Martini et al. 2011; Tang et al. 2015). Fine-scale analysis of crossover and noncrossover products in yeast, mouse, human, and *Arabidopsis* support the tenet that crossovers and noncrossovers arise from distinct intermediates (Jeffreys and May

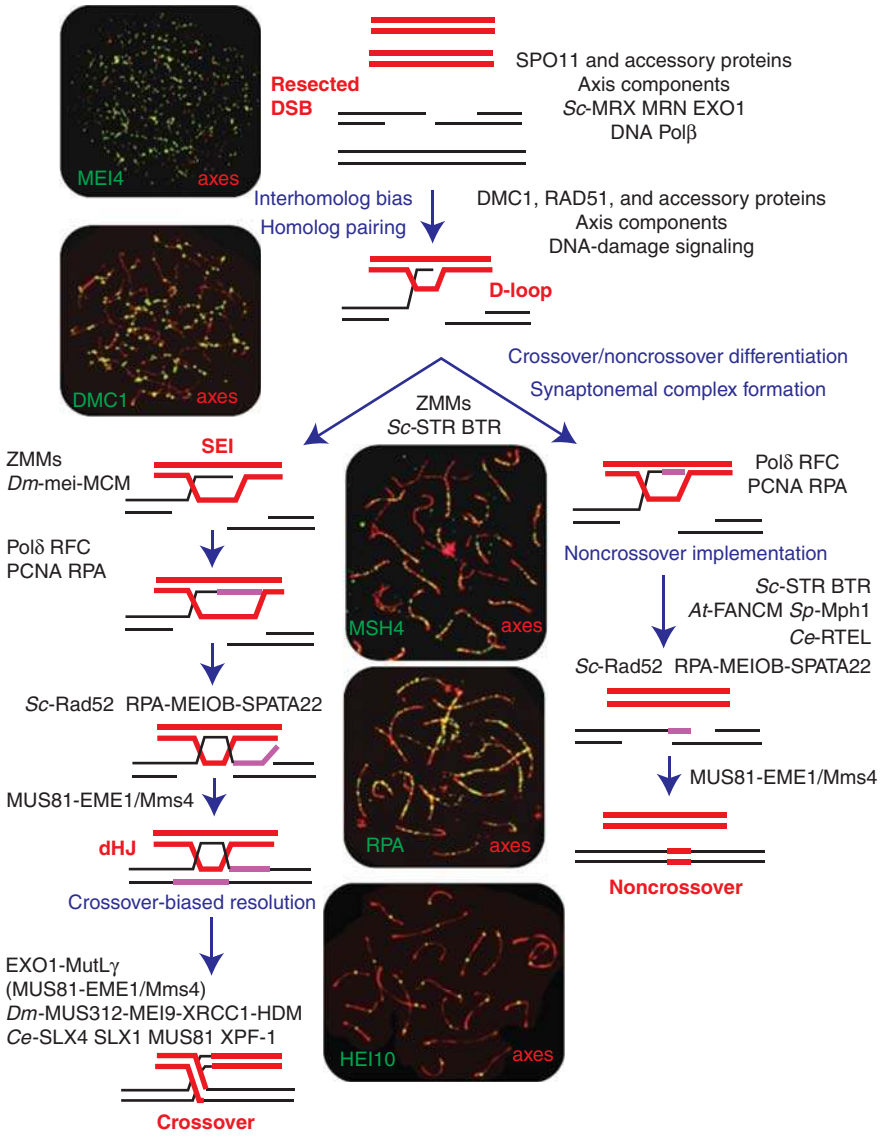

Figure 1. Model of meiotic recombination. Schematic diagram showing the DNA intermediates of meiotic recombination highlighting the major pathways and key transitions (for more comprehensive models, see Martini et al. 2011; Kaur et al. 2015; Tang et al. 2015). Magenta lines indicate new DNA synthesis. During double-Holliday junction (dHJ) formation along the crossover branch, only one possible mechanism for engagement of the second double-strand break repair (DSB) end is shown, involving end-first displacement of the extended invading strand and annealing (Allers and Lichten 2001b; Lao et al. 2008). Alternative models include annealing of the second DSB end to an expanded D-loop, or a second strand invasion analogous to the first DSB end (Szostak et al. 1983; Martini et al. 2011). Proteins implicated in each step are shown; prefixes indicate proteins specific to a given organism: *At*, *Arabidopsis thaliana*, *Ce*, *Caenorhabditis elegans*; *Dm*, *Drosophila melanogaster*; *Sc*, *Saccharomyces cerevisiae*; *Sp*, *Schizosaccharomyces pombe* (see main text for details). Accompanying images show surface-spread mouse spermatocyte nuclei at the corresponding prophase stages, immunostained for pertinent recombination factors. In all images, homolog axes are visualized using SYCP3 antibodies. MEI4 is a SPO11-accessory protein required for DSB formation (Kumar et al. 2010). PCNA, Proliferating cell nuclear antigen.

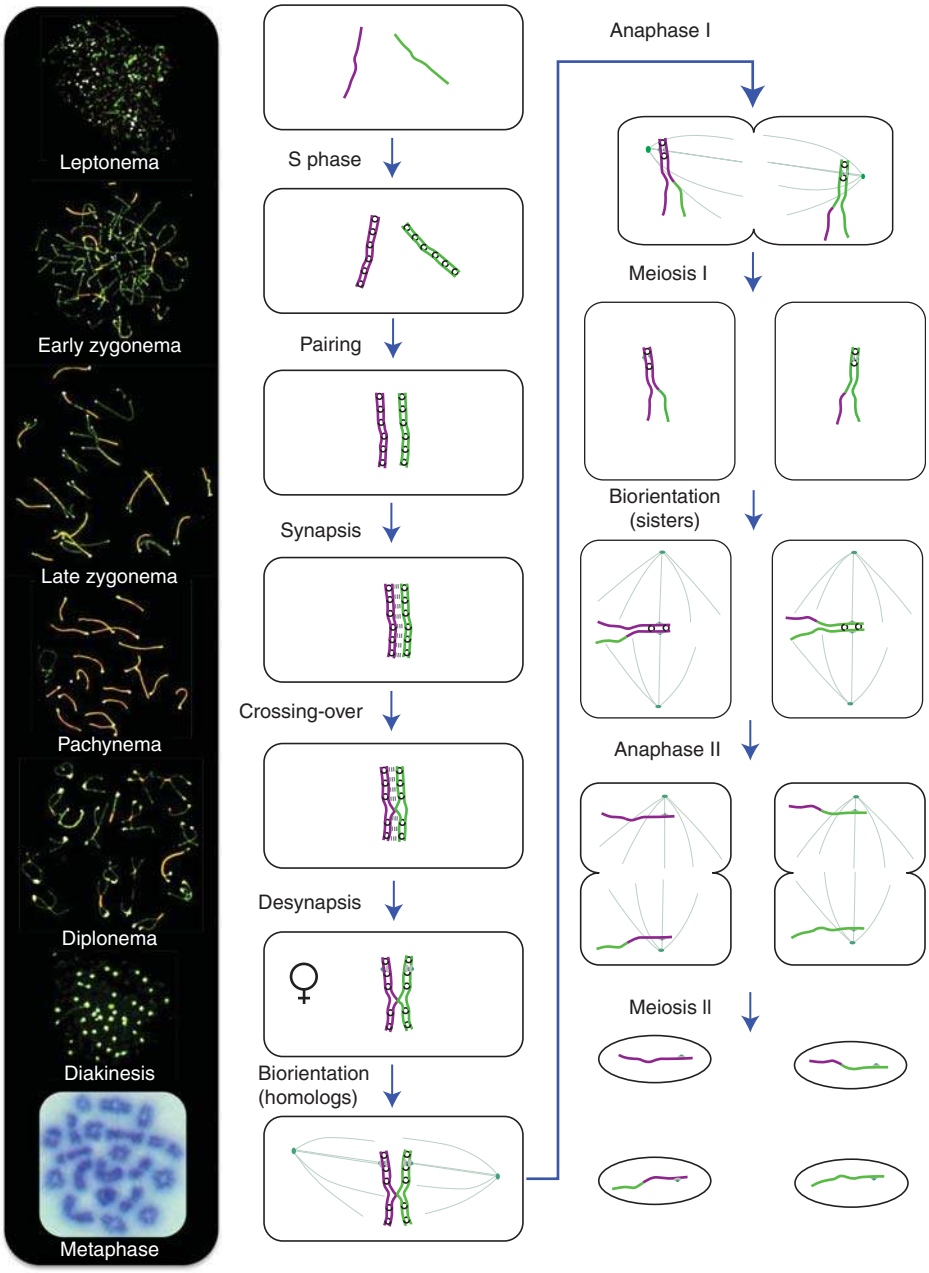

Figure 2. Chromosomal events of meiosis. The main stages of meiosis are shown for a single pair of homologous chromosomes (green and purple lines). Black rings indicate cohesion complexes connecting the sister chromatids. The synaptonemal complex is indicated by the triple-dashed line located between the homologs. Gray disks represent the kinetochores. Spindle microtubules are shown as thin green lines. The Venus symbol indicates the dictyotene stage at which prophase arrests in females. The images on the *left-hand* side show the corresponding prophase-I stages in surface-spread mouse spermatocyte nuclei immunostained for homolog axes (SYCP3, green) and the central region of the synaptonemal complex (SYCP1, red, but appears orange because of signal overlap). The final image shows a metaphase-I nucleus stained with Giemsa.

2004; Guillon et al. 2005; Mancera et al. 2008, 2011; Cole et al. 2010, 2014; Martini et al. 2011; Drouaud et al. 2013; Rockmill et al. 2013; Wijnker et al. 2013). However, this feature may not be universal; for example, patterns of heteroduplex in *Drosophila* are consistent with both crossovers and noncrossovers arising from a common intermediate (Crown et al. 2014).

INTERHOMOLOG INTERACTIONS

In most organisms, recombination is coerced to do work in meiosis, specifically to bring each pair of homologous chromosomes into close end-to-end juxtaposition and thereby facilitate their synapsis (Fig. 2) (e.g., Baudat et al. 2000; Romanienko and Camerini-Otero 2000; Peoples et al. 2002; Tesse et al. 2003; Henderson and Keeney 2004; Zickler and Kleckner 2015). Interhomolog crossing-over occurs within the context of the synapsed chromosomes. Crossovers combine with sister-chromatid cohesion, which was established during premeiotic S phase, to create connections called chiasmata that supersede synaptonemal complexes and are only resolved when cohesion between the chromosome arms is cleaved at anaphase I. Chiasmata are essential for efficient homolog disjunction at the first meiotic division because they allow homolog pairs to stably biorient on the meiosis-I spindle in much the same way that cohesion allows sister chromatids to biorient on the mitotic spindle (Fig. 2) (Petronczki et al. 2003; Hunter 2013).

Specific organizational features of meiotic prophase chromosomes and their coupling to meiotic recombination enable local DNA interactions to effect the juxtaposition of whole chromosomes. A central feature is the organization of sister chromatids into linear arrays of chromatin loops connected by a common cohesin-based axis that is augmented by meiosis-specific proteins (Zickler and Kleckner 1999; Pelttari et al. 2001; Blat et al. 2002; Syrjanen et al. 2014; Zickler and Kleckner 2015). This organization produces semicondensed prophase chromosomes with relatively rigid axes that define the pairing and interaction faces of each homolog pair. Direct physical and functional coupling of recombination complexes to the axes (Blat et al. 2002; Panizza et al. 2011; Borde and de Massy 2013) enables local DNA interactions to juxtapose associated homolog axes and ultimately bring about end-to-end chromosome pairing. Locally, recombinational interactions mediate the formation of visible bridges between pairs of axes, a subset of which nucleate the polymerization of the synaptonemal complex central region to lock in nascent pairing interactions (Albini and Jones 1987; Zickler and Kleckner 1999, 2015). Morphogenesis of homolog axes and synaptonemal complexes define the stages of meiotic prophase (Fig. 2). Axes develop during leptonema coincident with DSB formation and homolog pairing; during zygonema, synaptonemal complexes polymerize between aligned axes; when synapsis is complete, meiocytes enter pachynema and crossing-over occurs; finally, during diplonema, synaptonemal complexes are disassembled and bivalents connected by chiasmata emerge (Hunter 2013).

To efficiently promote pairing, synapsis and formation of chiasmata, recombinational interactions during meiosis are biased to occur between homologs, sharply contrasting somatic recombination, which occurs almost exclusively between sister chromatids (Fig. 1) (Kadyk and Hartwell 1992; Johnson and Jasin 2000; Bzymek et al. 2010; Lao and Hunter 2010; Humphryes and Hochwagen 2014; Brown and Bishop 2015). Although the precise mechanism of this meiotic interhomolog bias remains unknown, coupling of recombination to homolog axes also provides a means for communication between sister chromatids to limit intersister recombination. In budding yeast, where interhomolog bias has been most clearly elucidated, an important aspect of interhomolog bias is modulation of the recombination complex by inhibiting Rad51 (which nonetheless retains an essential supporting role) and switching to Dmc1-mediated DNA pairing and strand exchange (Tsubouchi and Roeder 2006; Niu et al. 2009; Cloud et al. 2012; Hong et al. 2013; Lao et al. 2013; Liu et al. 2014b). Evidence suggests that this feature may be conserved, at least in *Arabidopsis* (Kurzbauer et al. 2012; Da Ines et al. 2013). Local axis-based

checkpoint signaling is also inferred to locally remove a constraint to interhomolog strand exchange that is imposed by cohesin complexes (Kim et al. 2010), and to limit use of the sister-chromatid template (Wan et al. 2004; Niu et al. 2005; Goldfarb and Lichten 2010).

Feedback between homolog pairing and recombination coordinates the two processes such that synapsis is constrained to occur between homologous chromosomes, and progression of recombination beyond the nascent strand-exchange step is prevented until synapsis is ongoing (Hunter and Kleckner 2001). In this way, the reversibility of pairing interactions is maintained until homologous interactions become stabilized by synapsis, thereby limiting chromosome entanglement and facilitating the resolution of interlocked chromosomes as synapsis ensues (Storlazzi et al. 2010).

PROGRAMMED DSB FORMATION

In stark contrast to recombinational repair in somatic cells, meiotic recombination is a programmed event initiated by the deliberate induction of DSBs throughout the genome. Consequently, all chromosomes simultaneously engage in recombination at multiple positions. DSB formation is intimately associated with meiotic chromosome architecture, and is subject to exquisite spatial and temporal regulation (Keeney et al. 2014; Subramanian and Hochwagen 2014; Lam and Keeney 2015; Székvölgyi et al. 2015).

The DSB-forming machinery, centered around the SPO11 transesterase, has been reviewed extensively (e.g., Keeney 2001, 2008; Hunter 2006; Keeney and Neale 2006; Borde and de Massy 2013; de Massy 2013; Yamada and Ohta 2013; Lam and Keeney 2015; Székvölgyi et al. 2015). Local determinants of DSB location include *cis*-acting DNA sequences, transcription factors, histone modifications, and chromatin accessibility (Hwang and Hunter 2011; Lichten and de Massy 2011; Tischfield and Keeney 2012; Baudat et al. 2013; Yamada and Ohta 2013; Fowler et al. 2014). DSB formation is facilitated by factors that are components of the homolog axes (e.g., Schwacha and Kleckner 1994; Mao-Draayer et al. 1996; Ellermeier and Smith 2005; Goodyer et al. 2008; Kugou et al. 2009; Daniel et al. 2011), and the ensuing recombination complexes are visibly associated with these structures (Zickler and Kleckner 1999). However, the DSB sites themselves map to DNA sequences located in chromatin loops, whereas axis-associated sequences define DSB cold spots (Blat et al. 2002; Ito et al. 2014). These observations inspired the "tethered loop-axis complex" (TLAC) model, in which DSB sites located in loops must interact with the axis to trigger DSB formation (Blat et al. 2002). This dependency is inferred to establish axis association of recombination complexes effectively coupling interhomolog interactions at the DNA and axis levels. Although direct proof remains elusive, the TLAC model is supported by a number of observations. For example, essential DSB factors localize to the axes before DSB activation (Panizza et al. 2011), and bridging proteins, which connect DSB sites located in loops with axis-associated DSB factors, have recently been identified in budding and fission yeasts (Miyoshi et al. 2012; Acquaviva et al. 2013; Sommermeyer et al. 2013).

Global and local coupling to S-phase cell-cycle kinases, together with a meiotic S-phase checkpoint, confine DSB formation to replicated chromatids (Borde et al. 2000; Henderson et al. 2006; Ogino et al. 2006; Sasanuma et al. 2008; Wan et al. 2008; Blitzblau and Hochwagen 2013; Murakami and Keeney 2014). Local feedback regulation, involving kinase signaling by components of the DNA-damage response, also helps to optimize the DSB distribution by promoting even spacing, and locally limiting DSBs to one per four chromatids (Lange et al. 2011; Zhang et al. 2011; Carballo et al. 2013; Cooper et al. 2014; Garcia et al. 2015). As homolog pairing ensues, feedback regulation locally attenuates DSB formation, while delayed pairing appears to locally up-regulate DSBs (Kauppi et al. 2013; Lao et al. 2013; Thacker et al. 2014). Finally, full synapsis and satisfactory progression toward crossing-over appears to shut down the ability to make DSBs (Argunhan et al. 2013; Rosu et al. 2013; Stamper et al. 2013; Thacker et al. 2014).

CROSSOVER CONTROL

Crossover Assurance and Interference

Despite the stochastic nature of crossing-over, which to a first approximation can occur at any site along the chromosomes, crossovers are subject to tight regulation (Jones 1984; Jones and Franklin 2006). Although large numbers of DSBs form per nucleus, the total number of crossovers is very low, typically in the range of one per chromosome to one per chromosome arm. Thus, the popular view that meiotic recombination "scrambles" the genome is misleading. On the contrary, meiotic recombination is relatively conservative and as many as half of all chromatids can emerge from meiosis with parental haplotypes. However, each homolog pair obtains at least one crossover, as a prerequisite for accurate segregation, defining a regulatory feature termed "crossover assurance" (also known as the obligatory crossover). Also, when a single chromosome pair experiences multiple crossovers they tend to be widely and evenly spaced—the classical phenomenon of "crossover interference" that was already noted in the first genetic map constructed by Alfred Sturtevant in 1913 (1913a,b). Most models of interference assume that an inhibitory zone is established around DSB sites that have become committed to crossing-over (Hillers 2004; Berchowitz and Copenhaver 2010; Zhang et al. 2014b). Other DSBs within this zone of inhibition are prevented from becoming crossovers and instead mature as noncrossovers.

Together, crossover assurance and interference dictate the lower and upper limits for crossover numbers and underpin the phenomenon of crossover homeostasis: a low variation in crossover numbers per meiosis despite much larger variations in the numbers of recombinational interactions (Martini et al. 2006; Rosu et al. 2011; Cole et al. 2012; Yokoo et al. 2012). Interference (intercrossover) distances are generally large relative to chromosome length, which drives minimization of crossover numbers. In extreme cases, such as *C. elegans*, interference is effective over the entire length of the chromosomes such that the combined output of crossover assurance and interference is precisely one crossover per chromosome pair (Hillers and Villeneuve 2003). Not only does minimization of crossover numbers create a unique regulatory challenge for meiotic cells, its raison d'être remains unclear. Excess crossovers, per se, do not appear to interfere with homolog segregation (e.g., Seguela-Arnaud et al. 2015), favoring the idea that limiting exchange has an adaptive benefit, such as preserving favorable haplotypes and/or minimizing deleterious nonallelic recombination.

The mechanisms responsible for crossover assurance and interference remain elusive in part because of the complexity of studying these processes. Crossover assurance comprises temporally and functionally distinct designation/commitment and implementation/execution steps. As such, perturbation of any biochemical process required to implement crossing-over at a designated site (such as dHJ resolution) will reduce the efficiency of crossover assurance without being informative about the crossover designation process per se. Similarly, readouts of crossover interference are not readily amenable to high throughput screening and defining mutants that unambiguously perturb this process has proven both challenging and labor intensive (e.g., Zhang et al. 2014d). Moreover, interpretation of mutant phenotypes is complicated by the existence of a (typically minor) class of crossovers that does not show an interference distribution (Berchowitz and Copenhaver 2010). Thus, mutants that specifically diminish interfering crossovers (termed class I events) can show an apparent loss of interference caused by increasing prevalence of noninterfering class II crossovers (Stahl 2012).

Assuming a model in which interference establishes an inhibitory zone around designated crossover sites, a true interference mutant is expected to show a hypercrossover phenotype (Zhang et al. 2014d). However, hypercrossover mutants do not a priori define genes involved in crossover patterning. For example, hyperrecombination is seen for a number of DNA helicase mutants, but this is because of an interference-independent defect in implementing noncrossovers via synthesis-dependent strand annealing. In these cases, the distribution of class I cross-

overs remains largely unperturbed, whereas class II events are increased at the expense of noncrossovers (Rockmill et al. 2003; Youds et al. 2010; Crismani et al. 2012; Yokoo et al. 2012; Seguela-Arnaud et al. 2015).

Despite these impediments, important advances in our understanding of crossover control have been made in recent years. Several studies have established that the metric of crossover interference is the physical lengths of prophase chromosomes (as opposed to genetic distance or genomic distance, i.e., bps of DNA) (Martini et al. 2006; Drouaud et al. 2007; Petkov et al. 2007; Zhang et al. 2014b). Thus, crossover rates for the same chromosomes vary coordinately with changes in axis lengths, which reflect differences in chromatin packaging with respect to the size and density of chromatin loops (Lynn et al. 2002; Hillers and Villeneuve 2003; Kleckner et al. 2003; Tease and Hulten 2004; Qiao et al. 2012b; Gruhn et al. 2013; Baier et al. 2014). For example, in humans, variation in the lengths of prophase chromosomes account for long-known differences in recombination rates between males and females. Oocyte prophase chromosomes are about twice as long as their spermatocyte counterparts, have shorter, denser chromatin loops, and experience ~60% more crossovers (Gruhn et al. 2013). However, interference distances (expressed as μm of synaptonemal complex) are comparable between the sexes (Petkov et al. 2007). Although the basis for such variation in chromatin organization remains unclear, levels of cohesin subunits and other axis components may be important (Novak et al. 2008; Mets and Meyer 2009; Vranis et al. 2010; Murdoch et al. 2013).

A number of studies indicate that axis integrity and continuity are important for regulating crossover rate and interference (Hillers and Villeneuve 2003; Kleckner et al. 2004; Nabeshima et al. 2004; Novak et al. 2008; Storlazzi et al. 2008; Tsai et al. 2008; Joshi et al. 2009; Mets and Meyer 2009; Thacker and Keeney 2009; Zanders and Alani 2009; Qiao et al. 2012b; Libuda et al. 2013; Murdoch et al. 2013; Zhang et al. 2014d). These data suggest that homolog axes may be the conduits for transmission of interference signaling, or at least that axis integrity is important for spreading of interference (e.g., Zhang et al. 2014d). However, it is notable that mice lacking the major axis component, SYCP3, show apparently normal interference despite overt changes in axis length (de Boer et al. 2007).

Crossover homeostasis is, at least in part, a consequence of crossover interference (Martini et al. 2006; Rosu et al. 2011; Cole et al. 2012; Yokoo et al. 2012; Wang et al. 2015). When DSBs are made at a low density relative to the effective interference distance, a given recombination site has a lower probability of being subject to interference from an adjacent site, whereas, for a high density of DSBs, the opposite is true such that similar numbers of crossovers will emerge in both cases (Zickler and Kleckner 2015). These effects are locally manifested as changes in the ratios of crossovers to noncrossovers observed at assayed loci (Martini et al. 2006; Yokoo et al. 2012; Lao et al. 2013). The other essential component of homeostasis is crossover assurance, which requires regulatory inputs at each step of recombination. Preconditions for crossover assurance include forming sufficient numbers of DSBs and efficiently converting them into stable interhomolog interactions (Martini et al. 2006; Rosu et al. 2011; Kauppi et al. 2013; Lao et al. 2013). Faced with conditions that delay stable homolog engagement—such as inadequate DSB numbers, inefficient interhomolog template bias, or delayed/defective progression toward crossing-over—cells attempt to compensate by continuing to form DSBs (Sourirajan and Lichten 2008; Argunhan et al. 2013; Gray et al. 2013; Kauppi et al. 2013; Lao et al. 2013; Rosu et al. 2013; Stamper et al. 2013; Thacker et al. 2014). Successful synapsis and formation of crossover-competent joint molecules are inferred to attenuate both DSB formation and interhomolog bias (Rosu et al. 2011, 2013; Kauppi et al. 2013; Stamper et al. 2013; Thacker et al. 2014).

In the absence of interference from neighboring recombination sites, the crossover outcome is specifically implemented with extremely high efficiency (Martini et al. 2006; Rosu et al. 2011; Lao et al. 2013). However, the processes that ensure that a crossover outcome is triggered

for at least one DSB site per chromosome pair (the obligatory crossover) remain unknown. Evidence from a variety of organisms indicates that the patterning processes that designate crossover sites occur before and independently of synapsis (Page and Hawley 2001; Borner et al. 2004; Fung et al. 2004; Higgins et al. 2005; de Boer and Heyting 2006; de Boer et al. 2006; Zhang et al. 2014a). These data rule out the idea that bidirectional polymerization of synaptonemal complex is the major mode of interference signaling (King and Mortimer 1990). However, in *C. elegans*, subtle perturbation of synaptonemal complex composition elevates the crossover rate and attenuates, but does not abolish, interference (Hayashi et al. 2010; Libuda et al. 2013). Crossing-over is also elevated in the synapsis-defective *zep1* mutant in *Oryza* (Wang et al. 2010). Thus, synaptonemal complex is clearly important for limiting crossing-over in at least some organisms. Notably, in budding yeast, although synaptonemal complex is required for the majority of crossovers, it also acts to suppress centromere-proximal crossing-over (Chen et al. 2008).

Cytological analysis of crossover-specific proteins (that mark class I crossovers) circumvents problems associated with genetic analysis of interference, and permits the study of mutants that are unable to complete meiosis. This approach has been exploited in budding yeast to identify an interference pathway involving topoisomerase II, the axis component Red1, and posttranslational modification of both proteins by SUMO (small ubiquitin-like modifier) (Zhang et al. 2014d). Importantly, this analysis indicates that several mutants that show diminished interference when assayed genetically have normal patterning of crossover markers when assayed cytologically, and are, therefore, unlikely to be involved directly in interference. Involvement of topoisomerase II is compatible with a model in which expansion of axis-constrained chromatin drives crossover designation, which subsequently triggers chromatin contraction that emanates from the crossover site and spreads bidirectionally to inhibit crossing-over at neighboring recombination sites (Kleckner et al. 2004; Zhang et al. 2014b). Direct evidence of the predicted mechanical properties is currently lacking. However, consonant with such effects is the observation that crossover designation in *C. elegans* induces a local expansion and elongation of the chromosome (Libuda et al. 2013).

Crossover/Noncrossover Differentiation

The crossover control processes described above indicate that the outcome of meiotic DSB repair is tightly regulated. In a number of organisms, the initial differentiation of crossover and noncrossover pathways is temporally and functionally coupled to the onset of synapsis (Bojko 1985; Zickler et al. 1992; Hunter and Kleckner 2001; Borner et al. 2004; Fung et al. 2004; Reynolds et al. 2013; Zhang et al. 2014a). Moreover, in budding yeast, there appears to be a 1:1 correlation between designated crossover sites (marked by crossover-specific markers) and initiation sites for polymerization of synaptonamal complex (Fung et al. 2004; Henderson and Keeney 2004). In other organisms, these sites are also correlated, but synaptonemal complex-initiation sites outnumber crossover sites (Zickler et al. 1992; Zickler and Kleckner 1999; Brown et al. 2005; Gruhn et al. 2013; Zhang et al. 2014a).

At the DNA level, the appearance of metastable crossover-correlated joint molecules, the SEIs, is coincident with formation of synaptonemal complexes (Fig. 1) (Hunter and Kleckner 2001; Borner et al. 2004). In budding yeast, both transitions require the ZMM factors, which include Zip1, Zip2, Zip3, Zip4, Msh4-Msh5 (the MutSγ complex), Mer3, and Spo16 (also defined as synapsis initiation factors [SICs]) (Fung et al. 2004; Hunter 2006; Lynn et al. 2007). The ZMMs act to stabilize nascent joint molecules and coordinately promote polymerization of synaptonemal complexes, ultimately being required for the formation of class I crossovers. Although ZMMs were initially defined as crossover-specific factors in budding yeast, it seems likely that in most organisms a much larger fraction of all recombinational interactions benefit from at least transient stabilization by some or all of the ZMM factors, perhaps as

a prerequisite for crossover designation. For example, in mouse, plants, *C. elegans*, and *Sordaria*, initial numbers of MutSγ immunostaining foci greatly outnumber final crossover numbers (de Vries et al. 1999; Edelmann et al. 1999b; Kneitz et al. 2000; Higgins et al. 2008b; Yokoo et al. 2012; De Muyt et al. 2014; Zhang et al. 2014c).

The ZMMs define a functionally diverse set of proteins that act on distinct facets of recombination and chromosome synapsis. MutSγ (Msh4–Msh5) and Mer3 interact directly with DNA to stabilize nascent joint molecules. MutSγ is related to the MutS-family of DNA mismatch-repair proteins, and binds specifically to model D-loops and Holliday junctions (HJs) in vitro (Snowden et al. 2004). In vivo analysis supports the inference that MutSγ stabilizes joint molecules by embracing the involved duplexes (Borner et al. 2004; Snowden et al. 2004; Jessop et al. 2006; Oh et al. 2007). MutSγ (and other ZMMs) also appears to protect joint molecules from being dissociated by the anticrossover activity of the Sgs1–Top3–Rmi1 complex (see below) (Jessop et al. 2006; Oh et al. 2007; Kaur et al. 2015; Tang et al. 2015). Mer3 is a DNA helicase that can promote heteroduplex extension during D-loop formation and unwinds a number of DNA structures in vitro (Nakagawa and Kolodner 2002; Mazina et al. 2004). In vivo, Mer3 is required for efficient formation of SEIs, limits chromosome entanglement, and promotes efficient synapsis (Nakagawa and Ogawa 1999; Borner et al. 2004; Chen et al. 2005; Mercier et al. 2005; Tanaka et al. 2006; Sugawara et al. 2009; Wang et al. 2009; Guiraldelli et al. 2013). Localization studies in *Sordaria* reveal numerous pairs of opposing Mer3 foci associated with coaligned chromosome axes, suggesting that recombination complexes have a defined architecture at this stage, with Mer3 engaging both ends of a DSB. In this scenario, one DSB end engages the homolog, associating with its axis; while the second DSB end remains associated with its axis of origin (Storlazzi et al. 2010).

Whether the other ZMM members directly interact with DNA is unknown. Zip2-related proteins share homology with the XPF family of structure-selective endonucleases, although the active site motif is not conserved (Macaisne et al. 2008). Moreover, in *Arabidopsis*, the Zip2-relative SHOC1 interacts with an ERCC1-related protein called PTD (parting dancer), implying formation of an XPF–ERCC1-like complex that might bind nascent joint molecules (Macaisne et al. 2011). In budding yeast, Zip2 forms a functional unit together with Zip4, predicted to be an extensive TPR-repeat protein (Perry et al. 2005; Tsubouchi et al. 2006), and the small coiled-coil motif protein, Spo16 (Shinohara et al. 2008). Although the putative Zip2–Zip4–Spo16 complex is important for synapsis in budding yeast, mutation of Zip2 and Zip4 homologs in both plants and mouse causes relatively minor synapsis defects, although synapsis is inferred to initiate from fewer sites than in wild type (Chelysheva et al. 2007; Kuromori et al. 2008; Macaisne et al. 2008; Yang et al. 2008; Shen et al. 2012). Thus, synapsis initiation appears to be less strictly coupled to crossover designation in organisms other than yeast.

Budding yeast Zip3 is a RING-domain E3 ligase inferred to catalyze SUMO conjugation and is required for the normal localization of all other ZMMs (Agarwal and Roeder 2000; Cheng et al. 2006; Shinohara et al. 2008). Zip3 and the proline isomerase Fpr3, ensure that synapsis is rendered dependent on recombination and the Zip2–Zip4–Spo16 complex (Macqueen and Roeder 2009). This layer of regulation may be absent from other organisms as mutation of Zip3-related proteins—ZHP-3, RNF212, and HEI10—do not cause overt synapsis defects (Jantsch et al. 2004; Ward et al. 2007; Bhalla et al. 2008; Chelysheva et al. 2012; Wang et al. 2012a; Reynolds et al. 2013; Qiao et al. 2014). Also, although yeast Zip3 localizes primarily to crossover sites, other family members show dynamic localization patterns along synaptonemal complexes. Abundant focal/linear staining patterns are observed as synapsis ensues, followed by the loss of most staining, with retention/concentration only at designated crossover sites (Agarwal and Roeder 2000; Henderson and Keeney 2004; Jantsch et al. 2004; Bhalla et al. 2008; Chelysheva et al. 2012;

Wang et al. 2012a; Yokoo et al. 2012; Reynolds et al. 2013; De Muyt et al. 2014; Qiao et al. 2014).

With the exception of mammalian HEI10, a function that appears to be shared by Zip3-family proteins is the stabilization of recombination factors at designated crossover sites (Agarwal and Roeder 2000; Shinohara et al. 2008; Yokoo et al. 2012; Reynolds et al. 2013; De Muyt et al. 2014). For example, in mouse, only a subset of the abundant RNF212 complexes detected along newly synapsed chromosomes actually localize with recombination sites marked by MutSγ (Reynolds et al. 2013). Sites of stable RNF212–MutSγ colocalization persist and ultimately go on to recruit crossover-specific factors and mature into crossovers, whereas the majority of RNF212 and MutSγ complexes are lost from the chromosomes. Thus, the differentiation of crossover and noncrossover pathways seen at the DNA level (Hunter and Kleckner 2001; Borner et al. 2004) is underpinned by differential stabilization of recombination factors at the protein level.

Whether selective localization of RNF212 (and other Zip3-family proteins) to precrossover sites represents the crossover designation process, per se, or is a downstream manifestation of that process is unclear. In mouse, normal patterning of RNF212 and MutSγ, dissociation of these factors from synapsed chromosomes, and progression of DSB repair require HEI10 and the cyclin-related protein, CNTD1 (see below) (Holloway et al. 2014; Qiao et al. 2014). Mouse HEI10 is not detected along chromosomes at early stages of synapsis, but ultimately concentrates at crossover sites where it supersedes RNF212 (Fig. 1) (Qiao et al. 2014). Although Zip3 and RNF212 are inferred to catalyze SUMO conjugation, human HEI10 has been implicated as a ubiquitin E3-ligase (Toby et al. 2003; Cheng et al. 2006; Reynolds et al. 2013; D Kulkarni and N Hunter, unpubl.).

Together, these observations suggest a model in which association of RNF212 with recombination sites is limited by a process involving HEI10-mediated ubiquitylation (Qiao et al. 2014). At most recombination sites, the absence of RNF212 renders factors such as MutSγ unstable leading to their dissociation or degradation. Consequently, nascent joint molecules are destabilized and dissociated by DNA helicases (see below) to promote a noncrossover outcome. At designated crossover sites a positive-feedback loop, involving SUMOylation, promotes the mutual stabilization of RNF212 and MutSγ, which in turn stabilizes nascent joint molecules to facilitate dHJ formation. Finally, HEI10 accumulates at these sites, where it acts to displace RNF212 and MutSγ to allow the final steps of crossing-over to be implemented (Qiao et al. 2014).

Identification of COSA-1 as a cyclin-related protein that is essential for crossing-over in *C. elegans* implies that CDK-driven phosphorylation is another facet of crossover regulation via posttranslational protein modification (Yokoo et al. 2012; Holloway et al. 2014). Consistently, in mouse, CDK proteins localize to sites of meiotic recombination (Ashley et al. 2001); CDK4 concentrates at DSB sites as chromosomes synapse and is succeeded by a much smaller number of CDK2 complexes that localize specifically at crossover sites (CDK2 also concentrates at telomeres). *C. elegans* COSA-1 also accumulates specifically to crossover sites, and is required for the local retention and concentration of ZHP-3 and MSH-5 (Yokoo et al. 2012). The phenotypes of mice lacking the COSA-1 ortholog, CNTD1, are remarkably similar to those of *Hei10* mutants (Holloway et al. 2014). Moreover, in somatic cells, human HEI10 interacts with cyclin B1 and can down-regulate cyclin B levels (Toby et al. 2003; Singh et al. 2007). These data suggest that phosphorylation, driven by a CNTD1/COSA-1–CDK complex, and ubiquitylation, targeted by HEI10, are coupled to effect crossover regulation.

Additional complexity to the regulatory circuitry defined by mammalian RNF212–HEI10 is suggested by the existence of multiple RNF212 spliceforms, and an RNF212 ortholog (RNF212B) (Kong et al. 2008; Reynolds et al. 2013). Similarly, the *C. elegans* genome encodes multiple ZHP-3-related proteins; however, it lacks an obvious HEI10 ortholog (M Zetka, personal communication). Curiously, *Sordaria* and plants encode only a single HEI10-like protein, with localization characteristics of both

RNF212 and HEI10 in mammals (Chelysheva et al. 2012; Wang et al. 2012a; De Muyt et al. 2014). Similarly, budding yeast contains a single Zip3 homolog. Despite this variation and complexity, the relationships between Zip3-family proteins, selective stabilization of MutSγ, and crossing-over appear to be conserved (Agarwal and Roeder 2000; Henderson and Keeney 2004; Jantsch et al. 2004; Bhalla et al. 2008; Chelysheva et al. 2012; Wang et al. 2012a; Yokoo et al. 2012; Reynolds et al. 2013; De Muyt et al. 2014; Qiao et al. 2014).

Pro-Crossover Role of the Synaptonemal Complex

Although not essential for interhomolog DSB repair, synaptonemal complex is required for efficient interhomolog crossing-over in most organisms (Zickler and Kleckner 2015). In mutants lacking components of the synaptonemal complex central region recombination stalls at an intermediate stage and, in mouse, markers such as CDK2, HEI10, RNF212, and MutLγ fail to localize to designated crossover sites (Sym et al. 1993; Borner et al. 2004; de Vries et al. 2005; Reynolds et al. 2013; Qiao et al. 2014). Synaptonemal complex is inferred to act locally to stabilize procrossover factors and at later stages may facilitate the exchange of homolog axes that must accompany exchange at the DNA level (Storlazzi et al. 1996; Borner et al. 2004; de Boer et al. 2007; Shinohara et al. 2008; Qiao et al. 2012a; Voelkel-Meiman et al. 2015). As described above, an inhibitory role for synaptonemal complex that limits crossovers has also been demonstrated (Chen et al. 2008; Hayashi et al. 2010; Wang et al. 2010; Libuda et al. 2013). In *Arabidopsis*, synapsis has been shown to help ensure the fidelity of meiotic recombination, probably by limiting nonallelic recombination (Higgins et al. 2005).

Recombination-Associated DNA Synthesis

De novo DNA synthesis must accompany all recombinational repair, to allow DSB ends to anneal during noncrossover formation, and for the formation of dHJs during crossover formation (Fig. 1) (Lao et al. 2008). Recombination-associated DNA synthesis is assumed to be distinct from replicative DNA synthesis in that it is: (1) primed by the 3′ terminus of the invading DSB end; (2) uncoupled from lagging strand synthesis; and (3) only limited synthesis is required, sufficient to replace the sequences removed by DSB resection (Haber 2013).

The molecular details of the DNA synthesis associated with meiotic recombination remain poorly characterized. Classic electron microscope (EM) autoradiography studies showed that DNA synthesis is indeed associated with sites of meiotic recombination (Carpenter 1981; Moses et al. 1984). Mapping of newly synthesized DNA in budding yeast confirmed the predicted patterns and timing of DNA synthesis associated with crossover and noncrossover products. Crossover-correlated synthesis occurs on either side of the assayed DSB site, whereas synthesis associated with noncrossovers spans the DSB site. Also, crossover-associated synthesis tracts were longer and occurred later than those associated with noncrossovers (Fig. 1) (Terasawa et al. 2007). These observations are consonant with data from a variety of organisms showing that gene-conversion tracts associated with crossovers are generally much longer than those associated with noncrossovers (Jeffreys and May 2004; Guillon et al. 2005; Cole et al. 2010, 2014; Drouaud et al. 2013; Wijnker et al. 2013).

Mutant phenotypes implicate a number of replication factors in meiotic recombination. In budding yeast, *pol3-ct*, an allele of the lagging-strand polymerase Polδ, reduces crossing-over and results in shorter gene-conversion tract lengths, indicative of shorter stretches of heteroduplex (Maloisel et al. 2004). In vitro, D-loop extension by Polδ requires the proliferating cell nuclear antigen (PCNA) replicative clamp (Li et al. 2009). Consistently, *pol30-201,* an allele of budding yeast PCNA confers a phenotype similar to that of the *pol3-ct* mutation, with shorter heteroduplex tracts and reduced crossing-over (Stone et al. 2008). These phenotypes suggest that the extent of initial DNA synthesis is an important aspect of crossover/noncrossover differentiation that may influence the stability

of nascent D-loops, the efficiency of second-end capture to form a dHJ, and/or the structure of the ensuing dHJs and their propensity to be resolved specifically into crossovers (Fig. 1).

Additional mutant phenotypes are consistent with the idea that the mode and processivity of DNA synthesis associated with crossing-over is distinct from that associated with noncrossovers. In *Arabidopsis*, a hypomorphic mutation in the replication factor C (RFC) clamp-loader complex diminishes class I crossovers (Wang et al. 2012b). Given that one role of RFC is polymerase switching during Okazaki fragment initiation (switching Polα primase for Polδ) (Maga et al. 2000; Mossi et al. 2000), Wang et al. (2012b) suggested that lagging-strand synthesis might occur during crossover formation, where it could function to stabilize the expanding D-loop to promote dHJ formation. However, the primary function of RFC in recombination-associated DNA synthesis could be to load PCNA.

Arabidopsis and *Oryza* possess multiple paralogs of the replication protein A (RPA) complex subunits and several *rpa* mutant alleles have been shown to specifically reduce class I crossovers, whereas overall DSB repair remains efficient (Osman et al. 2009; Li et al. 2013). In budding yeast, meiotic DSB repair shows a general dependence on RPA (Soustelle et al. 2002), but RPA phosphorylation modulates crossover patterning (Bartrand et al. 2006). *Drosophilia HDM* (*Hold'em*) encodes an OB-fold protein related to RPA70 that is required for a majority of crossover and interacts with the joint-molecule resolving endonuclease complex, MEI9–ERCC1–MUS312 (Joyce et al. 2009). In mammals, the RPA1-related MEIOB protein and associated factor, SPATA22, form an RPA-associated complex that is required for intermediate steps of recombination and normal synapsis (La Salle et al. 2012; Ishishita et al. 2013, 2014; Luo et al. 2013; Souquet et al. 2013). MEIOB–SPATA22 is inferred to act after initial strand exchange, perhaps to promote strand annealing in both SDSA and dHJ pathways, acting analogously to the budding yeast Rad52 protein (Lao et al. 2008; Luo et al. 2013). A 3′-5′ exonuclease activity associated with MEIOB has led to the proposal that MEIOB–SPATA22–RPA also mediates digestion of 3′-flaps that may form on annealing of DSB ends, as a consequence of excess DNA synthesis relative to DSB resection (Fig. 1) (Luo et al. 2013).

The MCM complex has essential functions in the initiation of replication and acts as the replicative helicase during elongation (Bochman and Schwacha 2009). However, roles in a variety of other chromosomal processes have been invoked, including checkpoint signaling and DNA repair (Forsburg 2004; Shukla et al. 2005; Bailis et al. 2008). Unexpectedly, a hypomorph of *Drosophila mcm5* specifically reduces crossing-over without perturbing DSB repair (Lake et al. 2007). Three additional MCM-related proteins in *Drosophila*, REC/MCM8, MEI217, and MEI218, are also required for crossing-over and *rec* mutants have shorter gene conversion tracts suggesting that a meiotic MCM complex, Mei-MCM, comprising REC–MEI217–MEI218 and perhaps MCM5, enhances the processivity of recombination-associated DNA synthesis (Manheim et al. 2002; Matsubayashi and Yamamoto 2003; Bhagat et al. 2004; Blanton et al. 2005; Kohl et al. 2012). Suppression of the *rec/mcm8* crossover defect by mutation of the BLM helicase ortholog, MUS309, led Sekelsky and colleagues to propose that mei-MCM is the functional analog of the MutSγ complex, which is absent from the *Drosophila* genome (Kohl et al. 2012). Consistent with this idea, absence of MCM8 or MCM9 in species that possess MutSγ confers a general defect in DSB repair, but not the crossover-specific phenotype seen for *Drosophila mei-MCM* mutants (Lutzmann et al. 2012; Crismani et al. 2013).

Alternative DNA polymerases are involved in a variety of damage-repair processes and mediate damage tolerance by facilitating the bypass of template lesions (Goodman and Woodgate 2013). Several studies have suggested a role for such polymerases in meiotic recombination (Leem et al. 1994; Plug et al. 1997; Garcia-Diaz et al. 2000; Uchiyama et al. 2004; Arbel-Eden et al. 2013; Rattray et al. 2015). Notably, the nucleotide-excision repair factor, DNA polymerase β, localizes to synaptonemal complex-

es in mouse spermatocytes and is required for normal synapsis and DSB repair (Plug et al. 1997; Kidane et al. 2010). Moreover, the early defects of Polβ-deficient spermatocytes imply an unanticipated function for DNA Polβ in DSB processing (Kidane et al. 2010).

The translesion synthesis (TLS) DNA polymerases allow the replication machinery to bypass template lesions (Goodman and Woodgate 2013). In budding yeast, deficiency for the three TLS factors Rev1, Polζ (zeta), and Polη (eta) reduces the frequencies of both allelic and nonallelic gene conversion (Arbel-Eden et al. 2013). Moreover, direct interaction between Rev1, Polζ, and components of the DSB-forming machinery (Spo11, Mei4, Rec114) is suggested by yeast two-hybrid interactions (Arbel-Eden et al. 2013). Further support for a role of TLS polymerases in meiosis comes from the observation that Polζ also makes a major contribution to the elevated mutation rate that is associated with meiotic recombination (Arbeithuber et al. 2015; Rattray et al. 2015). Recruitment of alternative DNA polymerases to damage sites is mediated by ubiquitylation of PCNA at K164 (Dieckman et al. 2012). In mice expressing a K164R substitution allele, chromosome synapsis and crossover differentiation appear to occur normally, but meiosis arrests during pachytene, which may reflect defective DSB repair (Roa et al. 2008).

RESOLVING, DISSOLVING, AND UNWINDING JOINT MOLECULES TO IMPLEMENT CROSSOVER AND NONCROSSOVER FATES

The last 15 years have witnessed major advances in our understanding of joint-molecule resolution in eukaryotes (Schwartz and Heyer 2011; Bizard and Hickson 2014; Matos and West 2014; Wyatt and West 2014). During meiosis, joint-molecule resolution must achieve efficient implementation of crossing-over to promote accurate homolog disjunction, and the timely and efficient resolution of all remaining joint molecules to allow chromosomes to cleanly separate (De Muyt et al. 2012; Zakharyevich et al. 2012). These two biological imperatives are achieved through precise spatial and temporal regulation of joint-molecule-processing enzymes (Fig. 1).

Differential Timing and Regulation of Crossover and Noncrossover Formation

In budding yeast, crossover and noncrossover pathways of joint-molecule processing show differential dependence on the transcription factor, Ndt80, which defines a late-pachytene transition that commits cells to crossing-over and meiotic divisions (Allers and Lichten 2001a; Winter 2012). *ndt80* mutants arrest in pachytene with unresolved joint molecules and very low levels of crossovers, whereas noncrossovers form at wild-type levels (Allers and Lichten 2001a). Thus, the joint molecules that accumulate in *ndt80* mutants give rise primarily to crossovers, indicating the existence of an Ndt80-activated, crossover-biased resolution factor. This inference is consonant with the early designation of crossover sites, described above. Although Ndt80 regulates the transcription of hundreds of genes, expression of just one protein, the polo-like kinase Cdc5, is sufficient to induce joint-molecule resolution and crossing-over (Clyne et al. 2003; Sourirajan and Lichten 2008).

MutLγ and EXO1 Define a Crossover-Specific Resolving Factor

In budding yeast, plants, and mammals, the vast majority of crossovers is dependent on two conserved endonuclease activities defined by the mismatch-repair factors, MutLγ (comprising MLH1 and MLH3) and EXO1, and the structure-selective endonuclease, MUS81–EME1/Mms4 (Mus81–Mms4 in budding yeast) (Baker et al. 1996; Hunter and Borts 1997; Wang et al. 1999; Khazanehdari and Borts 2000; Kirkpatrick et al. 2000; Tsubouchi and Ogawa 2000; Lipkin et al. 2002; Wei et al. 2003; Jackson et al. 2006; Berchowitz et al. 2007; Higgins et al. 2008a; Holloway et al. 2008; Jessop and Lichten 2008; Nishant et al. 2008; Oh et al. 2008; Zakharyevich et al. 2010; Hunter 2011; Zakharyevich et al. 2012; Ranjha et al. 2014; Rogacheva et al. 2014). Joint-molecule formation occurs normally in budding yeast *exo1* and *mlh1/3*

mutants, but crossing-over is specifically diminished, indicating that Exo1 and MutLγ define the anticipated crossover-specific resolution factor (Zakharyevich et al. 2010, 2012). EXO1 is a member of the XPG/Rad2 nuclease superfamily and plays a major role in meiotic DSB resection in addition to its role in DNA mismatch repair (Keelagher et al. 2010; Zakharyevich et al. 2010). Importantly, the nuclease activity of EXO1 is not required for its meiotic crossover function, although interaction with MutLγ is important (Zakharyevich et al. 2010). Consistent with a late function in meiotic recombination, MutLγ localizes specifically to future crossover sites in a number of organisms, including humans (Kolas and Cohen 2004), and has become an invaluable marker for the cytological analysis of crossing-over. Like other MutL-family members, MutLγ is an endonuclease and this activity is essential for its procrossover function, consistent with a direct role in dHJ resolution (Nishant et al. 2008; Zakharyevich et al. 2012; Ranjha et al. 2014; Rogacheva et al. 2014). Moreover, MutLγ preferentially binds to HJs in vitro, although targeted incision of joint molecules has not yet been demonstrated (Ranjha et al. 2014).

A General Role for MUS81 Enzymes in Meiotic Joint Molecule Processing

MUS81–EME1/Mms4 is an XPF-family endonuclease capable of cleaving a variety of branched DNA structures in vitro including 3′-flaps, D-loops, and nicked-HJs, favoring substrates with a nick or gap adjacent to the branch point that is ultimately incised (Schwartz and Heyer 2011; Mukherjee et al. 2014). Genetic studies provide compelling evidence that MUS81 enzymes can process meiotic joint molecules in vivo, although the exact substrate(s) remains uncertain (Boddy et al. 2001; Osman et al. 2003; Cromie et al. 2006; Berchowitz et al. 2007; Higgins et al. 2008a; Holloway et al. 2008; Jessop and Lichten 2008; Oh et al. 2008; Hickson and Mankouri 2011; Oke et al. 2014). The cleavage patterns observed with joint molecule substrates in vitro and the predominant role of Mus81–Eme1 in promoting crossovers in fission yeast has led to a sequential D-loop nicking model that specifically produces crossovers (Osman et al. 2003; Gaskell et al. 2007). However, MUS81–EME1/Mms4 is responsible for only a minority of crossovers in most organisms (~5%–25%), although its activity is generally important for efficient joint molecule resolution (Jessop and Lichten 2008; Oh et al. 2008). Analysis in budding yeast reveals an early function for Mus81–Mms4 in the efficient formation of interhomolog joint molecules, in addition to a late function in joint-molecule resolution (De Los Santos et al. 2003; Oh et al. 2008; Matos et al. 2011). A general, early function for Mus81–Mms4 is further supported by the increased frequency of gene conversions and longer gene-conversion tracts seen in *mus81/mms4* mutants (De Los Santos et al. 2003; Oke et al. 2014). These phenotypes are suggested to derive from aberrant processing of 3′-flaps formed when extended DSB ends anneal (Fig. 1). Aberrant processing in the absence of Mus81–Mms4 may result in longer heteroduplex tracts through assimilation of the 3′-flap, or because uncleaved flaps provoke reinvasion of the template chromosome. The late resolution function of Mus81–Mms4 involves its hyperactivation by Cdc5-mediated phosphorylation (Matos et al. 2011; Matos and West 2014).

The STR/BTR Ensembles Are Master Regulators of Meiotic Joint Molecule Metabolism

The third major joint-molecule-processing enzyme in meiosis is the STR "dissolvase" complex in budding yeast, or the analogous BTR complex in metazoans (Bizard and Hickson 2014). These complexes comprise RecQ helicases, Sgs1/BLM, their cognate type-I topoisomerases, Top3/TOPIIIα, and accessory factors Rmi1/RMI1–RMI2. In isolation, Sgs1/BLM can migrate HJs and unwind protein-free D-loops (Karow et al. 2000; van Brabant et al. 2000; Bachrati et al. 2006; Cejka and Kowalczykowski 2010; Fasching et al. 2015), but in combination with the single-strand passage activity of Top3–Rmi1/TOPIIIα–RMI1–RMI2, the STR/BTR complexes perform a unique re-

action to dissociate dHJs into component duplexes. This convergent branch migration and decatenation reaction yields exclusively noncrossover products and has been termed dissolution to distinguish it from endonuclease-mediated resolution (Wu and Hickson 2003; Wu et al. 2006; Bussen et al. 2007; Singh et al. 2008; Xu et al. 2008; Cejka et al. 2010; Bocquet et al. 2014). Consistent with this activity, STR/BTR has potent anticrossover activity in vivo and is required for efficient homolog separation at meiosis I (Jessop et al. 2006; Oh et al. 2007; Chu and Hickson 2009; Bzymek et al. 2010; Holloway et al. 2010; Mankouri et al. 2011; Seguela-Arnaud et al. 2015). However, the decatenase activity of Top3–Rmi1/TOPIIIα–RMI1–RMI2 is not limited to dHJ dissolution, but is also required for the dissociation of D-loops formed by Rad51-mediated strand exchange (Fasching et al. 2015). These in vitro data imply that topological complexity impedes simple unwinding of D-loops. Consistent with a general requirement for a decatenase activity in vivo, Top3–Rmi1 is required for all functions previously defined for Sgs1 during meiotic recombination (Kaur et al. 2015; Tang et al. 2015). These include channeling joint molecules into physiological crossover and noncrossover pathways, and suppressing nonallelic recombination by dissociating the products of promiscuous strand exchange. In the absence of STR, intersister joint molecules and aberrant "multi-chromatid" structures comprising three and four interconnected chromosomes become prominent intermediates (Oh et al. 2007). Consequently, joint-molecule resolution and formation of both crossovers and noncrossovers becomes deregulated, acutely dependent on Ndt80 and the structure-selective endonucleases (Mus81–Mms4, Slx1–Slx4 and Yen1, discussed further below), and independent of MutSγ and MutLγ, which define the class I crossover pathway (Jessop et al. 2006; Oh et al. 2007, 2008; Jessop and Lichten 2008; De Muyt et al. 2012; Zakharyevich et al. 2012; Oke et al. 2014; Kaur et al. 2015; Tang et al. 2015). Thus, STR plays both a procrossover role, specifically facilitating formation of class I crossovers, and promotes noncrossover formation via synthesis-dependent strand annealing (Fig. 1). Similar inferences have been made for the *C. elegans* BLM ortholog, HIM-6 (Schvarzstein et al. 2014). Consistent with this conclusion, in budding yeast, the high levels of crossovers seen when all three structure-selective endonucleases (Mus81–Mms4, Slx1–Slx4 and Yen1) are absent are dependent on both MutLγ and Sgs1 (De Muyt et al. 2012; Zakharyevich et al. 2012). At designated crossover sites, the anticrossover function of STR is thought to be antagonized by MutSγ and other ZMM factors (Jessop et al. 2006; Oh et al. 2007; Chelysheva et al. 2008; Kaur et al. 2015; Seguela-Arnaud et al. 2015; Tang et al. 2015). Thus, the concerted action of stabilizing and destabilizing activities guides dHJ formation along the class-I crossover pathway.

Top3–Rmi1/TOPIIIα–RMI1–RMI2, but apparently not Sgs1/BLM, is also required during joint-molecule resolution to remove recombination-dependent chromosome entanglements (Hartung et al. 2008; Kaur et al. 2015; Tang et al. 2015). This late role of Top3–Rmi1/TOPIIIα–RMI1–RMI2 is absolutely essential for chromosome separation and again consistent with topological complexity in meiotic joint molecules that can only be eliminated with the aid of a decatenase activity.

SLX4-Associated Endonucleases and the GEN1/Yen1 Resolvase

Three other structure-selective endonucleases make variable contributions to meiotic joint-molecule processing depending on the context and the organism. SLX1 comprises an UvrC-intron (URI)-endonuclease domain and carboxy-terminal PHD-type zinc finger characteristic of the URI–YIG family of endonucleases (Dunin-Horkawicz et al. 2006). Nuclease activity depends on interaction with the scaffold protein, SLX4 (also called BTBD12), which mediates transition from an inactive SLX1 homodimer to an active SLX1–SLX4 complex (Gaur et al. 2015). Recombinant SLX1–SLX4 complexes from budding yeast and human can cleave Y-junctions, 5′-flaps, and HJs (Fricke and Brill 2003; Munoz et al. 2009; Svendsen

et al. 2009). In metazoans, SLX4 also interacts with MUS81–EME1 and XPF–ERCC1 to assemble and regulate composite nuclease ensembles (budding yeast Slx4 interacts with XPF–ERCC1 ortholog, Rad1–Rad10, but not Mus81–Mms4) (Flott et al. 2007; Fekairi et al. 2009; Munoz et al. 2009; Svendsen et al. 2009; Castor et al. 2013; Wyatt et al. 2013).

In budding yeast *slx1/4* single mutants, slight delays in joint-molecule resolution can be inferred but meiotic recombination is largely unperturbed. Only when *SGS1* is also mutated, does Slx1–Slx4 become essential for resolution of a subset of joint molecules (De Muyt et al. 2012; Zakharyevich et al. 2012). In mouse, *Slx4/Btbd12* mutation delays meiotic DSB repair, and while final crossover numbers are normal, the fraction of events that are processed via the class-I pathway defined by MutLγ appears to be increased (Holloway et al. 2011). SLX4 orthologs are important for crossing-over in *Drosophila* and *C. elegans* (Yildiz et al. 2002; Saito et al. 2009). The crossover function of *Drosophila* SLX4 ortholog MUS312 involves not SLX1, but the XPF–ERCC1-family nuclease, MEI9–ERCC1, which is responsible for the vast majority of crossovers in this organism (Andersen et al. 2009). In *C. elegans,* XPF-1 also promotes crossing-over, functioning in parallel with a second pathway defined by MUS81 and SLX1 (Agostinho et al. 2013; Bellendir and Sekelsky 2013; O'Neil et al. 2013; Saito et al. 2013). However, even when both pathways are mutated, ≥50%–70% of normal crossover levels can still form indicating the existence of a third major pathway of joint molecule resolution in *C. elegans* meiosis. SLX1 also plays an intriguing and unanticipated anticrossover role to suppress exchange in the central regions of *C. elegans* chromosomes (Saito et al. 2013).

GEN1/Yen1 (Yen1 in budding yeast) was identified as a Rad2/XPG endonuclease family member with HJ-resolving activity in vitro (Furukawa et al. 2003; Ishikawa et al. 2004; Ip et al. 2008). GEN1/Yen1 meets the criteria for a bona fide HJ-resolvase, cutting via concerted symmetrical cleavages analogous to the archetypal prokaryotic RuvC resolvase (Ip et al. 2008; Rass et al. 2010). Although GEN1/Yen1 are not essential for resolving recombination intermediates in mitotically cycling cells, Yen1 partially suppresses the recombination and damage-sensitivity phenotypes of *mus81* mutants (Blanco et al. 2010; Ho et al. 2010; Tay and Wu 2010; Agmon et al. 2011). Similarly, Yen1 is not normally important for meiotic recombination, but its function becomes essential specifically when Mus81–Mms4 is absent (Matos et al. 2011; De Muyt et al. 2012; Zakharyevich et al. 2012). Yen1 is subject to inhibitory phosphorylation and only activated very late in meiosis, at the second division (Matos et al. 2011). Thus, GEN1/Yen1 may define the resolvase of last resort that can be called on to resolve rare joint molecules that escape Mus81–Mms4.

The SMC5/6 Complex Facilitates Joint Molecule Formation and Resolution

SMC5 and SMC6 form a large ring-like structure characteristic of the "structural maintenance of chromosome" proteins and combine with up to six non-SMC subunits (Nse1-6 in budding and fission yeasts) to form the SMC5/6 complex (Jeppsson et al. 2014). The SMC5/6 complex is essential for chromosome metabolism, promoting normal replication, cohesion, repair, and segregation. A primary role for SMC5/6 occurs following chromosome replication, where it helps alleviate topological entanglement of sister chromatids, working in concert with topoisomerases (Torres-Rosell et al. 2007; Tapia-Alveal et al. 2010; Kegel et al. 2011). Specifically, SMC5/6 is suggested to embrace nascent intertwinings between sister chromatid to create topologically isolated domains that help to limit supercoiling stress ahead of replication forks (Kegel et al. 2011).

In budding yeast meiosis, Smc5/6 influences early and late steps of recombination. Similar to cells lacking STR function, mutation of the Smc5/6 complex increases the levels of intersister and multichromatid joint molecules and the expense of interhomolog dHJs (Copsey et al. 2013; Lilienthal et al. 2013; Xaver et al. 2013). Analysis in both budding and fission yeasts shows that additional aberrant joint-molecule structures arise when Smc5/6 is defective

(Wehrkamp-Richter et al. 2012; Copsey et al. 2013). Notably, in fission yeast, a subset of the joint molecules that accumulates in an *nse6Δ* mutant contain single-stranded DNA and is suggested to contain hemicatenane structures (Wehrkamp-Richter et al. 2012).

In addition to its early role, Smc5/6 is also essential for resolution of a subset of joint molecules and mutants show a complete block to chromosome segregation (Farmer et al. 2011; Wehrkamp-Richter et al. 2012; Copsey et al. 2013; Lilienthal et al. 2013; Xaver et al. 2013). However, crossovers and noncrossovers are only slightly reduced in budding yeast *smc5/6* mutants and remain dependent on the physiological pathways defined by STR and MutLγ (Copsey et al. 2013; Lilienthal et al. 2013; Xaver et al. 2013). These observations are consistent with the idea that Smc5/6 influences alternative resolvase pathways defined by the structure-selective endonucleases, Mus81–Mm4, Slx1–Slx4, and/or Yen1. Although the relationship between Smc5/6 and the structure-selective endonucleases appears to be complex, existing evidence indicates that Smc5/6 acts locally at recombination sites to recruit and regulate the activity of at least one resolvase, Mus81–Mms4 (Wehrkamp-Richter et al. 2012; Copsey et al. 2013; Xaver et al. 2013).

The Nse2/Mms21 component of the budding yeast Smc5/6 complex is a SUMO E3 ligase (Zhao and Blobel 2005). Intriguingly, the early and late functions of the Smc5/6 complex are separated by the ligase-defective *mms21-11* allele, which causes aberrant joint molecule formation, but is proficient for resolution (Xaver et al. 2013). Application of the temperature-sensitive *smc6-56* allele confirms that the early and late functions of the Smc5/6 complex are separable: aberrant joint molecules caused by early inactivation of Smc5/6 function can still be resolved if Smc5/6 function is restored at the time of resolution (Lilienthal et al. 2013; Xaver et al. 2013).

Collectively, yeast studies point to models in which the Smc5/6 complex embraces DNA to demarcate the borders of ongoing recombination events, where it influences joint molecule formation and resolution involving Mus81–Eme1/Mms4 and perhaps other factors, such as Mph1 and its cofactors Mhf1–Mhf2 (see below), which interact genetically and physically with Smc5/6 (Chen et al. 2009; Chavez et al. 2011; Xue et al. 2015).

Whether the meiotic functions of the Smc5/6 complex defined in yeast are conserved in metazoans is currently unclear. In *C. elegans*, *smc-5/6* mutations are required for efficient meiotic DSB repair, but defects appear to be specific to intersister recombination (Bickel et al. 2010). This phenotype may reflect the limited role of MUS81 in meiosis in *C. elegans* (Bellendir and Sekelsky 2013). In *Arabidopsis,* analysis of an *mms21* mutant reveals phenotypes consistent with defective joint molecule processing including anaphase bridges, chromosome missegregation, and fragmentation (Liu et al. 2014a). In mammals, SMC5/6 localizes to synaptonemal complex, consistent with a role in meiotic recombination (Gomez et al. 2013; Verver et al. 2014), but mutant analysis is currently lacking.

Implementing Noncrossover Formation

As discussed above, the STR/BTR complexes are essential for the physiological noncrossover pathway, indicating that active disassembly of extended D-loops is required for efficient synthesis-dependent strand annealing (Chelysheva et al. 2008; Kaur et al. 2015; Seguela-Arnaud et al. 2015; Tang et al. 2015). Analysis in *Arabidopsis* and *S. pombe* reveals that orthologs of the FANCM (Fanconi anemia of complementation group M) DNA translocase also promote noncrossover formation (Crismani et al. 2012; Knoll et al. 2012; Lorenz et al. 2012). FANCM limits the formation of class-II crossovers involving Mus81–Eme1, but functions in parallel to STR/BTR suggesting that these enzymes act on distinct DNA substrates (Seguela-Arnaud et al. 2015). Analogous to STR/BTR and FANCM, the DEAH-family helicase, RTEL (regulator of telomere length) limits MUS81-dependent crossovers in *C. elegans,* but is thought to act via a distinct mechanism, by limiting interhomolog strand invasion as opposed to implementing interhomolog noncrossover formation (Youds et al. 2010; Rosu et al. 2011).

CLINICAL SIGNIFICANCE OF MEIOTIC RECOMBINATION

Aneuploidy, Crossing-Over, and Advancing Maternal Age

Human reproduction is prone to errors: ~15% of couples are affected by infertility and, even for fertile couples, around a quarter of all pregnancies will end in miscarriage. At least a third of miscarriages are caused by fetal aneuploidy (trisomy or monosomy) that derives from defects in meiosis. Aneuploidy is also the leading single cause of congenital birth defects, occurring at a frequency of ~0.3% (Nagaoka et al. 2012; Herbert et al. 2015). Less than 5% of human aneuploidies originate from errors in the male germline, consistent with the relatively low levels of aneuploidy detected in sperm (Templado et al. 2013). In sharp contrast, an estimated 20% to 70% of eggs are aneuploid (Nagaoka et al. 2012). Although the factors that contribute to the high rate of aneuploidy in the human female germline are clearly complex, two key factors have been identified: suboptimal crossing-over and advancing maternal age.

In humans, the association between altered crossover patterns and ensuing aneuploidy has been known for more than 20 years (Fisher et al. 1995; Hassold et al. 1995; Lamb et al. 1996; Hassold and Hunt 2001; Oliver et al. 2008). Two patterns are observed, a simple failure to crossover and suboptimal placement of crossovers, located either close to telomeres or close to the centromeres. Crossover failure creates an obvious risk for missegregation because unconnected homologs cannot attain a stable bipolar orientation on the meiosis-I spindle (Fig. 2). Distal crossovers are an aneuploidy risk because they are less efficient at promoting biorientation than more proximal exchanges (Lacefield and Murray 2007; Sakuno et al. 2011). In addition, connection of homologs by a single distal crossover is dependent on the short stretches of cohesion between the exchange point and the telomeres. Such "weak" chiasmata may be susceptible to premature resolution (Hassold et al. 1995; Koehler et al. 1996; Lamb et al. 1996; Ross et al. 1996).

Cohesion between sister centromeres is important for the monopolar behavior of sister-kinetochore pairs that enables homolog biorientation on the meiosis-I spindle. In addition, centromeric cohesion must be maintained until the second meiotic division when sister kinetochores now biorient on meiosis-II spindles (Fig. 2) (Watanabe 2012). Centromere-proximal crossovers are associated with the premature separation of sister chromatids at meiosis I, suggesting that centromeric cohesion is compromised by local crossing-over (Koehler et al. 1996; Lamb et al. 1996; Hassold and Hunt 2001; Rockmill et al. 2006). The local disruption of cohesion seen at chiasmata supports this idea (e.g., Kleckner 2006; Garcia-Cruz et al. 2010).

Inherent variability during meiotic prophase in human oocytes also appears to contribute to the highly elevated risk of aneuploidy seen in females (Lenzi et al. 2005). Although oocytes form ~60% more crossovers than spermatocytes, their distribution appears to be less well regulated, resulting in an estimated ~10% of oocytes that contain an achiasmate chromosome pair (Cheng et al. 2009). Moreover, crossover rate varies significantly between individuals and has a strong heritable component (Broman et al. 1998; Kong et al. 2002, 2008, 2014; Lenzi et al. 2005; Coop et al. 2008; Chowdhury et al. 2009; Fledel-Alon et al. 2011). Intriguingly, correlations between female crossover rate and fecundity have emerged from population studies. Mothers inheriting a higher crossover rate have slightly more children (Kong et al. 2004; Stefansson et al. 2005; Coop et al. 2008). Moreover, the crossover rate appears to increase with advancing maternal age. Specifically, more crossovers are detected in children born to older mothers, implying that oocytes that give rise to viable offspring in older mothers tend to have more crossovers (Kong et al. 2004; Coop et al. 2008; Campbell et al. 2015; Ottolini et al. 2015). Extra crossovers are proposed to buffer against the effects of advancing maternal age, in particular, the erosion of sister-chromatid cohesion (discussed below). Thus, crossover rate may be under selection in human populations.

Both common and rare human alleles have now been linked to heritable variation in crossover rate (Stefansson et al. 2005; Kong et al.

2008, 2014; Chowdhury et al. 2009; Fledel-Alon et al. 2011; Campbell et al. 2015). These include alleles of genes known to regulate meiotic recombination: the crossover regulators, *RNF212*, *HEI10 (CCNB1IP1)*, and *MSH4* (described above); *RAD21L* and *REC8*, which encode meiosis-specific cohesin subunits (Uhlmann 2011); and the DSB regulator, *PRDM9* (Baudat et al. 2013).

Selection for oocytes with higher crossover numbers is inferred to be a manifestation of the maternal-age effect—the exponential increase in oocyte-derived aneuploidy that begins after ~35 years of age (Hassold and Hunt 2001). Advancing maternal age is the major risk factor for human aneuploidy because of the deterioration that occurs during the extremely protracted dictyotene stage that is peculiar to oogenesis (Herbert et al. 2015). Meiosis in females initiates during fetal development, but arrests around birth after crossing-over has been completed and synaptonemal complexes have disassembled (Fig. 2). Resumption of meiosis and completion of the first division occurs only in the mature oocytes that are about to be ovulated. These oocytes will have been in the dictyotene stage for somewhere between ~11 and 50 years (menarche through menopause). Thus, chiasmata must be maintained for decades in resting oocytes. In contrast, spermatocytes proceed directly into the meiotic divisions.

Although aging clearly impacts oocyte chromosome segregation via multiple pathways (Hassold and Hunt 2001; Selesniemi et al. 2011; Nagaoka et al. 2012), a number of studies indicate that progressive weakening of sister-chromatid cohesion is likely to be a major mechanism (Wolstenholme and Angell 2000; Jeffreys et al. 2003; Jessberger 2010, 2012; Nagaoka et al. 2012). Mouse studies indicate that cohesion is not replenished during dictyotene (Revenkova et al. 2010; Tachibana-Konwalski et al. 2010) and that both cohesion subunits and factors that function to protect centromeric cohesion until meiosis II are depleted in older animals (Hodges et al. 2005; Liu and Keefe 2008; Chiang et al. 2010; Lister et al. 2010; Shomper et al. 2014; Yun et al. 2014). Although definitive proof of analogous "cohesion exhaustion" in aging human oocytes has been harder to obtain, the weight of evidence suggests that this is the case (Angell 1991; Angell et al. 1994; Pellestor et al. 2003; Garcia-Cruz et al. 2010; Fragouli et al. 2011; Tsutsumi et al. 2014; Ottolini et al. 2015).

The effects of cohesin depletion in aging oocytes appear to be several-fold. Chiasmata may be prematurely lost, or become terminalized, both of which will impact the ability of homologs to biorient at meiosis I (Ross et al. 1996; Lacefield and Murray 2007; Sakuno et al. 2011; Watanabe 2012). Diminished centromeric cohesion weakens the normally tight association of sister kinetochores, increasing the frequency and stability of aberrant sister biorientations on the meiosis-I spindle, thereby elevating the risk of premature separation of sister chromatids (Watanabe 2012; Tachibana-Konwalski et al. 2013). Angell inferred that premature separation of sister chromatids is the major route to nondisjunction (Angell 1991; Angell et al. 1994), a proposal that is strongly supported by more recent studies (Pellestor et al. 2003; Fragouli et al. 2011; Handyside et al. 2012; Hou et al. 2013; Ottolini et al. 2015). Unexpectedly, it appears that achiasmate homologs, which were predicted to undergo canonical meiosis-I nondisjunction, instead tend to biorient their sister chromatids on the meiosis-I spindle, thereby evading the spindle-assembly checkpoint (LeMaire-Adkins and Hunt 2000; Kouznetsova et al. 2007; Nagaoka et al. 2011; Ottolini et al. 2015). The ensuing separation of sister chromatids at meiosis I is followed by segregation of nonsister chromatids at meiosis II in a process termed reverse meiosis (Ottolini et al. 2015). Aneuploidy may result from nondisjunction of the nonsister chromatids in meiosis II, whereas successful disjunction effectively rescues the original defect, producing a euploid ovum. Finally, nonexchange chromatids appear to be selected against via an unknown mechanism that preferentially segregates them into the polar body at meiosis II (Ottolini et al. 2015). Thus, suboptimal crossing-over, which is established in fetal oocytes, impacts events that occur decades later, affecting chromosome segregation during both meiosis-I and meiosis-II divisions in unexpected ways.

Meiotic Recombination and Genomic Disorders

Nonallelic meiotic recombination between low-copy dispersed repeats is frequent and generates reciprocal chromosome rearrangements that are generally deleterious. For example, copy-number variants resulting from the reciprocal deletion and duplication products of nonallelic recombination are associated with dozens of recurrent human disorders (Stankiewicz and Lupski 2002; Shaw and Lupski 2004; Sharp et al. 2005; Turner et al. 2008; Abyzov et al. 2015; Martin et al. 2015). These include hereditary neuropathy with liability to pressure palsies and Charcot–Marie–Tooth disease type 1A (Chance et al. 1994), Prader–Willi syndrome/Angelman syndrome and 15q11q13 duplication (Long et al. 1998), velocardiofacial syndrome and dup22(q11.2q11.2) (Edelmann et al. 1999a), Smith–Magenis syndrome and Potocki–Lupski syndrome (Potocki et al. 2000), and Williams–Beuren syndrome and dup7(q11.23) (Somerville et al. 2005). Other rearrangements, such as translocations, may create gene imbalances that are incompatible with fetal development, as seen for most aneuploidies. Thus, selection for higher crossover rates to enhance the fidelity of meiotic chromosome segregation may be countered by selection to preserve genomic stability.

Defective Recombination and Infertility

Meiotic recombination represents a huge mutational target and variants of recombination genes are likely to contribute to infertility. However, infertility defies conventional pedigree-based genetic analysis. A number of variants in recombination genes have been identified in infertile individuals, but causal relationships have proven hard to establish (e.g., Miyamoto et al. 2003, 2008, 2012; Stouffs et al. 2005; Martinez et al. 2007; Hikiba et al. 2008; Xu et al. 2010; Ji et al. 2012; Ghalkhani et al. 2014; Llano et al. 2014; Sazegari et al. 2014). However, a recent survey of azoospermic men revealed that 1% carried mutations in the X-linked *TEX11* gene (encoding the Zip4 ortholog) and causality could be confirmed by functional analysis in the mouse (Yang et al. 2015). Thus, rare and spontaneously arising mutations in meiotic recombination genes are likely to be a significant factor for human infertility.

CONCLUDING REMARKS

The centrality to sexual reproduction and heredity places meiotic recombination at the forefront of biological research. Many pressing and outstanding questions remain. For example: why does DSB formation require a dozen or more accessory proteins; how are elastic DNA interactions bolstered to bring homologs into close juxtaposition; how is recombination functionally integrated with chromosome morphogenesis and the progression of meiotic prophase; how are crossover sites selected and how is exchange implemented with high efficiency at these sites; why do crossover numbers tend to be minimized and what conditions might select for altered recombination rates; why is recombination less well regulated in human females; and what contribution does defective recombination make to human infertility? Despite intrinsic challenges to studying meiosis, the advances made in recent years, highlighted here and in the associated collection of reviews (Subramanian and Hochwagen 2014; Brown and Bishop 2015; Herbert et al. 2015; Lam and Keeney 2015; Székvölgyi et al. 2015; Zickler and Kleckner 2015), promise rapid progress toward answering these and other important questions.

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